A 100 year update on diagnosis of tuberculosis infection

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Background: Diagnosis and treatment of latent tuberculosis infection (LTBI) is a cornerstone of tuberculosis (TB) control in the developed world. In the last century, the tuberculin skin test (TST) was the only means of diagnosing LTBI. ELISpot and whole-blood ELISA, collectively known as interferon-gamma release assays (IGRAs), are promising new tools.

Areas of agreement: IGRAs are more specific than TST for diagnosis of LTBI as they are not confounded by previous bacille Calmette-Guerin (BCG) vaccination. Assessing IGRA sensitivity in the absence of a gold standard for LTBI is challenging. Studies have therefore used surrogate markers such as active TB and correlation with degree of TB exposure in contact investigations. These studies suggest that sensitivity of ELISpot is higher than TST while whole-blood ELISA has similar sensitivity to TST. Recent longitudinal studies demonstrating the prognostic power of these tests for development of active TB provide definitive evidence that positive IGRA results reflect infection with dormant yet viable bacilli.

Areas of controversy: Is the prognostic power of IGRAs greater than the TST? What are the false-negative rates in immunocompromised individuals with LTBI at high risk of progressing to active TB?

Growing points: IGRAs have been incorporated into national guidelines, although their optimal deployment in diagnostic algorithms is evolving. The health economic benefits of utilizing IGRAs are increasingly recognized, partly because their high specificity avoids unnecessary chemoprophylaxis in BCG-vaccinated persons with false-positive TST results.

Areas timely for developing research: Current IGRAs are being improved and next-generation tests, with improved sensitivity, could enable the reliable exclusion of LTBI in immunocompromised individuals.

Keywords: latent tuberculosis/interferon-gamma release assays/tuberculosis infection/review
Introduction

Globally, tuberculosis (TB) continues to be one of the leading infectious causes of morbidity and mortality accounting for an estimated 9 million cases and 2 million deaths per year. This failure to adequately control the global epidemic may partly reflect the slow progress that has been made, over the last century, in developing innovative diagnostic tools for TB. However, the potential to significantly advance TB control now exists with the development of novel diagnostic modalities for latent TB infection (LTBI).

The global epidemiology of latent TB infection

With an estimated one-third of the world’s population latently infected with TB (LTBI), and therefore potentially at future risk of developing active disease, increasing importance is being accorded to the effective identification and treatment of individuals with LTBI, particularly in low TB burden countries where latently infected migrants and recently infected contacts of smear-positive cases account for the bulk of the TB case-load.

Data on TB natural history suggest that in the first 2 years following initial infection with tubercle bacilli 5% of infected individuals will progress to active disease; if the bacilli are brought under immune control they may lie dormant for several decades with only a further 5–10% of infected immunocompetent people eventually going on to develop active disease over their lifetime. As a result, the diagnosis and treatment of LTBI will be most effective if it is specifically targeted at those individuals with the highest risk of progression from LTBI to active disease including: recently infected individuals and all those with underlying immunosuppression.

Methods of diagnosing LTBI

Making the diagnosis of LTBI is constrained by a low bacteria load that makes it impossible to directly detect Mycobacterium tuberculosis and a weak humoral response that makes serological testing unreliable. As a consequence, for much of the previous century, diagnosis of LTBI has been defined as a positive tuberculin skin test (TST) in an asymptomatic person exposed to tuberculosis with no other evidence of active disease. The utility of the TST is that it detects a cutaneous delayed-typed hypersensitivity response to purified protein derivative (PPD),
a mixture of over 200 \textit{M. tuberculosis} proteins. However, the TST is neither specific, as the antigens present in PPD cross-react with bacille Calmette-Guerin (BCG) and environmental mycobacteria, nor sensitive, due to anergy in those individuals with a compromised immune system (such as HIV, iatrogenic immunosuppression and children).

