Tuberculosis

Increase in extrapulmonary tuberculosis in England and Wales 1999–2006

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Abstract

Background: Extrapulmonary tuberculosis appears to be increasing in England and Wales. The trends in extrapulmonary tuberculosis and factors associated with these trends were examined.

Methods: National tuberculosis surveillance data from 1999–2006 for England and Wales were used, including demographic, clinical and laboratory information. Trends in the proportion of tuberculosis cases with extrapulmonary disease were investigated using the χ² trend test and associated factors using logistic regression.

Results: Among all the cases of tuberculosis, the proportion with extrapulmonary disease increased from 48% in 1999 (2717 cases) to 53% in 2006 (4205 cases, p<0.001). Regression analysis showed that the rise in extrapulmonary disease was associated with an increase in the proportion of non-UK born cases (odds ratio 2.7, 95% CI 2.6 to 2.8). A more than threefold increase was observed in the proportion of all tuberculosis cases with miliary tuberculosis from 0.7% of all cases (38 cases) to 2.2% (180 cases, p<0.001). This rise was not associated with changes in place of birth or in any of the other risk factors identified.

Conclusions: The proportion of cases with extrapulmonary disease has increased over the study period. To a large extent this is due to an increasing proportion of non-UK born cases. Reasons for the rise in miliary tuberculosis require further investigation. Clinicians should have a higher index of clinical suspicion of extrapulmonary tuberculosis in non-UK born cases.

Tuberculosis remains a major global public health issue.1 The most common form of the disease is tuberculosis of the lungs, but it can affect almost any part of the body including lymph nodes, gastrointestinal tract, bones and joints, genitourinary tract and central nervous system, and it may affect multiple organs.2 Miliary disease and meningitis are associated with particularly poor outcomes.3

The diagnosis and management of extrapulmonary tuberculosis poses particular challenges. The diagnosis is often difficult owing to the wide spectrum of clinical presentations, the limited specificity of the manifestations and difficulties in obtaining specimens for culture.4 It is frequently made using histological or radiological evidence in combination with signs or symptoms, but can only be confirmed by microbiological culture.4

Managing cases with extrapulmonary tuberculosis is complicated owing to the sometimes longer course of treatment5 and difficulties in monitoring progress in the absence of follow-up samples.

Many industrialised nations have noted an increase in the proportion of cases presenting with extrapulmonary tuberculosis.5-7 In the USA the proportion increased from 16% in 1993 to 21% in 2006.8 Recent reports from the Netherlands and Canada suggest that it now affects nearly 40% of tuberculosis cases.9-10 Changes in the demographic characteristics of tuberculosis cases and the HIV epidemic are thought to be responsible for this increase.6-7 Factors associated with extrapulmonary tuberculosis include female gender,11-14 young age,11-13 Asian and African origin11-14,16 and HIV infection.12,14,15,17

In the UK, more than 40% of cases reported currently have extrapulmonary tuberculosis (without pulmonary involvement).10 Nevertheless, the trends and the factors associated with any changes have not been investigated. We therefore analysed national surveillance data to examine recent trends in extrapulmonary tuberculosis in England and Wales between 1999 and 2006 and explored which factors could be responsible for this increase.

Methods

Data sources and record linkage

In England and Wales, clinical and demographic information on tuberculosis cases are reported voluntarily to the Enhanced Tuberculosis Surveillance (ETS) system. All cases reported between 1 January 1999 and 31 December 2006 were included in the analysis. Treatment outcome is collected for cases reported to the ETS 1 year after the start of treatment and is available for cases reported between 2000 and 2005. Drug susceptibility testing results for culture-confirmed cases are reported through the UK Mycobacterial Surveillance Network (MycobNet) and matched to case reports annually. Information on HIV status was obtained by matching to the national HIV/AIDS reports database, as described previously.19,20

Definitions

The case definition for national surveillance includes culture-confirmed cases with a positive culture of Mycobacterium tuberculosis complex (including M tuberculosis, M bovis and M africanum), and other than culture-confirmed cases who, in the absence of culture confirmation, meet the following criteria: (1) clinician’s judgement that the patient’s clinical and/or radiological signs and/or symptoms are compatible with tuberculosis, and (2) decision to treat the patient with a full course of antituberculosis treatment.

