Pre-placement screening for tuberculosis in healthcare workers

P. Giri¹, S. Basu¹, T. Sargeant¹, A. Rimmer¹, O. Pirzada² and A. Adisesh³

¹Sheffield Occupational Health Service, Silverwood, Northern General Hospital, Herries Road, Sheffield S5 7AU, UK, ²Department of Respiratory Medicine, Northern General Hospital, Sheffield S5 7AU, UK, ³Dalhousie Medicine New Brunswick (DMNB), Saint John, New Brunswick E2L 4L5, Canada.

Correspondence to: S. Basu, Sheffield Occupational Health Service, Silverwood, Northern General Hospital, Herries Road, Sheffield S5 7AU, UK. Tel: +44 (0)114 226 9424; fax: +44 (0)114 271 4844; e-mail: subhashis.basu@sth.nhs.uk

Background Healthcare workers (HCWs) are at occupational risk of contracting and transmitting tuberculosis (TB). Despite national guidance, the optimal process for the pre-placement screening of new entrant HCWs for TB in the UK is not certain, nor the appropriateness of using a one-step interferon gamma release assay (IGRA) screening programme.

Aims To assess the potential for an IGRA-only TB screening programme for new entrant HCWs, and identify cost savings achieved through this process.

Methods We conducted a retrospective analysis of IGRA and tuberculin skin tests (TST) within our occupational health service over a 3-year period. HCWs with markedly discordant test results (IGRA negative, TST positive) were followed up to determine whether they developed active TB. We also estimated the yearly cost savings if the existing two-step process was replaced with an IGRA-only programme.

Results Totally, 96/1258 (8%) HCWs had positive IGRA results; 788 TSTs were performed for newly screened IGRA-negative HCWs without Bacille Calmette–Guérin scars, among which 597 (76%) tested negative (TST <6 mm). None of the 10 individuals with grossly discordant test results (TST >15 mm) developed active TB during the study period. We calculated savings of £20 453 if the two-step process was replaced with an IGRA-only programme.

Conclusions The absence of disease progression in individuals with markedly discordant results in this study suggest that an IGRA-only screening programme for new HCWs in the UK is feasible, and may be safe although our follow-up period was insufficient. Our results also suggest that substantial cost savings can be made by using this programme.

Key words Epidemiology; interferon gamma; mantoux; occupational health; tuberculosis; vaccination.

Introduction

Screening of new entrant healthcare workers (HCWs) for tuberculosis (TB) remains important due to their occupational risk of contracting and potentially transmitting TB to patients. This risk is greater in HCWs working with laboratory TB specimens and in clinical areas such as respiratory units, infectious disease wards and emergency departments [1].

The most commonly used tests in TB screening are the tuberculin skin test (TST) and the more recently developed interferon gamma release assays (IGRAs). The TST is based on a type IV delayed hypersensitivity reaction that occurs when those infected with Mycobacterium tuberculosis are exposed intradermally to standardized mycobacterial antigens. Although the TST has well-established cut-off points to indicate the need for preventive therapy it has many limitations. These include variable specificity for M. tuberculosis, as a result of immunological cross-reactivity with other strains of mycobacteria and antigens present in Bacille Calmette–Guérin (BCG) vaccination. Other shortcomings include measurement variability between trained personnel in interpreting results and poor compliance due to the need for multiple appointments [2].

More recently, IGRA tests have provided an additional tool to identify suspected cases of TB. Two blood assay
Occupational Health Service (SOHS) in 2009–12 were and health science students presenting to Sheffield All new National Health Service (NHS) employees Methods be made through using a single-step IGRA-only pro lowing screening in IGRA negative/TST positive HCWs populations, the likelihood of developing active TB fol ing delays and variability in phlebotomy technique. Non-specific IGRA test result changes may be misinterpreted, perhaps resulting in overtreatment.

The development of IGRAs has stimulated research into determining how these tests can be used as part of dual and single-step (IGRA only) screening programmes [8,9]. However there is substantial global variation in the use of IGRA and TST in TB screening programmes, including the order in which they are performed [10]. Guidance for the use of IGRA and TST in screening made by the National Institute for Health and Clinical Excellence (NICE), Department of Health (DoH) in England and the Centers for Disease Control and Prevention in the USA has evolved in recent years [11–13]. In 2006 NICE suggested that IGRA may be used as an alternative to TST for pre-placement screening for TB in new entrant UK HCWs. More recent NICE guidance suggests following the recommendations of the DoH’s ‘Green Book’ in that IGRA negative HCWs without evidence of prior BCG vaccination should be offered TST prior to offering BCG [11]. This means that the current recommendation is to follow a two-step screening process including both IGRA and TST.

