Rethinking TB screening: politics, practicalities and the press

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INTRODUCTION

Worldwide, tuberculosis (TB) causes 1.3 million deaths each year, and there are at least 9.27 million new cases annually.[1] Global population mobility on a scale never seen before means that the UK, along with many other countries with a previously low incidence of the disease, has over the last two decades seen a sharp rise in TB. Indeed most doctors are probably more likely to see a case of TB in the next year than at any other time in their professional lives. In the UK, there are now in excess of 8400 new cases per annum, >70% of them occurring in individuals born outside the country,[2] and the picture is similar in the USA, where over half of all cases occur in those born abroad.[3] The annual UK rate of TB for those born abroad (87/100 000) is >20 times higher than that for the UK-born population (including UK-born members of ethnic minority groups). For the Black African population in the UK who were born outside this country the rate (at 309/100 000) is 75 times higher than in the UK-born population generally, reflecting the very high TB rates associated with HIV co-infection in sub-Saharan Africa.[2]

Clearly, current methods of TB screening for new entrants, largely for active TB only, are not working, and debate about how they might be improved has spread beyond health professionals to become the focus of media comment, often hostile, and the subject of political attention and debate.[4] We discuss the limitations of current UK screening methods, suggest that the natural history of infection with the TB bacterium means that they cannot succeed and consider alternative approaches.

THE PRESENT SITUATION

Since 1971 the UK has had a mechanism (the Port of Arrival Scheme) aimed at screening immigrants from countries with an annual TB incidence >40/100 000 and who plan to stay for ≥6 months. Some individuals are offered a chest x-ray at the airport, but the criteria by which these are selected are not clearly defined, most x-rays being carried out on asymptomatic individuals. All others should be referred onto a local chest clinic for assessment, but there is often either no local system to capture them or if they do not go to their declared 'intended district of residence' they are lost to potential TB screening. Other countries—for instance Norway and The Netherlands—have a stricter (just 3 months) residency criterion for screening, and appear much more successful in encouraging attendance—in the case of The Netherlands perhaps because a residency permit is only issued after screening has occurred.[5] In the UK, another problem is that the system is triggered by migration status and not just by TB risk: a long-standing resident in a very high incidence country may have a high TB risk, but if not subject to immigration controls (perhaps as a British passport holder) then the Port of Arrival system is not implemented. Additionally, those seeking asylum are subject to screening under a different system: if asylum is claimed after arrival, and TB screening has not yet taken place, they may not be caught in the net at all. Neither, self-evidently, will be illegal immigrants.

THE LIMITATIONS OF SCREENING

Crucial to an understanding of what screening can, and cannot, achieve is an awareness of the distinction between the state of being ill with active TB disease, and that of asymptomatic latent TB infection. Those 8400+ reported annual UK cases were of active disease, but it is estimated that one-third of the earth's population—about 2 billion people—have latent TB infection.[1] This third would include a high proportion of the over 65s born in the UK (and probably many healthcare workers). Identification of the infected state may be important, because roughly 1 in 10 of these currently healthy but infected individuals will progress to active TB disease in their lifetime, with the greatest risk in the first 5 years after initial TB infection,[6] but active TB can develop years and even decades after. They therefore are a risk to themselves and potentially to others in their lifetime Chest x-rays on arrival for migrants only detect active respiratory TB, and will miss non-respiratory TB (the sites of disease in 44% of new arrivals[2]). Chest x-rays also do not detect latent infection, the source of most cases of TB in recent migrants.

We fear this misconception about the effectiveness of chest x-rays, often expressed in the press, may be shared by some senior politicians. In fact, in 2007, ~80% of the 5300 or so cases of active TB occurring in those born outside the UK developed *2* years or more after their first arrival.[2] In the USA, half of those cases occurring in the foreign-born were detected ≥5 years after their arrival.[3] The proportion of individuals who will actually have active pulmonary disease, detectable on chest x-ray, coincident with their time of arrival in their destination country is very small indeed.[7 8] This is reflected in the extremely low pick-up of active TB by x-ray screening at UK airports, and the practical difficulties of performing x-rays on large numbers in a very short time are great. In 2004, ~280 000 individuals subject to immigration control and planning to stay >6 months arrived in the UK from high TB incidence countries. Only a quarter (70 000) had chest x-rays, and only ~100 cases of pulmonary TB were found. In contrast, probably 100 000 of those arrivals had latent TB infection, with the likelihood that at least 10 000 of them will develop active TB at some future date. The conclusion of the Health Protection Agency, which reviewed these findings and the earlier literature, was that 'There is little if any evidence to support the continuation of chest x-rays at the Port of Entry as a screening method.'[9]

