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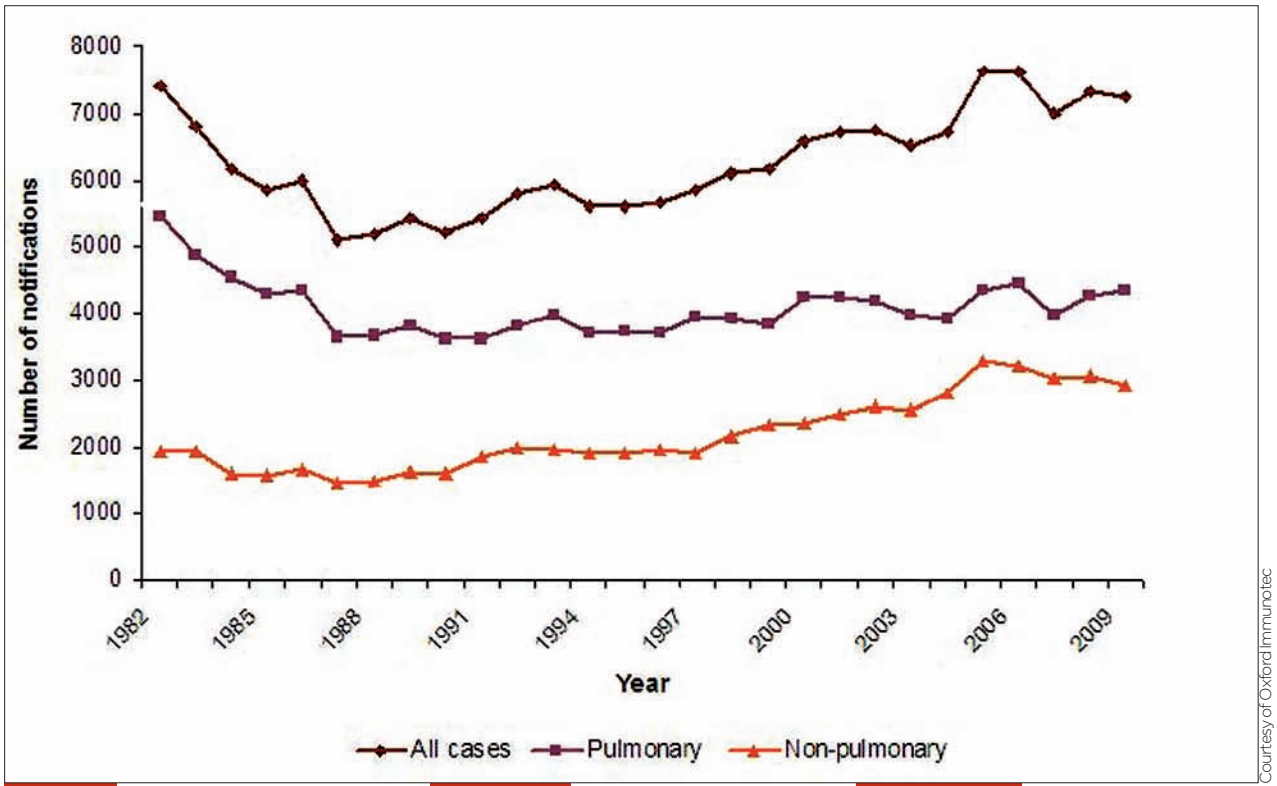

Courtesy of Oxford Immunotec

FIGURE 1
Tuberculosis notifications by site of disease (pulmonary/non-pulmonary), England and Wales, 1982-2009[2]

How should TB be diagnosed?

TUBERCULOSIS (TB) REMAINS ONE OF THE GREATEST CAUSES OF MORTALITY WORLDWIDE, with approximately 9 million new cases of active infection and 1.5 million deaths annually.[1]

In the UK, after a century of declining incidence, over the past 20 years numbers of cases of active TB have increased substantially. In 2009, there were 7,240 cases reported to the Health Protection Agency in England and Wales, compared with 5,086 in 1987,[2] see figure 1, above. This increase has occurred almost exclusively in individuals born outside the UK, who now constitute more than two-thirds of cases.

What new diagnostic tests are available?

ACTIVE VS LATENT INFECTION

TB is a remarkable infection in that, in a normal host, only roughly one in ten people who are infected will ever develop active disease.

The remaining 90% are presumed to have so-called latent TB infection (LTBI), where viable mycobacteria are thought to persist for decades, and may reactivate if the host's immune system is weakened, for example, by malignancy, chemotherapy, HIV infection, renal failure, diabetes or old age.