A programme based on single-step screening is potentially attractive as it offers convenience, cost savings and increased organizational efficiency. There are, however, unanswered questions as to whether the HCW group shows the same pattern of test concordance as other populations, the likelihood of developing active TB following screening in IGRA negative/TST positive HCWs without current symptoms and the cost saving which can be made through using a single-step IGRA-only programme. This study aimed to address these questions.

Results
A total of 1258 IGRA tests were carried out at SOHS for the purpose of pre-placement screening during the study period; 8% of cases (96/1258) were IGRA positive, and in the absence of satisfactory evidence of prior BCG

Methods
All new National Health Service (NHS) employees and health science students presenting to Sheffield Occupational Health Service (SOHS) in 2009–12 were assessed for TB using a two-stage protocol as shown in Figure 1 based on NICE and DoH guidance [11,13]. Guidance from NICE (2006) indicated that IGRA was an alternative to TST for pre-entrant health clearance of prospective and new HCWs [12]. We adopted IGRA as our first-line screening test at SOHS for a number of reasons. Firstly, evidence suggests that the IGRA test has greater specificity for M. tuberculosis than TST among prospective HCWs [2,5]. Secondly, we wished to improve the efficiency of health clearance by offering a single appointment in contrast to the two required for TST and the high rates of missed appointments with the latter. Thirdly, we wished to assess whether those HCWs who had tested IGRA negative could be safely offered BCG. We used Quantiferon™-TB Gold In-Tube, which has a sensitivity of 93% and specificity 89% according to the manufacturer (Cellestis Ltd) as the first-line screening test. HCWs with positive IGRAs were referred to chest clinic to exclude active TB and for consideration of chemoprophylaxis.

A retrospective analysis of all IGRA and TST results performed in SOHS for new entrant HCWs from 1 April 2009 to 31 March 2012 was carried out by extracting data from our computerized record system (COHORT; Medgate software) and examining the clinical records for risk factors. Data analysis was performed using Microsoft Excel. A negative TST was defined as an induration of <6 mm, and a strongly positive test >15 mm [11].

All HCWs were followed up during the period of the study to assess the development of active TB through liaison with chest clinic and infection control leads of all contracted organizations to identify whether any screened HCWs had developed active TB, or if there had been any reported instances of disease transmission from HCWs to patients.

Estimated cost savings per year through the introduction of a single-step (IGRA only) screening programme were calculated using prices specified by the online costing tool Software Tool for Efficiency Modelling (STEM) developed by NHS Health at Work [14]. A description of costs for IGRA, TST administration and reading is shown in Table 1.

The study was ethically approved as a service evaluation project through the Clinical Effectiveness Unit at Sheffield Teaching Hospitals. All electronic data was stored on a protected database only accessible to the researchers. Patient notes were stored within a locked storage facility at SOHS.

Formats are currently available: Quantiferon™-TB Gold In-Tube test (Cellestis Ltd, Chadstone, Victoria, Australia) which measures interferon-gamma, and the T-SPOT TB test (Oxford Immunotec Inc., Marlborough, MA) which measures activated T-cell secreting interferon-gamma. Advantages of IGRAs over the TST include greater specificity for M. tuberculosis infection; a single appointment process and reduction of reader variability. Further, the cost-effectiveness of IGRA over TST has been established in a number of settings, including screening programmes for adult contacts of individuals with TB, and for screening immigrants to the UK [3–5]. Recent work has, however, identified sources of error which can affect the interpretation of IGRA results. These include methods of storage and transport where unused assay tubes may be subject to high temperatures [6] and test processing delays and variability in phlebotomy technique. Non-specific IGRA test result changes may be misinterpreted, perhaps resulting in overtreatment [7].
vaccination, 68% (788/1162) of HCWs with a negative IGRA result required a TST. Test concordance and discordance rates are shown in Table 2 below.

Of the 191 individuals that were IGRA negative and TST positive, 10 had TST >15 mm. These 10 individuals were referred to the chest clinic where current active TB was ruled out and BCG offered. No cases of active TB were reported by infection control leads or chest clinic up to March 2013 in HCWs who had been screened at SOHS.