\textit{T-cell interferon gamma release assays}

T-cell interferon gamma release assays (IGRAs) have been developed as an alternative immunodiagnostic approach to the TST for detecting \textit{M. tuberculosis} infection.\cite{7} Currently 2 \textit{ex vivo} assays are available: the ELISpot that directly counts the number of IFN-\gamma secreting T-cells and the whole-blood ELISA that measures the concentration of IFN-\gamma secretion. Commercially, the ELISpot assay is available as the T-SPOTTM.TB (Oxford Immunotec, Abingdon, UK) and the ELISA as the QuantiFERONTM-TB Gold In-Tube (Cellestis, Carnegie, Australia). Both IGRAs incorporate two antigens—early secretory antigen target-6 (ESAT-6) and culture filtrate protein-10 (CFP-10)—which are strong targets of Th1 T-cells in \textit{M. tuberculosis} infection but also deleted from all strains of BCG and the majority of environmental mycobacteria (except \textit{M. Kansasi}, \textit{M. szulgai}, \textit{M. marinum}, \textit{M. flavescens} and \textit{M. gastrii}).\cite{8,9} Therefore, in comparison with the TST, T-cell responses to these antigens are not confounded by prior BCG vaccination and hence a more specific marker of TB infection.\cite{2}

\textbf{Performance of IGRAs in the diagnosis of LTBI}

Objectively comparing the diagnostic performance of the IGRAs and the TST is hindered by the lack of a gold standard reference test for LTBI that makes it impossible to directly measure sensitivity and specificity. As a result, investigators have utilized proxy markers of LTBI including:\cite{1} degrees of exposure to infectious cases,\cite{2} active TB as a surrogate for LTBI and, to assess specificity,\cite{3} the presence of IGRA negativity in healthy BCG-vaccinated individuals at low risk of TB infection due to the absence of epidemiologic risk factors for tuberculosis exposure.

\textbf{Clinical performance of IGRAs in immunocompetent individuals}

\textit{Correlation with TB exposure of IGRA results}

An important facet of TB transmission is that the risk of acquiring \textit{M. tuberculosis} is primarily determined by the frequency, duration and
proximity of contact with an infectious source case.\textsuperscript{10} Hence, if a new test is more sensitive and specific than the TST it should correlate more closely with the level of exposure to \textit{M. tuberculosis} and be independent of BCG status.\textsuperscript{11}

Outbreak and contact-tracing investigations have made use of this theory to compare the diagnostic accuracy of IGRAs and the TST\textsuperscript{11,12} and concluded that both IGRAs correlate either as well as, or better than, the TST with levels of exposure to tuberculosis whilst also being independent of BCG status. In one of the largest, and earliest, studies of this type the ELISpot was employed in a large school outbreak investigation comprising 535 students.\textsuperscript{12} ELISpot results, but not TST results, were independent of the BCG vaccination status, indicating higher specificity. Overall, ELISpot also correlated better with tuberculosis exposure (based on proximity and duration of exposure to the index case) than TST suggesting a higher diagnostic sensitivity for LTBI.\textsuperscript{12} Other work from varying TB burden settings has also confirmed that the ELISpot significantly correlates with TB exposure.\textsuperscript{13–17} In a recent study of South African children, positive ELISpot and TST results were found to be significantly associated with the degree of exposure to smear-positive index cases.\textsuperscript{17}

Studies have also confirmed that the ELISA significantly correlates with exposure to TB.\textsuperscript{18–21} In a recent case–control study from Nigeria, a dose–response relationship was found between bacillary load in the sputum of index cases and ELISA positivity in child contacts,\textsuperscript{20} children who had been in contact with the most heavily smear-positive index cases, rather than smear-negative adults, were more likely to be TST and ELISA positive.\textsuperscript{20} However, in contrast, a study from a South African township of children at high risk of LTBI does not find any significant relationship between ELISA positivity and levels of exposure.\textsuperscript{22}

An important outcome of these studies is an assessment of the level of concordance between the IGRAs and TST. In BCG-vaccinated populations, there are lower levels of agreement between IGRAs and the TST. This is to be expected as the TST, but not IGRAs, are confounded by BCG vaccination. Where the ELISpot assay has been studied, generally moderate to high levels of agreement with the TST have been found.\textsuperscript{12,13,15,23}

On the other hand, the concordance between the ELISA and the TST appears to be more variable; across a variety of TB burden settings investigators have found agreement between the ELISA and TST ranges from high to poor.\textsuperscript{13,18,19,21} Studies in non-BCG vaccinated children from Australia and Spain, which are low TB burden countries, have found that the ELISA remained negative in a significant proportion of children with a positive TST.\textsuperscript{13,21} These data suggest that the ELISA may have a lower sensitivity than the TST in diagnosing LTBI in children.
However, the significance of discordant TST/IGRA results cannot be reliably elucidated by these cross-sectional studies and will require data from longitudinal studies.