Recently, it has been recognised that a proportion of this 90% of infected individuals with LTBI may in fact have cleared their infection – however, we currently have no test that will distinguish between individuals in whom infection has been eradicated and those with true LTBI.[3]

In the UK, TB control hinges on the detection of both active and latent TB, as outlined in the Chief Medical Officer's TB Action Plan.[4] Although there has been recent interest in the development of novel diagnostic tests for active TB, for example, a recently developed polymerase chain reaction-based assay, the GeneXpert MTB/RIF test[5] or the use of immunological biomarkers,[6] these currently have limited clinical applications, or are still research tools, and the mainstay of diagnosis of active TB remains the isolation of the organism by culture of appropriate clinical specimens.

Around half of cases of active TB overall are pulmonary, and here the optimal method of diagnosis is through the microscopy and culture of three spontaneous sputum samples.[7] »

Which individuals should receive prophylaxis?

Table 1

Summary of NICE recommendations[16]

Group	Age	Recommendations
Household contacts of patient with active TB	<4 weeks (contact of sputum smear-positive TB)	● Start on isoniazid ● TST after 3 months ● If negative, repeat TST with IGRA ● If either positive, assess and treat ● If both negative, give BCG vaccine
	4 weeks - 2 years (contact of sputum smear-positive TB)	● Start on isoniazid if no prior BCG vaccination ● TST ● If negative, repeat TST with IGRA at 6 weeks ● If both negative, give BCG if not already vaccinated
	2-5 years	● TST ● If negative, but contact of patient with sputum smear-positive TB, repeat TST with IGRA at 6 weeks
	5-35 years	● TST ● If positive, confirm with IGRA or ● IGRA alone if TST likely to be less reliable, or if screening large groups
New entrants from high-incidence countries (incidence >40 per 100,000 per year)	<5 years	● TST
	5-35 years	● TST ● If positive, confirm with IGRA ● Consider IGRA alone if aged 16-35
Immunocompromised individuals:		
HIV infection		● CD4 <200 cells/mm^3 TST and concurrent IGRA ● CD4 200-500 cells/mm^3 TST and concurrent IGRA, or IGRA alone
Other immunocompromise		● TST and concurrent IGRA, or IGRA alone
Healthcare workers:		
No evidence of BCG, not new entrant		● TST ● If positive, confirm with IGRA ● If negative, consider BCG
New entrant or TB-exposed		● IGRA alone ● If negative, consider BCG if not already vaccinated

However, this relies on high levels of awareness and knowledge of TB among front-line medical practitioners:[8] this is difficult to achieve when a GP in a moderate- or low-incidence area in the UK may see less than one case of active TB per year.

It is important to consider the possibility of TB in the context of protracted cough, especially if productive, in association with fever, sweats and weight loss. Haemoptysis is a particularly important symptom, and should trigger a chest X-ray, sputum samples and referral to a TB specialist as appropriate. However, non-pulmonary TB may present with focal symptoms and little systemic upset, or may mimic other conditions, particularly malignancy, and this makes early diagnosis more challenging. Raising awareness of TB is an important issue highlighted in the TB Action Plan.[4]

In a country such as the UK with a low incidence of TB, a high proportion of cases result from reactivation of latent TB, rather than transmission by infectious cases. If individuals with LTBI can be identified and treated with antituberculous drugs to reduce their risk of developing active TB later in life, this would contribute significantly to national TB control.

DIAGNOSTIC TESTS

Until recently our only diagnostic test for LTBI was the tuberculin skin test (TST), in the form of the Heaf or Mantoux test. However, the TST has low sensitivity and specificity, the latter arising mainly because of cross-reactivity with prior BCG vaccination, and also operational difficulties in that it requires two visits, one to place the test and the second to read the result.

Interferon-gamma release assays

In the past ten years a novel type of diagnostic test for LTBI has been developed: the interferon-gamma release assays (IGRAs).[9,10] Like the TST, these detect the immune response to *Mycobacterium tuberculosis* antigens, rather than detecting TB directly. However, unlike the TST they are rapid overnight blood tests, and use carefully selected peptides from antigens highly specific to *M. tuberculosis* complex, rather than a broad mix of proteins shared by many mycobacterial species. Thus their major advantage over the TST is that they are not affected by prior BCG vaccination.

