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ABSTRACT

Setting Blackburn, Hyndburn and Ribble Valley Local Government areas of England and Wales, the former a high tuberculosis (TB) prevalence district.

Background The incidence of tuberculosis in new entrants aged 16–34 with positive tuberculin skin tests but normal chest X-rays after initial entry is not definitely known, and was previously estimated from cross-sectional national surveys and derived data for the 2006 and 2011 NICE economic appraisals of new entrant TB screening.

Methods New entrants aged 16–34 years predominantly from South Asia (India, Pakistan and Bangladesh), with tuberculin tests inappropriately positive for their BCG history were identified for the years 1989–2001 inclusive from a new entrant database. These entrants were compared with the current GP registration database to see if local residence could be confirmed and the local TB notification database to October 2008. Survival analysis was carried out using Kaplan–Meier survival curves and a Cox Regression model.

Results Four hundred and seventy-nine such new entrants with normal initial chest X-rays were identified. Of these 402 (84%) registered with a General Practitioner in East Lancashire for a period of time and could be followed up by this study. The crude incidence density of active TB amongst these individuals with latent disease was 1297 per 100 000 person-years (95% CI; 991–1698 per 100 000 person-years). After 10 and 15 years of follow-up 13.5 and 16.3% of individuals, respectively, had progressed on to active disease.

Conclusion This patient-derived, rather than estimated, data shows a minimum risk of TB disease of 16.3% at 15 years. The 2006 NICE economic appraisal, suggested that treatment for latent TB infection (LTBI) was cost-effective when the incidence of clinical TB over 15 years surpassed 18% in these populations. The 2011 NICE economic appraisal reduced this to 12% active TB over 15 years, and showed that at 16% active TB over 15 years a single interferon gamma release assay was the most cost-effective strategy. Further cohort studies are urgently needed to confirm or revise the assumptions behind the 2011 NICE economic appraisal.

Keywords chemoprophylaxis, cohort study, immigrant, latent TB, tuberculin positive

Introduction

New entrant screening for tuberculosis was recommended by the Joint Tuberculosis Committee of the British Thoracic Society from 1983.1 Subsequent advice in 1990,2 1994,3 and 20004 also recommended this. For those individuals found to be inappropriately tuberculin positive for their BCG history, the recommendations varied with age. For those aged 0–15, with normal chest X-rays, chemoprophylaxis was recommended.1–4 For those aged 16–34 the recommendations

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allowed either chemoprophylaxis,1,2 or ‘advise and inform’ management if chemoprophylaxis was not given.3,4 The yield of new entrant screening for active disease at first entry is relatively low, but has been found to be 1/200 (500/100 000 pa) from South Asia,5,6 and up to 1/100 (1000/100 000 pa) with asylum seekers/refugees from Somalia.7 The utility of new entrant screening for TB has recently been examined in the NICE guidelines in both 20068 and 2011.9 These economic appraisals of the efficacy of new entrant screening required a number of estimates to be made in terms of yield and incidence of subsequent active TB.8,9 New entrants can be found through notifications from the Port of Arrival system, GP new registrations or through other channels,8,9 with screening through notifications from the Port of Arrival system, GP a chest physician (LPO).

In the Blackburn, Hyndburn and Ribble Valley districts of East Lancashire comprehensive new entrant screening has been carried out since 1981, and its yield of active disease on first entry is published.5,6 Whilst chemoprophylaxis was given to all under the age of 16 years, those individuals aged 16–34 with inappropriately positive tuberculin skin tests (Heaf 2–4 with no BCG history; Heaf 3–4 with prior BCG) and normal chest X-rays were not given chemoprophylaxis because of the numbers involved, but ‘advise and inform’ management to themselves and their GP’s. Details of such individuals not treated by chemoprophylaxis were recorded on the TB system’s database and allow the calculation of their age at screening. For those few knowing their year, but not exact date of birth, these were assumed to be on the first of July to allow the calculation of their age at screening.

The following criteria had to be met for inclusion as a case of LTBI:

(i) Documented evidence of recent immigration into the UK. Screenings of individuals returning from trips abroad were excluded.
(ii) New immigrants were included in the study if aged between 16 and 34 years at the date of their first screening. For those few knowing their year, but not exact date of birth, these were assumed to be on the first of July to allow the calculation of their age at screening.
(iii) Tuberculin skin test was positive Heaf grade 2–4 in those without prior BCG (Mantoux equivalent 6 mm or greater), or Heaf grade 3–4 with prior BCG history (Mantoux equivalent 15 mm or greater), and having no clinical or chest X-ray evidence of disease confirmed by a chest physician (LPO).