In the two-step process, the cost incurred through TST alone over the 3-year study period was £30 543. There were 1188 missed appointments for TST administration or reading which were re-booked at a total cost of £23 023. We estimated, assuming no missed appointments, that

Table 1. Cost breakdown of tests

<table>
<thead>
<tr>
<th></th>
<th>IGRA</th>
<th>TST administration or reading</th>
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</thead>
<tbody>
<tr>
<td>Staff cost</td>
<td>£12.20</td>
<td>£12.20</td>
</tr>
<tr>
<td>Occupational health</td>
<td>£5.78</td>
<td>£1.90</td>
</tr>
<tr>
<td>overhead</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital overhead</td>
<td>£6.93</td>
<td>£2.28</td>
</tr>
<tr>
<td>Materials and clinical</td>
<td>£34.00</td>
<td>£3.00</td>
</tr>
<tr>
<td>supplies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total time</td>
<td>20 min</td>
<td>20 min</td>
</tr>
<tr>
<td>Total cost</td>
<td>£58.91</td>
<td>£19.38, *Add £11 if BCG necessary</td>
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*Add £11 if BCG necessary

Figure 1. Two-step tuberculosis screening programme at SOHS. CXR, chest X-ray.
if a single-step (IGRA only) programme had been in place, the total cost of the programme would have been £58,561 as opposed to £136,916 for the two-step programme. Our results indicate that at least £51,355 would have been saved during the 3-year period of the study, equating to £17,118 per year, despite the costs incurred through additional BCG vaccinations using a single-step programme. Over the 3 years of the study, the saving would have been 1000 h of nursing time and 65 h of administration time (Table 3).

All 96 IGRA-positive HCWs were referred to the chest clinic where they were further assessed for the presence of latent and active TB. In total, 82% of HCWs (79/96) attended, with the remaining 17 having ceased employment at the trust prior to their appointment; 62% (49/79) accepted the offer of chemoprophylaxis, with the remaining choosing a ‘wait and watch’ policy for the development of symptoms and signs of active TB. Thirty-seven HCWs who accepted chemoprophylaxis were contactable following completion of their treatment, of which 35 (94%) had achieved this successfully.

Discussion

Our findings suggest that a single-step IGRA-only programme for new HCWs in the UK was practical, cost-effective and probably safe [15,16]. Although none of our 788 IGRA negative cases developed active TB, and only 10 HCWs with discordant test results had TST >15 mm (1%), it should be noted that our follow-up period was short and the study population was small.

One potential drawback of a single-step programme is that it could lead to additional cases of active disease since, at least theoretically, those HCWs with markedly discordant results (IGRA negative and TST >15 mm) may progress to active TB. Previous work has identified that IGRA and TST concordance is affected by a number of issues including the cut-off values used for a positive test result, the specificity of the test within the screened population and logistical factors such as pricing and patient preference [17].

None of the 10 HCWs in this study with such results went on to develop active TB, the numbers were limited and the follow-up period relatively short. The superior pooled negative predictive value of IGRA in ruling out progression to active TB compared with TST (99.7 versus 99.4%, \( P < 0.01 \)) provides some further reassurance in this area [13]. Our findings are also consistent with previous work which found that no individuals with IGRA negative but TST-positive results developed active TB over a 4-year follow-up period [18]. In times of financial austerity our estimated cost savings resulting from the introduction of a one-step TB screening programme may be attractive to UK occupational health departments responsible for the health clearance of new HCWs, and the organizations they serve. The single-step approach also reduces delays in the health clearance process.

Our work has a number of limitations. In particular, the follow-up period for those HCWs most likely to develop active TB was a maximum of 4 years (beginning with those seen in 2009 at SOHS), following which outcomes are unknown. This is an important area of further work in determining the safety of a single-step (IGRA only) screening programme in this setting. Our estimated cost saving resulting from the introduction of a one-step TB screening programme for new entrant HCWs is also location-specific, but is likely to apply to most UK Occupational Health departments.

Several questions about the design, implementation and evaluation of a single-step process of screening for TB in HCWs remain unanswered. The clinical benefit of BCG vaccination in protecting HCWs from contracting TB has been debated. In particular, work suggests that existing BCG vaccines have limited efficacy in preventing the development of active pulmonary disease in adults [19], which has led to work in developing a more effective alternative. The safety of additional BCG vaccination in those that may