There are currently two available IGRAs. In the first, the T-Spot.TB (TS.TB), a blood sample is taken and transported to the laboratory where T cells are extracted and a defined number placed in wells with a range of TB antigens. Any T cells present within the sample that recognise TB antigens will become activated and release interferon-gamma, which is captured on the bottom of the well by a monoclonal antibody specific for interferon-gamma. The wells are then developed and the result is a dark spot at the site of each TB-specific T cell. These spots can be counted and the result expressed as a positive (i.e. indicative of infection with *M. tuberculosis*), negative or indeterminate result.

The other test, the Quantiferon-TB Gold In-Tube (QFT-GIT), is technically

key points

SELECTED BY

Dr Peter Saul
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In the UK over the past 20 years the numbers of cases of active TB have increased substantially. This increase has occurred almost exclusively in individuals born outside the UK, who now constitute more than two-thirds of cases. Only around one in ten people who are infected will ever develop active disease. The remaining 90% are presumed to have so-called latent TB infection (LTBI) where viable mycobacteria are thought to persist for decades, and may reactivate if the host's immune system is weakened. In a country such as the UK with a low incidence of TB, a high proportion of cases result from reactivation of latent TB, rather than transmission by infectious cases.

We currently have no test that will distinguish between individuals in whom infection has been eradicated and those with true LTBI. The mainstay of diagnosis of active TB remains the isolation of the organism by culture of appropriate clinical specimens. Until recently our only diagnostic test for LTBI was the tuberculin skin test (TST). In the past 10 years a novel type of diagnostic test for LTBI has been developed: the interferon-gamma release assays (IGRA). Their major advantage over the TST is that they are not affected by prior BCG vaccination and they have a specificity of well over 90%. One extremely important limitation of these tests is that they are unable to distinguish between active and latent TB infection: this distinction must be performed purely on clinical grounds. It is important that individuals with a positive test are assessed carefully by a clinician with expertise in managing TB to ensure that there is an appropriate management plan for each patient. The role of IGRAs in diagnosis of active TB is limited since in a patient with suspected active TB a positive result may indicate LTBI in combination with an alternative diagnosis.

At a population level screening and chemoprophylaxis does contribute usefully to TB control although only those with LTBI who are under the age of 35 should receive prophylaxis, since after this age the increasing risks of hepatotoxicity begin to outweigh the diminishing benefits of prophylaxis. The exceptions to this recommendation are healthcare workers, where the benefits are not just to the individual but also extend to their patients, and immunocompromised patients whose risk of reactivation is much higher. The recent NICE guidance focuses also on patients who are contacts of individuals with active TB and new entrants to the UK from countries with high TB incidence.

A major unanswered question remains the ability of the IGRAs to predict progression to active TB over many years of an individual's life although early data suggest that they may perform better in this than the TST.
The IGRAs represent a major development in the diagnosis of LTBI. While currently most of their use is through established TB screening services, it is likely in future that they will also be used routinely in general practice to screen individuals at high risk of having LTBI, for example, at registration with a new practice.

simpler in that the assay is performed directly on whole blood without the need for isolation of T cells: here a blood sample is taken directly into three tubes, containing TB antigens, positive and negative controls respectively. After overnight incubation, the amount of interferon-gamma released into the supernatant is quantified and again results are expressed as positive, negative or indeterminate.

Thus in both assays, only a single visit by the patient is required and results are available within 24 hours. Both have specificity of well over 90% and thus a positive result in either test is highly likely to indicate that the individual has been infected with *M. tuberculosis*.[11] Both have a sensitivity of between 80 and 90%: current evidence suggests that the sensitivity of the TS.TB may be higher than the QFT-GIT, particularly in immunosuppressed individuals,[12] since a defined number of T cells is used in the assay, and thus one can correct for lymphopenia in the patient's blood sample. However the QFT-GIT is cheaper and less technically demanding, and may be more appropriate for use in the developing world.[13]

'Only a single visit by the patient is required and results are available within 24 hours'

In the UK, cost considerations in particular may promote the use of QFT-GIT over TS.TB, especially where large numbers of tests are being carried out at a time: e.g. a large contact tracing exercise, for instance in a school outbreak, or screening a cohort of new entrants to the UK.[14] However, which test is used locally is likely to depend on availability, and the experience and preference of local TB specialists.[13,14]

One extremely important limitation of both tests is that they are unable to distinguish between active and latent TB infection: this distinction must be performed purely on clinical grounds. Thus it is important that individuals with a positive test are assessed carefully by a clinician with expertise in managing TB to ensure that there is an appropriate management plan for each patient. This would normally be a respiratory or infectious diseases physician based in secondary care.[15]

The development of the IGRAs has raised many questions about how they should be applied in clinical practice. Recently, NICE has produced updated guidance on TB which includes new recommendations on the use of IGRAs in the diagnosis of latent TB.[16] It was concluded that their role in diagnosis of active TB is limited: this is logical since in a patient with suspected active TB a positive result may indicate LTBI in combination with an alternative diagnosis, rather than active TB. It is always important to consider the significance of a positive or negative IGRA in an individual patient prior to requesting the assay – a positive or negative IGRA may provide circumstantial evidence for or against active TB, but should not be relied on as an absolute.