Any person with a history of previous active TB disease was excluded, as was any person who received treatment of LTBI for other reasons such as close contact with an infectious case. Any person without a clear yes or no to prior BCG vaccination, or with an equivocal tuberculin test result, e.g. grade 1/2 or 2/3, was also excluded. All screening records were manually reviewed twice by IWC to reduce errors and confirm entry criteria were met. Screened immigrants satisfying the inclusion criteria had name, date of birth, sex, address, date of initial skin test, family history of TB, Heaf result, initial chest X-ray and any chest clinic follow-up recorded on an Excel spreadsheet.

This closed cohort was followed up retrospectively to one of the following defined endpoints:

(i) Diagnosed and notified as having active tuberculosis disease.
(ii) Deceased from some other cause.
(iii) Emigrated out of the East Lancashire area.
(iv) Remaining in East Lancashire and free of active TB disease at the end of follow-up (1 October 2008).

Methods

From 1983 onwards, new immigrants to the East Lancashire area were invited to a community clinic to be screened for tuberculosis. Immigrants were either referred after registering with a local GP (primary care physician) or identified from the Port of Arrival data sent by immigration officials. The clinic located in Blackburn holds index card records for all such immigrants who attended screening. For the purpose of this study, these records were manually searched to identify new entrants, aged 16–34, who had been screened between 1989 and 2001 and subsequently found to have LTBI on entry into the UK.

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Retrospective follow-up of this cohort was carried by cross referencing the original demographic data from the screening records against GP registration details. Records were traced using the NHS Strategic Tracing System (NSTS) and the GP registration databases of Blackburn and Darwen Primary Care Trust, East Lancashire Primary Care Trust and the Lancashire and South Cumbria Agency (LaSCA). A positive trace would confirm that an individual was still alive and residing in the locality. Tracing also identified individuals who had been residing in the East Lancashire area but had subsequently moved out of the area and registered with a GP outside of the locality. If an immigrant had transferred his primary medical care to a GP outside of East Lancashire then the date of transfer of care was used as the date of emigration out of the locality. Tracing also identified individuals who had been residing in the East Lancashire area but had subsequently moved out of the area and registered with a GP outside of the locality. If an immigrant had transferred his primary medical care to a GP outside of East Lancashire then the date of transfer of care was used as the date of emigration out of the locality.
East Lancashire and exits from the cohort. GP registration records also identified the small number of individuals who died before the 1 October 2008, the end of follow-up.

To determine the disease status of these individuals, demographic details of the cohort were cross referenced against TB notification lists held in the Chest Clinic of the Royal Blackburn Hospital and also at the local Cumbria and Lancashire Health Protection Unit in Chorley. If patients had moved outside of the locality any diagnosis and subsequent notification of TB would have occurred at chest clinics of other hospitals. This is why patient migration out of the East Lancashire catchment area was considered as exiting the cohort.

A number of individuals had been screened on entry into the country but had no subsequent record of ever registering with a local GP or of ever being notified with active TB in the East Lancashire area. It was assumed that these individuals had not been resident in East Lancashire having moved to another location in the country soon after entry. Such individuals were excluded from the analysis.

After cleaning, the data were anonymized and analysed using SPSS v17. A survival analysis was conducted using Kaplan–Meier survival curves and also a Cox regression model. The following variables were included in the proportional hazards regression: sex, age at screening, year of screening, history of TB in the family, definite evidence of BCG scar and Heaf grade.

Results

Four hundred and seventy-nine new entrants were identified as meeting the criteria for LTBI. Of these, 402 (84%) were followed up to one of study endpoints; notification of active TB disease, death from another cause, migration out of the East Lancashire area or free of TB disease and still residing in East Lancashire at the end of follow-up. Seventy-six individuals (from the original 479) had no NHS records of ever having registered with a GP in the East Lancashire area and were excluded from this study. One further individual was excluded due to insufficient information on the date of their initial screening. The 402 individuals were followed up for an average of 121.9 months with the total follow-up time being 4086.75 years.

Table 1 displays the basic demographic and screening data for the study population. The majority of the cohort (59%) was male and the mean age at initial screening was 24.2 years. Historically, most immigrants to East Lancashire herald from South Asia, India and Pakistan in particular. In this cohort ethnicity was only recorded for 52% of individuals but of these 52% and 34% were from Pakistan and India, respectively. Nineteen per cent of individuals had a definitive BCG scar and 81% of these had a normal chest X-ray at screening. Seven per cent of individuals had a minor CXR abnormality not thought to represent TB.

During follow-up, 69 (17.1%) individuals emigrated out of the locality, 2 died from causes unrelated to TB and 53 individuals (13.2%) developed active TB. A total of 278 individuals remained disease free within the locality at the end of the study.

Amongst clinical cases a slight majority (29/53) were female and the mean age for cases was 22.7 years. The majority (58%) of cases was non-respiratory with over half of these (17/31) having peripheral lymphadenopathy. Seven patients had disease at >1 site. Fourteen patients (26%) had pulmonary disease, seven (14%) had intra-thoracic lymphadenopathy and four (8%) had disease involving the pleura. The mean time from initial screening to notification of active disease for cases was 55.2 months (range 1–174 months, median 49 months). Two cases detected 1 month and 4 months after screening are included, but could be failures of detection of active disease (Fig. 1).