Does moving the place of the chest x-ray to the country of origin have anything to offer? Australia, Canada and the USA have such policies for those planning a stay of >6 months, but Canada is selective about the countries of origin upon which it imposes that policy. Australia may ask for a chest x-ray for those planning stays <6 months if the

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visitor is from a particularly high incidence country. The Home Office, responsible for immigration policies in the UK, has run a trial of x-ray screening in four countries: Tanzania, Sudan, Thailand and Bangladesh. Under this scheme aspirant migrants to the UK underwent chest x-ray, followed by sputum testing if abnormal. Those with sputum smear-positive (and therefore potentially infectious) TB had to be treated for TB, for a period of 6 months, before reapplying. An initial evaluation of the system[10] suggested that such individuals comprised well under 0.1% of those undergoing x-ray, consistent with the yield of chest x-ray screening elsewhere.[7 8] The effectiveness (and cost-effectiveness) of such screening must be questioned, particularly in the light of the discussions set out above. Further, the oft-cited argument that it is infectious pulmonary TB which is of paramount importance might be strictly correct from the public health perspective, but is of little comfort to the large number of patients who later develop spinal, gut, renal or cerebral TB. From the health economic point of view in the destination country it is a weaker argument still: it is the latter cases, not pulmonary disease, which are more difficult to diagnose and more expensive to manage.

In summary, the very great majority of TB cases which occur amongst migrants from abroad will not be detected by chest x-ray immediately prior to, or at the time of, arrival. Although it is impossible to determine precise proportions, it is almost certain that most cases of TB in immigrants represent reactivation of latent TB infection acquired abroad, with some contribution from spread of active disease between members of immigrant groups after arrival in their destination country. There is also evidence that revisits to the country of origin may be a source of infection leading to disease.[11 12]

IS THERE A BETTER WAY?

The ideal screening process would achieve three aims. First, it would identify the small number with active TB disease; they are in need of treatment both for their own benefit and because some may be infectious to others. Secondly, it would identify those with latent TB infection. In these, intervention with drug treatment would substantially reduce, but not remove completely, the risk of later progression to active TB disease.[13]

Unfortunately, identification of latent infection is not straightforward; impaired immunity may lead to false-negative tuberculin skin tests (such as the Mantoux test), and prior BCG vaccination and exposure to environmental mycobacteria to false-positive results. New blood tests—interferon γ release assays (IGRA)—may have significant advantages, detecting the release of interferon γ from lymphocytes when exposed to antigen.[14] The antigens used are specific to TB and (unlike skin tests) not present in BCG or most environmental mycobacteria. They thus appear more specific than skin testing. HIV co-infection, however, can also reduce the utility of both Mantoux and IGRA tests. Individuals with suspected or proven TB, from a risk group with a high HIV prevalence, should be offered HIV testing.[15] The third attribute of an effective screening programme for TB is that it should identify those with neither evidence of disease nor infection. Some of these may benefit from BCG vaccination against acquiring TB.[16]

With an understanding of the distinction between TB infection and active TB disease, and with the threefold benefits of an ideal screening programme in mind, it is possible to see what different approaches might be capable of achieving. Clearly, x-ray screening simply prior to, or at the time of arrival is not enough. Although the 2006 Guidelines from the National Institute for Health and Clinical Excellence (NICE)[13] do recommend screening after arrival it does seem in practice this is still envisaged as a one-off 'snapshot' assessment. In any case it is still going to miss many of those with latent infection, because skin testing is now limited to all those aged 0–15, and those aged 16–34 from sub-Saharan Africa,[13] and at least 10% of untreated latently infected young adults from South Asia develop clinical TB within 10 years.[17] Compared with the 'before' or 'at' arrival options, screening in the community after entry offers the opportunity for all the above interventions. Unfortunately, this 'after' entry process is provided by local TB services already stretched by increasing numbers of active TB cases, and even when numbers were lower the system had failings.[18] It has been shown that when active intervention to improve screening of new arrivals is undertaken, the outcomes, in terms of people screened and where appropriate, vaccinated, were greatly improved when carried out in primary care.[19]