The following sites of disease are distinguished in the ETS: pulmonary (tuberculosis affecting the lung parenchyma), bone/joint, cryptic disseminated, extrathoracic lymph nodes, gastrointestinal, genitourinary, intrathoracic lymph nodes, menin-
gtis, miliary, pleural, spinal tuberculosis, other extrapulmonary and unknown. If any site other than pulmonary or unknown was involved, cases were considered to have “extrapulmonary tuberculosis”.

To investigate the effect of migration and time since migration, a composite variable “place of birth/time since entry” was created differentiating between UK born and non-UK born, and subdividing non-UK born by time since entry. Ethnic groups were based on the Office of National Statistics classifications.

Analysis of data
For each site of disease, the number and proportion of new tuberculosis cases were tabulated by year of reporting. Trends in the proportion of cases by site of disease were assessed using the $\chi^2$ trend test. Numbers and proportions were also tabulated by potential explanatory variables which were selected based on previous literature (age group, gender, place of birth/time since entry, ethnic group, region of reporting, previous diagnosis and HIV status). Proportions may not always add up to 100% owing to missing information.

Factors associated with extrapulmonary tuberculosis were investigated using univariable and multivariable logistic regression models comparing all cases with extrapulmonary involvement to exclusively pulmonary cases using Stata 10. Factors explored were the potential explanatory variables and year of reporting (to assess the trend). Multivariable models were built using a forward-fitting approach (inclusion for $p<0.2$). Interactions with place of birth/time since entry were assessed (for $p<0.01$). Analyses were repeated for extrapulmonary sites showing substantial increases comparing all cases with the respective site of disease to those without.

RESULTS
Study population
A total of 55,607 cases of tuberculosis were reported in England and Wales between 1999 and 2006. Of these, 50% ($n = 27,762$) had exclusive pulmonary tuberculosis and 41% ($n = 22,935$) had exclusive extrapulmonary disease. In 8% of cases ($n = 4341$) both sites were involved and in 1% ($n = 571$) the site was unknown. Common extrapulmonary sites included extrathoracic lymph nodes, the pleura and intrathoracic lymph nodes, which were affected in 18%, 8% and 7% of all tuberculosis cases reported, respectively.

The overall median age of all tuberculosis cases was 36 years, 55% were male, 60% non-UK born, 25% of white ethnic group, 7% had a previous diagnosis, 5% were known to be HIV co-infected and 59% were culture-confirmed (table 1). The median age of cases with extrapulmonary disease was 35 years, 51% were male, 19% were UK born, 15% of white ethnic group, 6% had a previous diagnosis, 5% were known to be HIV co-infected and 53% of cases were culture-confirmed. Cases with only pulmonary disease were more often male (58%), born in the UK (37%), of white ethnic group (36%), culture-confirmed (66%) and more often had a previous diagnosis (9%).

Trends by site of disease
The total number of cases with extrapulmonary and pulmonary tuberculosis increased between 1999 and 2006 (table 2). The proportion of all cases that had extrapulmonary disease (with and without pulmonary involvement) rose from 48% in 1999 to 55% in 2006 ($p<0.001$)

The largest increase was seen in miliary tuberculosis where the proportion rose threefold from 0.7% to 2.2% ($p<0.001$). Tuberculosis meningitis, gastrointestinal and spinal tuberculosis also rose considerably compared with all tuberculosis cases ($p<0.001$, $p = 0.002$ and $p = 0.007$, respectively). A small decrease in laryngeal tuberculosis was observed ($p = 0.005$).