In this sample it took 82.5 months before three-quarters of notifications were detected and no notifications were detected after 174 months of follow-up.

The incidence density of active TB amongst these individuals with latent disease was 1297 per 100 000 person years
As expected, the crude risk of progression to active disease is not constant but rather decreases with time from 9% in the first 5 years after entry to 5% between 10 and 15 years after entry.

Using the Kaplan–Meier survival analysis, the actual 10-year and 15-year survival was estimated to be 0.865 and 0.837, respectively (Fig. 2). In other words, the risk of progression to active disease was 13.5 and 16.3%, respectively.

When hazard plots were compared for women and men (Fig. 3), females had a significantly higher risk of progression to active disease when compared with men (log rank test $P = 0.046$).

When hazard function was plotted by categorical age groups (Fig. 4), the youngest age group (16–19 years) had the highest hazard for progression to active disease. This was significant when compared with 25–29 year olds ($P < 0.001$) but not significant when compared with 30–34 year olds ($P = 0.087$).

Table 2 displays the variables included in a Cox proportional hazards model. Overall, the model was significant (Omnibus test of model coefficients, $P = 0.024$). In the multivariate Cox proportional hazards model only age at screening remained significant for survival. For each additional year of age, the subject had an $\approx 8\%$ reduction in their risk of progression to active disease. An interaction term was also added to test for an interaction between sex and gender but this was non-significant.

### Discussion

#### Main findings of this study

This retrospective cohort study of immigrants with presumed LTBI aged 16–34 has shown a cumulative incidence rate for progression to active clinical TB of 13.5% after 10 years of observation without preventive therapy. The 15-year cumulative incidence rate for the cohort was 16.3%. The median interval after the finding of presumptive LTBI and
The development of active disease was 49 months, with an upper quartile of 82.5 months, but no further cases after 174 months’ observation. The robustness of this estimate is enhanced by the fact that 84% of the cohort was followed up to a defined end-point in this study. Treatment of LTBI has the potential to reduce the progression to active disease by about two-thirds if chemoprophylaxis is given with either isoniazid for 6 months,10,11 or rifampicin and isoniazid for 3 months.10,12

What is already known on this topic
Five-yearly national TB surveys in the 1990s showed high rates of TB disease in the first 5 years after initial entry, gradually falling over the subsequent 10 years.13,14 We are not aware of estimates of the rate of progression from LTBI to TB disease in the UK.

What this study adds
To the best of our knowledge, this is the only study to have produced an estimate of the risk of progression to active TB for immigrants with LTBI entering the UK. Information is needed urgently to either confirm or amend the assumptions on which the 2011 NICE economic appraisal was based,19 in view of the continuing rise in numbers of active TB cases, of whom over 73% are non-UK born, many from South Asia.15

This is because the Guideline Development Group stated (page 194) that ‘the parameter with biggest impact on the cost-effectiveness of prophylaxis was the future risk of TB in people with latent tuberculosis at screening’. This had to rise to 12% over a 15-year time horizon of the model before prophylaxis appeared to be cost-effective.

Limitations of this study
Sixteen per cent of these immigrants did not register with a local GP after their initial entry screening. This could simply be because soon after arrival they relocated to another area of the UK. It is perhaps less likely that some individuals remain in the locality even after a minimum of 9 years and still not have registered with a GP. However, if they had developed signs and symptoms of TB and were subsequently notified in East Lancashire they would have been detected by our cross referencing of local notification records. The Enhanced TB Surveillance system would not help in detecting notified TB before 2000.

In terms of generalizability, it should be noted that this cohort comprised mainly of immigrants of South Asian heritage, which is still the case in East Lancashire. And thus the findings may not be applicable to all immigrant populations in the UK, particularly those of African heritage. Secondly, this cohort comprises individuals who attended for screening as the programme was not compulsory. Thirdly, this cohort shows increased rates in females in contrast to national data.13–15 However, in the Cox model only age was a significant predictor of risk. This cohort with LTBI may therefore not be fully representative of those persons in the UK developing active TB. The effects of subsequent return visits to South Asia were discounted because of separate local research.16

Whilst active disease developed at ~1% per annum for up to 15 years in those with presumed LTBI, the patients in this study are derived from a larger cohort, the exact size of which is not exactly known. The size of the overall numbers screened to derive the LTBI study population will clearly be crucial to any cost–benefit analysis. However, a later local new entrant cohort17 showed nearly 31% IGRA positivity, supported by similar data from Leeds.18
Even more recent data combining data from Blackburn, with Leeds and London, also showed near 30% IGRA positivity in South-Asian new entrants.19

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References