<table>
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<th>Table 2. Test results</th>
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<tr>
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<tr>
<td>IGRA negative/TST negative</td>
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<tr>
<td>IGRA negative/TST positive</td>
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<tr>
<td>Total</td>
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| Table 3. Cost-saving using single-step IGRA only TB screening programme |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Process                     | Two-step programme           | One-step programme           | Change          |
| IGRA administration         | \(1258 \times £58.91 = £74109\) | \(1258 \times £58.91 = £74109\) | Nil             |
| Chest X-ray                 | \(96 \times £29 = £2784\)    | \(96 \times £29 = £2784\)    | Nil             |
| TST administration          | \(788 \times £19.38 = £15271\) | Not applicable              | \(-£15271\)     |
| TST reading                 | \(788 \times £19.38 = £15271\) | Not applicable              | \(-£15271\)     |
| TST rebooking               | \(1188 \times £19.38 = £23023\) | Not applicable              | \(-£23023\)     |
| BCG administration          | \(587 \times £11 = £6457\)   | \(788 \times £11 = £8668\)  | \(£2,211\)      |
| Total 3-year cost           | £136,916                     | £85,561                     | £51,355         |
| Yearly cost                 | £45,639                      | £28,520                     | £17,118         |
have already received it has also been brought into question. It should be noted, however, that serious complications from BCG vaccination in previously unvaccinated individuals are rare, with significant local reactions estimated to occur at a rate of 1 per 1000 individuals vaccinated [20]. In addition, research into the effect of BCG revaccination suggests that it is well tolerated, with no serious adverse systemic effects [21]. The interpretation of IGRA results in serial testing has also been critically evaluated. Recent data indicates that IGRA tests yield high rates of conversions and reversions within serial testing programmes, introducing difficulties in determining appropriate cut-off points for offering chemoprophylaxis [22]. Finally, we have assumed that the risk that IGRA-positive HCWs go on to develop active TB is of sufficient magnitude to merit the use of this test as a screening tool. In the UK, at least such an assumption would appear currently to be justified. Current evidence suggests that the lifetime risk of disease progression for those with latent TB without immunosuppression is around 10%, adding weight to this assumption [23]. Nonetheless, the costs of delivering the programme must be evaluated against the likely number of cases of active TB prevented and the potential healthcare-associated disease outbreaks averted. In this regard, compliance with treatment and rates of disease progression in IGRA-positive cases, particularly in those HCWs that do not receive chemoprophylaxis for latent TB, also warrant further study. Such information can inform the utility and cost-effectiveness of a screening programme in these settings.

**Key points**

- Pre-placement screening for tuberculosis in healthcare workers remains an important occupational health task.
- Our study suggests that a one-step (interferon gamma release assay only) process for tuberculosis screening may be feasible.
- A significant cost saving can be made through the introduction of an interferon gamma release assay only screening programme for tuberculosis in healthcare workers.

**Conflicts of interest**

None declared.

**References**

Fifty years ago: ‘The appointed factory doctor’

It is now generally accepted that as a nation we have too few doctors, and this fact is frequently emphasized when expansion of occupational health services is under discussion. The appointed factory doctor system is thought by some to provide a possible solution to this difficulty. Here, it is urged, is a body of men who between them cover the whole of the country, and who are already working in industry, which could be used as a nucleus of a nation-wide occupational health service, without making demands on our medical manpower which could not be met without starving the curative health services.

Most of the 1700 A.F.D.’s are general practitioners whose main professional interests are in domiciliary medicine; for them the appointment can become an interesting but minor sideline. Increasingly the full-time industrial medical officer has entered the picture, but he is restricted to the examination of young persons and employees covered by special regulations. The volume of work performed by A.F.D.’s in 1963, to take a typical recent year, raises some interesting questions. 519 705 juveniles were examined; all but 21 167 were passed without conditions affecting their employability. Only 14 499 juveniles were completely rejected for employment, and of these a disproportionate number were girls. Over half the 848 females rejected suffered from pediculosis, and 212 of the 601 boys suffered from visual refractive errors. Both these conditions are quickly and eminently remediable. Their very existence as causes of rejection raises the question of the true functions and the proper use of the system of examining juveniles.

A further 358 904 examinations were performed in 1963 under the special regulations governing hazardous occupations, and they resulted in 999 suspensions from work. The low proportion of suspensions is almost certainly attributable to the efficiency of the physical control measures in force in these processes. In some trades, the control is obviously so efficient that the question arises whether the continuation of medical examinations is justified, and whether environmental control measures alone are now all that are needed.

It should not be forgotten that by far the greater part of the total work of the A.F.D. system is done in the thickly populated, highly industrialized conurbations. These unlovely areas have other pressing problems of medical care, morbidity is higher in such areas, they have fewer general practitioners and their hospitals attract fewer junior staff, so that supplemental staffing by local family doctors is often necessary. The medical resources of such towns are already severely over-strained and relatively small extra burdens, such as the work of the A.F.B., always mean robbing Peter to pay Paul.

The role and functions of the A.F.D. are, for this and other reasons, in need of re-appraisal and re-definition. Some of his existing duties seem to be superfluous, whilst others are not performed effectively. If the job is to be made more precise, it will be necessary to ensure that the appointees have not only the knowledge and training, but also the time to perform their new duties adequately. This latter factor is easily estimable and will become increasingly important as the medical man-power crisis deepens during the present decade.


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