Factors associated with the increase in extrapulmonary disease
We explored the trend in extrapulmonary disease further using logistic regression to investigate possible explanatory factors. Univariable analysis showed a statistically significant increased risk of tuberculosis cases presenting with extrapulmonary disease in 2004, 2005 and 2006 compared with 1999 (table 3). The odds ratios increased for each consecutive year since 2001.

On multivariable analysis, extrapulmonary cases were more likely to be female (odds ratio (OR) 1.27, 95% CI 1.21 to 1.32), born abroad with entry into the UK more than a year before diagnosis ($p<0.001$) and of non-white ethnic group ($p<0.001$) compared with pulmonary cases (table 3). They were also less likely to have had a previous diagnosis of tuberculosis (OR 0.72 (95% CI 0.67 to 0.78)), while HIV co-infection was not associated with extrapulmonary site of disease ($p = 0.687$).

After correcting for gender, age, place of birth/time since entry, ethnic group, region of reporting and previous diagnosis, there was no longer an increased risk of extrapulmonary disease in any year compared with 1999 (see multivariable model in table 3). Further exploration revealed that correcting for being non-UK born without adjusting for any of the other variables made the increase in extrapulmonary disease statistically non-significant.

Statistically significant interactions were found between place of birth/time since entry and ethnic group, previous diagnosis, age and sex. Inclusion of these interactions in the model altered the effect of year of reporting by less than 0.5% and was therefore not presented here.

Subgroup analyses showed that the proportion of extrapulmonary cases did not increase in most subgroups such as the UK born, non-UK born, recent entrants and the black African ethnic group. There was, however, a significant increase in the Indian, Pakistani, Bangladeshi ethnic group and in cases who entered the UK 5–10 years before being diagnosed with tuberculosis.

Culture confirmation of extrapulmonary cases increased from 51% in 1999 to 56% in 2006. When analyses were repeated among culture-confirmed cases only, the increase was smaller but still statistically significant for 2005 and 2006 (OR 1.11, 95% CI 1.01 to 1.21 and 1.17, 95% CI 1.07 to 1.28, respectively).

Miliary tuberculosis and tuberculosis meningitis
Owing to the considerable increase in miliary tuberculosis, factors associated with this site of disease were explored further (table 4). Cases with miliary tuberculosis were more likely to be over 60 years of age (OR 1.71, 95% CI 1.30 to 2.25), born abroad with entry into the UK more than a year before diagnosis ($p = 0.008–0.050$), of Indian, Pakistani, Bangladeshi ethnic group (OR 1.92, 95% CI 1.36 to 2.71) and co-infected with HIV (OR 4.48, 95% CI 3.43 to 5.84); and less likely to have had a previous diagnosis of tuberculosis (OR 0.60, 95% CI 0.42 to 0.86) compared with all other cases of tuberculosis. The increasing trend remained statistically significant for all years after correcting for sex, age, place of birth/time since entry, ethnic group, region of reporting, previous diagnosis and HIV co-infection. A similar increase was noted when the analysis was restricted to culture-confirmed cases.
DISCUSSION

The rise in extrapulmonary tuberculosis cases between 1999 and 2006 exceeded the increase in the number of cases with pulmonary disease. With 43% of cases presenting with exclusive extrapulmonary disease in 2006, England now has one of the highest proportions of extrapulmonary disease among western countries.5 8–10 The proportion of cases with miliary tuberculosis increased more than threefold.