**Active TB as a surrogate marker for LTBI**

As infection with *M. tuberculosis* is a prerequisite for active TB disease, this principle has been exploited as an alternative surrogate marker for TB infection by several studies evaluating the diagnostic sensitivity of IGRAs. Pai *et al.*²⁴ have recently systematically reviewed these studies and concluded that the ELISpot had a pooled sensitivity of 90% (range 83–100%) which was significantly higher than the pooled sensitivities of the second generation ELISA (78%, range 55–88%) and the latest generation ELISA (QuantiFERON-Gold in-tube, pooled 70%, range 64–93%).

**Clinical performance of IGRAs in immunocompromised individuals**

The strategy for diagnosis and treatment of LTBI is based on targeted tuberculin testing, which targets persons at highest risk of progression from LTBI to active tuberculosis. This group particularly includes HIV-positive individuals and people with immune-mediated inflammatory diseases (such as inflammatory bowel disease and inflammatory arthritides) who are iatrogenically immunosuppressed or receiving anti-TNF therapy.²⁵ In these populations with impaired cellular immunity, there is a need to assess the diagnostic performance of IGRAs as an alternative to the TST, which is well-recognized to have poor sensitivity.

**HIV-seropositive individuals**

Following the early reports on the diagnostic performance of IGRAs in HIV-positive individuals²⁶,²⁷ a number of studies have added to the evidence base to show that the ELISpot has a higher sensitivity than the TST.²⁶–³⁰ A recent German study of HIV-positive individuals found that the ELISpot was more sensitive than the TST and also correlated with previous active TB unlike the ELISA or TST.³⁰ Other studies from high-burden settings in Africa have also found that the ELISpot has a high sensitivity in both children and adults. Liebeschuetz *et al.*²⁷ conducted a prospective study in South African children with a high prevalence of HIV coinfection, which showed that the sensitivity...
of the ELISPOT was higher than that for the TST and unaffected by HIV infection, malnutrition and age under 3 years. Overall sensitivity of ELISPOT in children with culture confirmed, or highly probable, TB was 83%, rising to 91% when combined with the TST. Conversely, the TST alone had a sensitivity of only 36% in those with HIV infection. In a study looking at HIV-positive Zambian adults coinfected with sputum smear-positive TB, ELISPOT sensitivity was maintained at 92%. Subsequent studies with ELISPOT have shown that the results remain robust in HIV infection and independent of CD4 cell count. Independent work by Clark et al. and Dheda et al. has found that CD4 cell counts do not affect the ELISPOT performance in HIV-positive individuals—both in terms of positivity and the frequency of indeterminate results.

However, the experience gained from using the ELISA in HIV-positive individuals seems to be more inconsistent. Raby et al. recently evaluated the ELISA in a cross-sectional study of Zambian adults with smear-positive TB, and found that the sensitivity of the ELISA in HIV-positive individuals was 63%, which was significantly lower than the 84% sensitivity seen in HIV-negative individuals. In a South African study of HIV-positive individuals comparing the IGRAs and TST in the diagnosis of TB infection, the sensitivity of the ELISA (28%) was lower than that for the ELISPOT (61%) and the TST (41%). On the other hand, Balcells et al. found that in HIV-positive adults the ELISA had a higher positivity rate than the TST and correlated with TB exposure whilst the TST did not. In addition, CD4 cell counts did not have an adverse effect on ELISA results. However, other authors have found that in advanced HIV where there are low CD4 cell counts, the performance of the ELISA is compromised. Brock et al. conducted a large cross-sectional study of HIV-positive individuals in Denmark and found a significant association between low CD4 cell count and indeterminate ELISA results. Subsequent studies have also confirmed that with declining CD4 count, false negative and indeterminate results become increasingly common, which may affect the diagnostic utility of the ELISA in HIV-positive individuals.