SCREENING

When considering LTBI, however, the situation is different, in that here we are mainly considering screening individuals to allow us to target antituberculous chemoprophylaxis. As with all screening strategies, there will be a degree of uncertainty, with false-positive and false-negative results. As antituberculous chemoprophylaxis reduces the risk of developing active TB over a lifetime by only around two thirds,[17] a degree of uncertainty is acceptable (and should be highlighted to the patient).

However, at a population level, screening and chemoprophylaxis does contribute usefully to TB control, although it is important to note the recommendation that only those with LTBI who are under the age of 35 receive prophylaxis, since after this age the increasing risks of hepatotoxicity begin to outweigh the diminishing benefits of prophylaxis.

The exceptions to this recommendation are healthcare workers, where the benefits are not just to the individual but also extend to their patients, and patients with immunocompromise whose risk of reactivation is much higher. The recent NICE guidance focuses in detail on these two groups, and also on patients who are epidemiologically at higher risk of developing active TB. Thus the four groups comprise:

- Contacts of individuals with active TB, particularly those with sputum-positive (highly infectious) TB
- New entrants to the UK from countries with high TB incidence
- NHS staff with direct patient contact
- Immunocompromised individuals »

The NICE guidance considered only published literature on the IGRAs, and in many areas this was limited. In many situations the IGRA is recommended as a confirmatory test following a TST, to improve the specificity of the screening process, particularly in BCG-vaccinated individuals. However, for the first time, an approach using IGRA alone was recommended for screening large numbers of contacts, and for new entrants and healthcare workers.

In other areas, the evidence for the recommendations was much less clear-cut, for example, in the assessment of very young children for recent infection with *M. tuberculosis*, where the recommended strategy optimises sensitivity through a combination of TST and IGRA. Furthermore, the optimal strategy for screening patients with immunocompromise remains uncertain, and either an IGRA alone, or a combination of IGRA and TST was suggested (see table 1, p24). It is likely that the national guidelines will be modified as further evidence emerges.

'The IGRAs represent a major development in the diagnosis of latent TB'

The guidelines did not consider the relative benefits of the two types of IGRAs, and this will be the subject of future debate. In addition, there are ongoing studies using modified forms of the two tests to improve their sensitivity in different groups. A major unanswered question remains the ability of the IGRAs to predict progression to active TB over many years of an individual's life: although early data suggest that they may perform better in this than the TST, larger longitudinal studies with prolonged follow-up are needed to answer this question.[18]

CONCLUSION

TB remains a considerable problem in many parts of the UK, as well as globally, and diagnosis can be challenging. GPs represent the first point of contact with health services for most patients, and it is crucial that GPs are aware of the clinical features of active TB, and that diagnosis can frequently be made using simple and inexpensive tests such as chest X-rays and sputum samples.

There is a major focus on raising awareness of TB in frontline medical staff, through the activities of bodies such as the charity TB Alert, and the Department of Health's National Knowledge Service TB Project (see useful information box, below). At a local level, information and advice can readily be obtained through the local TB nursing service.

The IGRAs represent a major development in the diagnosis of LTBI. While currently most of their use is through established TB screening services, it is likely in future that they will also be used routinely in general practice to screen individuals at high risk of having LTBI, for example, at registration with a new practice.

However, their use is subject to significant limitations that need to be considered in putting them into clinical practice.

In the context of active TB, their use is very limited, and only likely to provide weight (or not) to a diagnosis of active TB that has already been made on clinical grounds.

In the context of LTBI, their high specificity has the potential to contribute significantly to national TB control, and the recent NICE guidelines have taken us forward in determining how they should be used in clinical practice.

However, there are still many unanswered questions, and further studies are needed in a range of areas to allow us to maximise their contribution to national and international TB control in the long term.

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Useful information

NICE CG117. Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control.
www.nice.org.uk

TB Alert
www.tbalert.org

The British Thoracic Society
www.brit-thoracic.org.uk

The National Knowledge Service TB Project
www.hpa.org.uk/ProductsServices/InfectiousDiseases/ServicesActivities/NationalKnowledgeServiceTB/

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