Extrapulmonary disease

Multivariable analysis showed that the increasing proportion of extrapulmonary cases could be explained by the growing proportion of non-UK born cases, a finding that is consistent with previous studies.71 11 6 One possible explanation for the increasing risk of extrapulmonary tuberculosis as a result of a rise in non-UK born cases could be an effect of “time since infection”. In the presence of widespread active transmission in tuberculosis endemic settings, the majority of new cases present with pulmonary disease. In contrast, many migrants acquired their infection prior to arrival in the UK and subsequently present with reactivation disease. This is consistent with the observation by Musellim et al that extrapulmonary disease was more likely to develop 5 or more years after contact, while pulmonary disease was more likely to develop early.22 In our study the odds ratios for extrapulmonary disease among the non-UK born increased with time since arrival, indicating that recent entrants, who are likely to have been infected more recently than those who arrived in the country a longer time ago, presented less often with extrapulmonary disease. This supports the notion that reactivation disease is more likely to

### Table 1

Demographic and clinical characteristics of tuberculosis cases reported in England and Wales, 1999–2006

<table>
<thead>
<tr>
<th></th>
<th>All cases (N = 55 607)</th>
<th>Extrapulmonary site (N = 27 274)</th>
<th>Only pulmonary site (N = 27 762)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>30380</td>
<td>55</td>
<td>13877</td>
</tr>
<tr>
<td>Median age (IQR)</td>
<td>36 (26–55)</td>
<td></td>
<td>35 (26–50)</td>
</tr>
<tr>
<td>UK born (11% unknown)</td>
<td>15658</td>
<td>28</td>
<td>5176</td>
</tr>
<tr>
<td>Ethnic group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>14042</td>
<td>25</td>
<td>3817</td>
</tr>
<tr>
<td>Black African</td>
<td>11412</td>
<td>21</td>
<td>6095</td>
</tr>
<tr>
<td>Indian, Pakistani, Bangladeshi</td>
<td>20212</td>
<td>36</td>
<td>12395</td>
</tr>
<tr>
<td>Other</td>
<td>7269</td>
<td>13</td>
<td>3646</td>
</tr>
<tr>
<td>Reported in London</td>
<td>23671</td>
<td>43</td>
<td>12291</td>
</tr>
<tr>
<td>Previous TB diagnosis*</td>
<td>3985</td>
<td>7</td>
<td>1568</td>
</tr>
<tr>
<td>HIV co-infection†</td>
<td>2602</td>
<td>5</td>
<td>1259</td>
</tr>
<tr>
<td>Culture confirmation</td>
<td>32204</td>
<td>59</td>
<td>14351</td>
</tr>
</tbody>
</table>

*20% unknown.
†For cases reported between 1999 and 2005.

IQR, interquartile range; TB, tuberculosis.

### Table 2

Number and proportion of tuberculosis cases reported with pulmonary and extrapulmonary tuberculosis, England and Wales 1999 and 2006