**Individuals with immune mediated inflammatory diseases**

Published experience of the performance of the IGRAs in diagnosing LTBI in immune mediated inflammatory diseases (IMID) is still fairly limited and is mainly drawn from small-scale cross-sectional studies that have concentrated on evaluating the concordance between the TST and IGRAs rather than correlating IGRA results with risk factors for TB infection. In general, these studies have found that agreement between
the TST and IGRAs is, at best, fair in individuals with IMID and that discordant TST-positive, IGRA-negative results are associated with prior BCG vaccination.\textsuperscript{37–39} Conversely, recent work from Italy by Bartalesi et al.\textsuperscript{40} where individuals with IMID were screened for LTBI using the ELISA and TST found a relatively higher concordance ($\kappa = 0.55$) and less TST-positive, IGRA-negative discordancy, which possibly reflects the low proportion of BCG-vaccinated individuals in their population.

Fewer studies have correlated IGRA and TST results in individuals with IMID with risk factors for LTBI. In a study of 142 patients with IMID, the ELISA was significantly more closely associated with the presence of risk factors for LTBI than TST. In addition, a positive TST, but not IGRA, was significantly associated with previous BCG vaccination.\textsuperscript{37} Martin et al.\textsuperscript{41} evaluated both IGRAs in individuals with inflammatory arthritides and found that both the ELISpot and the ELISA correlated with risk factors for LTBI. Data from a large Italian study revealed that individuals who had been in close contact with smear-positive TB patients were significantly more likely to have a positive ELISA and TST result.\textsuperscript{40}

On the basis of the current evidence, one can conclude that although false-negative IGRA results may occur, the diagnostic sensitivity of IGRAs is more robustly maintained than that of the TST in individuals with IMID on immunosuppressive treatment.

**Specificity of IGRAs**

To estimate the diagnostic specificity quantitatively, BCG-vaccinated individuals at an ultra-low risk of LTBI due to the absence of epidemiologic risk factors for tuberculosis exposure have been studied. The ELISA has been assessed in larger numbers of individuals in such studies than the ELISpot. In a recent systematic review the specificity of the ELISA ranged from 89 to 100\% with a pooled specificity of 99\% for the second-generation ELISA and 96\% for the latest generation, in-tube ELISA.\textsuperscript{24} The pooled specificity of the ELISpot was also high: 93\% (range 85–100\%).\textsuperscript{24} On the whole, both IGRAs have consistently been shown to have a higher specificity than the TST particularly in BCG-vaccinated populations.

**Reliability of the IGRAs in routine clinical use: indeterminate results**

Over the last few years the IGRAs have increasingly been incorporated into routine clinical use, which makes it imperative to evaluate
their reliability. Indeterminate results occur for both IGRAs\(^2\) and can arise for many reasons but the most significant cause is a failed positive control that usually reflects underlying cellular immune suppression. Studies suggest that indeterminate results are relatively common with the ELISA occurring in 5–40\% of cases with the second-generation ELISA but less frequently with the newer in tube ELISA.\(^{42–44}\) Indeterminate ELISA results seem to be associated with extremes of age (under 5 and over 80) and immunosuppression, especially HIV infection.\(^35\) In contrast, indeterminate results are rarer with the ELISpot occurring in 0–5.4\% of tests undertaken.\(^35\)

**Longitudinal data quantifying the prognostic value of IGRAs for progression to active TB**

Clinical benefits from chemoprophylaxis for LTBI can only occur if IGRA-positive contacts are truly at increased risk of subsequently progressing to active TB compared with IGRA-negative contacts. Longitudinal data, which can answer this important question, have recently begun to appear from studies that aim to assess the predictive value of IGRAs (see Table 1).\(^{46–50}\) Aichelberg et al.\(^50\) explored the prognostic power of a positive ELISA result in TB uninfected HIV-positive individuals. Over a median follow-up period of 19 months, 3/37 individuals with a positive ELISA at baseline went on to develop active TB whereas 0/738 with a negative ELISA subsequently developed TB. A German study in 601 contacts found that a significantly higher proportion of untreated household contacts with a positive ELISA progressed to TB disease as compared with contacts with a 5 mm positive TST; all six incident cases were ELISA positive at recruitment.\(^46\)