Looking to the future, country of origin x-rays are very unlikely indeed to make an impact on the numbers of subsequent UK cases of TB in those born abroad, whatever the press might say or politicians might think. Screening by chest x-ray to detect active TB, and also by skin testing and more recently IGRA testing to detect and then treat latent TB, is the USA dual strategy, with a particularly high yield for new entrants from South Asia and sub-Saharan Africa.[20] This policy may have contributed to stabilisation of the numbers of foreign-born cases, compared with an increase in England and Wales. In the USA, foreign-born cases have gone from 7403/24 825 (30%) in 1993, to 7750/13 243 (58%) in 2007,[20] an increase in proportion but little in absolute number (5%). In England and Wales foreign-born cases have gone from 1204/2458 (49%) (6 month data) in 1993[21] to 6060/8417 (72%), so over the same time period in England and Wales there has been an increase in both the proportion and, significantly, the absolute numbers of (1204 to 3030 per 6 months: 252%). Whilst both countries have been fairly successful in reducing TB in native-born persons by good local TB control and treatment, the USA has had little increase in absolute numbers of foreign-born TB, perhaps due to their more aggressive detection and treatment of latent TB infection.

The most effective screening programme for new entrants will be targeted at high risk groups by interventions in the community, ideally in GP surgeries and indeed the home, where latent TB infection can be diagnosed. People can then be vaccinated if testing suggests no evidence of latent TB infection, or referred to the local TB service (usually the Chest Service) for further assessment if testing is positive. If evidence is needed as to how many people with latent TB infection are being missed with the current policy, then this could soon be achieved by funding short studies in high TB prevalence areas: either to tuberculin skin test all new entrants up to age 35 and IGRA blood test those positive, and/or obtain data on yield from those districts who still test such individuals as per the previous British Thoracic Society guidance.[22] These could be focused on the new entrant groups with the highest TB rates (Black African 309/100 000) and South Asian (209/100 000), and in those aged under 35 years, who are more likely to benefit from the treatment of latent TB infection,[6] and also confirming their completion rates for such preventive treatment.

However comprehensive we make the approach to identification of those who should be screened, there will be individuals who may be missed. The problem of

those unregistered with GPs and those in anomalous positions—such as asylum seekers—will remain and will require alternative initiatives. Are sticks necessary as well as carrots—as in The Netherlands which links residency permits with TB screening? The autonomy of the individual in decisions about their own healthcare is fundamental in the UK and many other countries. The rights of those who actually have infectious TB which is a risk to others are, though, already constrained in the UK both by Act of Parliament (Public Health Act 1984) and potentially by decisions of the Courts. An extension of these limitations to those who merely might have active TB or who might get it in future would be a very hot political issue. TB, though, is already a hot political issue,[4] and a rational, informed and wide-ranging debate is overdue. The present system is not adequate, and the 'status quo' is no longer a sensible or scientific position, but merely x-raying all potential immigrants would be worse. Answers as to the utility, yield and cost of various screening strategies should be readily obtainable at little additional cost because of the heterogeneity of what actually is being done across England and Wales, in both primary and secondary care, and sometimes across the interface between the two.

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Live and let die: is neutrophil apoptosis defective in severe asthma?

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Patients with severe asthma make up a relatively small proportion of the total population of patients with asthma yet account for a disproportional amount of asthma-related morbidity and healthcare utilisation.[1 2] These patients are usually highly symptomatic, difficult to treat and can be extremely refractory to current treatments. As a consequence, understanding the mechanisms underlying this particular form of asthma is of paramount importance.

Morphological examination of the asthmatic airway reveals epithelial desquamation, thickening of the reticular basement membrane, mucus gland hyperplasia, goblet cell differentiation, angiogenesis and smooth muscle hypertrophy.[3] In addition to these structural changes, an inflammatory cell infiltrate is evident within the airways comprising eosinophils, mast cells, lymphocytes and neutrophils. While eosinophils are the most characteristic inflammatory cell type present in mild to moderate asthma, the neutrophil seems to take centre stage more often in patients with severe disease. In fact, the neutrophil is one of the earliest inflammatory cells recruited to the airways following allergen exposure and is particularly evident in bronchoalveolar lavage samples and bronchial and transbronchial biopsies from patients with