<table>
<thead>
<tr>
<th></th>
<th>1999</th>
<th>% (95% CI)</th>
<th>2006</th>
<th>% (95% CI)</th>
<th>% Increase in N</th>
<th>p Value (χ² trend)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET lymph nodes</td>
<td>1066</td>
<td>19 (18 to 20)</td>
<td>1575</td>
<td>20 (19 to 21)</td>
<td>47.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pleural</td>
<td>436</td>
<td>7.6 (7.0 to 8.4)</td>
<td>641</td>
<td>8.0 (7.4 to 8.6)</td>
<td>47.0%</td>
<td>0.041</td>
</tr>
<tr>
<td>IT lymph nodes</td>
<td>371</td>
<td>6.5 (5.9 to 7.2)</td>
<td>591</td>
<td>7.3 (6.8 to 7.9)</td>
<td>59.3%</td>
<td>0.001</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>175</td>
<td>3.1 (2.7 to 3.6)</td>
<td>315</td>
<td>3.9 (3.5 to 4.4)</td>
<td>80.0%</td>
<td>0.002</td>
</tr>
<tr>
<td>Spine</td>
<td>145</td>
<td>2.5 (2.2 to 3.0)</td>
<td>268</td>
<td>3.3 (3.0 to 3.7)</td>
<td>84.8%</td>
<td>0.007</td>
</tr>
<tr>
<td>Bone (not spine)</td>
<td>140</td>
<td>2.5 (2.1 to 2.9)</td>
<td>161</td>
<td>2.0 (1.7 to 2.3)</td>
<td>15.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>111</td>
<td>1.9 (1.6 to 2.3)</td>
<td>135</td>
<td>1.7 (1.4 to 2.0)</td>
<td>21.6%</td>
<td>0.008</td>
</tr>
<tr>
<td>Milary TB</td>
<td>38</td>
<td>0.7 (0.5 to 0.9)</td>
<td>180</td>
<td>2.2 (1.9 to 2.6)</td>
<td>373.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TB meningitis</td>
<td>86</td>
<td>1.5 (1.2 to 1.9)</td>
<td>165</td>
<td>2.0 (1.8 to 2.4)</td>
<td>91.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CNS other</td>
<td>41</td>
<td>0.7 (0.5 to 1.0)</td>
<td>70</td>
<td>0.9 (0.7 to 1.1)</td>
<td>70.7%</td>
<td>0.240</td>
</tr>
<tr>
<td>Cryptic disseminated</td>
<td>31</td>
<td>0.5 (0.4 to 0.8)</td>
<td>38</td>
<td>0.5 (0.3 to 0.6)</td>
<td>22.6%</td>
<td>0.075</td>
</tr>
<tr>
<td>Laryngeal</td>
<td>15</td>
<td>0.3 (0.2 to 0.4)</td>
<td>13</td>
<td>0.2 (0.1 to 0.3)</td>
<td>13.3%</td>
<td>0.005</td>
</tr>
<tr>
<td>Extrapulmonary only</td>
<td>2310</td>
<td>41 (39 to 42)</td>
<td>3480</td>
<td>43 (42 to 44)</td>
<td>50.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Extrapulmonary with pulmonary involvement</td>
<td>407</td>
<td>7.1 (6.5 to 7.8)</td>
<td>725</td>
<td>9.0 (8.4 to 9.7)</td>
<td>78.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary only</td>
<td>2923</td>
<td>51 (50 to 53)</td>
<td>3742</td>
<td>47 (45 to 48)</td>
<td>28.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All TB</td>
<td>5704</td>
<td>100</td>
<td>8051</td>
<td>100</td>
<td>41.1%</td>
<td>Ref</td>
</tr>
</tbody>
</table>

*χ² trend test with one degree of freedom for changes across each year.
95% CI, 95% confidence interval for proportions using Wilson procedure; ET, extrathoracic; IT, intrathoracic; TB, tuberculosis; extrapulmonary only, all extrapulmonary tuberculosis sites without pulmonary involvement; pulmonary only, pulmonary tuberculosis without extrapulmonary involvement; all TB, all tuberculosis cases including those with unknown or other extrapulmonary sites of disease; Ref, reference group.
present at an extrapulmonary site. The subgroup analysis showing a rise in extrapulmonary disease in the Indian, Pakistani, Bangladeshi ethnic group also supports this. This group is known to include a large proportion of migrants who arrived in the country many years ago. The observed trend may thus be driven by an increase among longer-term migrants with reactivation disease.

Alternative explanations have been proposed for the increasing trend of extrapulmonary tuberculosis among immigrants to the UK including differences in the genetic make-up of the host’s immune system, as well as the strain of organism prevalent in certain parts of the world. Further research is needed to investigate the role of these factors.

In contrast to other studies, we did not find an association between the rise in extrapulmonary tuberculosis and HIV co-infection. It is unlikely that an increase in HIV co-infection would have contributed significantly to the trend since these patients constituted a relatively small proportion of all cases. An alternative explanation for the lack of association may be due to the inclusion of a substantial number of cases with pleural tuberculosis as an extrapulmonary site in this study. As an inverse association has been reported between HIV co-infection and pleural tuberculosis, this may obscure an association.

Increased awareness of tuberculosis may also lead to an increase in extrapulmonary disease, as it could result in more clinical diagnoses being made in the absence of culture confirmation. This is, however, unlikely as an increasing trend was observed among culture-confirmed cases.