Bakir et al.\(^47\) conducted a large study of 908 child contacts in Turkey. During the follow-up period of 1.3 years, 15 incident cases occurred and the investigators found that contacts with a positive ELISpot had a significantly increased risk of developing active TB as compared with those contacts with a negative ELISpot. In this study, TB incidence in the ELISpot positive contacts was similar to that in TST positive contacts though the ELISpot predicted these from fewer contacts tested.\(^47\) However, a high proportion of the children received chemoprophylaxis which is likely to have resulted in the incidence rate ratios being underestimated.

Hill et al.\(^48\) followed up 2348 household contacts in the Gambia for 2 years. 11/649 ELISpot-positive individuals developed active disease as compared with 14/843 TST-positive individuals; 10/1087 ELISpot
Table 1: Currently published studies that have evaluated the prognostic value of the IGRA.

<table>
<thead>
<tr>
<th>Study population</th>
<th>Country</th>
<th>Period of follow up (years)</th>
<th>IGRA used</th>
<th>IGRA positive TST (5 mm)</th>
<th>TST (10 mm)</th>
<th>Number of incident cases</th>
<th>Progression to ATB of IGRA positive contacts</th>
<th>Progression to ATB of TST (5 mm) contacts</th>
<th>Progression to ATB of TST (10 mm) contacts</th>
<th>IGRA prognostic accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aichelburg et al.</td>
<td>Austria</td>
<td>1.6</td>
<td>QFT-G in tube</td>
<td>44/783 (56)</td>
<td>10/500 (2)</td>
<td>6/44 (14)</td>
<td>6/783 (1.5)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Diel et al.</td>
<td>Germany</td>
<td>2</td>
<td>QFT-G in tube</td>
<td>68/301 (22)</td>
<td>5/601 (0.8)</td>
<td>3/68 (4.4)</td>
<td>6/301 (2)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bakir et al.</td>
<td>Turkey</td>
<td>1.3</td>
<td>ELISPOT</td>
<td>381/908 (42)</td>
<td>550/908 (61)</td>
<td>462/908 (51)</td>
<td>15/381 (3.9)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hill et al.</td>
<td>Gambia</td>
<td>2</td>
<td>ELISPOT</td>
<td>659/1736 (37)</td>
<td>11/843 (1.1)</td>
<td>11/659 (1.7)</td>
<td>26/659 (3.9)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Doherty et al.</td>
<td>Ethiopia</td>
<td>2</td>
<td>ELISA (ESAT6 only)</td>
<td>9/24 (36)</td>
<td>10/9 (11)</td>
<td>7/9 (77)</td>
<td>42/9 (46.7)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Values in parentheses represent percentage values.
negative and 11/1387 TST negative contacts developed TB. The investigators concluded that neither the TST nor the ELISpot was prognostic of subsequent progression to tuberculosis. The reason for the lack of prognostic power of both TST and ELISpot in the African study is unclear but may relate to the highly endemic setting, in which de novo community transmission outside the household may account for a significant proportion of cases of tuberculosis.

Longitudinal, predictive, data from these studies provide the initial evidence to support the use of IGRAs in targeting chemoprophylaxis for recent IGRA-positive contacts. This is promising as it may potentially prevent a similar number of cases as when the TST is used but requiring the treatment of fewer contacts.

**Summary of clinical data**

As the evidence base for the performance of IGRAs expands, one can conclude that both IGRAs are not confounded by BCG vaccination and are therefore more specific than the TST in the diagnosis of LTBI. In LTBI, both tests are more sensitive than the TST, with the ELISpot having a higher sensitivity than the ELISA. In children, the ELISpot seems to be superior to the TST whilst the sensitivity of the ELISA appears to be comparable to the TST although the data are inconsistent. Whilst both tests are relatively robust in HIV infection, the ELISpot seems to perform better than the ELISA with a higher sensitivity and a lower proportion of indeterminate results, particularly when CD4 counts are low. In individuals with IMID undergoing immunosuppressive therapy, the performance of the ELISpot and ELISA seem to be equivalent.

**Impact of IGRAs on public health policy**

As the experience with IGRAs has increased, they have become an integral part of national guidelines that recommend their use in the diagnosis of LTBI. European guidelines advise that the IGRA should be used in individuals with a positive TST to confirm the diagnosis of LTBI and as a direct replacement for the TST in persons in whom TST is unreliable, e.g. in those with suppressed cellular immunity (see Fig. 1). Conversely, in the US and Japan, it is recommended that the IGRAs should completely replace the TST as the standard investigation for LTBI in all individuals.

Economics have been an important determinant in the diverse final recommendations framed by different countries. Although the IGRAs
are more expensive than the TST, health economic analyses have found that they are cost-effective as they reduce the number of individuals needing unnecessary chemoprophylaxis and monitoring whilst on drug therapy. The United Kingdom National Institute of Health and Clinical Excellence (NICE) economic analysis concluded that the two-step TST and confirmatory IGRA approach would be the most cost-effective model and this was the basis of the recommendations made for the UK and most other European countries.

One consequence of the European/Canadian recommendations is that immunocompetent individuals who are TST negative but who may have been IGRA positive may not be identified as having LTBI and hence left untreated. In contrast, the US/Japanese guidelines may result in the identification of individuals who are actually infected as LTBI who may then be treated appropriately.

Fig. 1 Algorithm of all possible outcomes resulting from parallel IGRA and TST testing.
in overtreatment of individuals who are IGRA positive/TST negative as the risk of progressing to active TB in this group is not known. This highlights the importance of prospective data that will quantify the predictive value of a positive IGRA result and the prognosis of contacts where the IGRA and TST results are discordant.

**Future directions for T-cell based TB testing**

IGRAs have revolutionized the diagnosis of LTBI but they remain a dynamic work in progress with attendant advantages and limitations. As a diagnostic tool, IGRAs are unable to differentiate between active and latent TB. In addition, longitudinal studies during treatment of active and TB and LTBI have shown that serial IGRA testing cannot be used for treatment monitoring or as test of cure.\(^2\) However, simultaneous measurement of IL-2 and IFN-\(\gamma\) secretion by *M. tuberculosis* specific T-cells correlate with therapeutic response and may allow treatment monitoring and potentially test of cure.\(^5,6\)

Studies are also exploring whether measuring alternative, downstream chemokines secreted by IFN-\(\gamma\)-activated macrophages such as inducible protein 10 (IP-10), in combination with IFN-\(\gamma\), may serve as a more amplified readout than IFN-\(\gamma\) alone thereby resulting in higher sensitivity.\(^7\)

Although the current IGRAs have superior diagnostic sensitivity than the TST, research indicates that next-generation assays will have an even higher sensitivity without compromising specificity. This will be achieved by including additional, novel, antigens such as RV3879c (in ELISpot\(^{PLUS}\))\(^8\) alongside ESAT-6 and CFP-10.

**Conclusions**

IGRAs represent a new paradigm with the potential to supersede the century old TST and, in the process, revolutionize the diagnosis, and thereby targeted chemoprophylaxis, of LTBI. The evidence base supporting their use has expanded dramatically over the last few years which has resulted in them becoming an important diagnostic tool in low prevalence settings. However, guidelines vary between countries, which is likely to reflect some underlying uncertainty about the prognostic value of a positive IGRA result. As a consequence there is an urgent need for further large, longitudinal studies to explicitly define the prognostic value of positive IGRA results for the development of active TB disease, particularly in high-risk groups and subgroups with discordant IGRA and TST results. Data of this type would provide...
a clear mandate for basing treatment decisions for LTBI on IGRA results.

Conflict of interest: Professor Lalvani is inventor for several patents underpinning T-cell-based diagnosis. The Lalvani ELISpot was commercialized by an Oxford University spin-out company (T-SPOT.TB®, Oxford Immunotec Ltd, Abingdon, UK) in which Oxford University and Professor Lalvani have a minority share of equity.

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