### Table 3

Univariable and multivariable analysis for the association between characteristics of tuberculosis cases and extrapulmonary site of disease

<table>
<thead>
<tr>
<th>Year</th>
<th>Number</th>
<th>Univariable</th>
<th>Multivariable*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EP</td>
<td>All</td>
<td>Univariable OR (95% CI)</td>
</tr>
<tr>
<td>1999</td>
<td>2717</td>
<td>5704</td>
<td>Reference</td>
</tr>
<tr>
<td>2000</td>
<td>2966</td>
<td>6271</td>
<td>0.98 (0.91 to 1.05)</td>
</tr>
<tr>
<td>2001</td>
<td>3058</td>
<td>6597</td>
<td>0.95 (0.88 to 1.02)</td>
</tr>
<tr>
<td>2002</td>
<td>3181</td>
<td>6794</td>
<td>0.98 (0.91 to 1.05)</td>
</tr>
<tr>
<td>2003</td>
<td>3359</td>
<td>6913</td>
<td>1.03 (0.96 to 1.11)</td>
</tr>
<tr>
<td>2004</td>
<td>3600</td>
<td>7240</td>
<td>1.09 (1.01 to 1.16)</td>
</tr>
<tr>
<td>2005</td>
<td>4188</td>
<td>8037</td>
<td>1.19 (1.11 to 1.27)</td>
</tr>
<tr>
<td>2006</td>
<td>4205</td>
<td>8051</td>
<td>1.21 (1.13 to 1.29)</td>
</tr>
</tbody>
</table>

### Gender

<table>
<thead>
<tr>
<th>Gender</th>
<th>Number</th>
<th>Univariable</th>
<th>Multivariable*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>13877</td>
<td>30380</td>
<td>Reference</td>
</tr>
<tr>
<td>Female</td>
<td>13343</td>
<td>25121</td>
<td>1.36 (1.31 to 1.40)</td>
</tr>
</tbody>
</table>

### Age group

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number</th>
<th>Univariable</th>
<th>Multivariable*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–14</td>
<td>1502</td>
<td>3209</td>
<td>0.90 (0.84 to 0.97)</td>
</tr>
<tr>
<td>15–29</td>
<td>8219</td>
<td>16391</td>
<td>Reference</td>
</tr>
<tr>
<td>30–44</td>
<td>8730</td>
<td>15732</td>
<td>1.25 (1.19 to 1.30)</td>
</tr>
<tr>
<td>45–59</td>
<td>4212</td>
<td>8570</td>
<td>0.97 (0.92 to 1.02)</td>
</tr>
<tr>
<td>60+</td>
<td>4620</td>
<td>11690</td>
<td>0.64 (0.61 to 0.68)</td>
</tr>
</tbody>
</table>

### Place of birth

<table>
<thead>
<tr>
<th>Place of birth</th>
<th>Number</th>
<th>Univariable</th>
<th>Multivariable*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Born in UK</td>
<td>5176</td>
<td>15658</td>
<td>Reference</td>
</tr>
<tr>
<td>Born abroad, entry &lt;1 year ago</td>
<td>1006</td>
<td>2757</td>
<td>1.17 (1.07 to 1.27)</td>
</tr>
<tr>
<td>Born abroad, entry 1–2 years ago</td>
<td>2191</td>
<td>3818</td>
<td>2.72 (2.53 to 2.92)</td>
</tr>
<tr>
<td>Born abroad, entry 2–5 years ago</td>
<td>4644</td>
<td>7583</td>
<td>3.21 (3.03 to 3.40)</td>
</tr>
<tr>
<td>Born abroad, entry 5–10 years ago</td>
<td>2719</td>
<td>4497</td>
<td>3.11 (2.91 to 3.34)</td>
</tr>
<tr>
<td>Born abroad, entry 10+ years ago</td>
<td>5350</td>
<td>9134</td>
<td>2.90 (2.75 to 3.06)</td>
</tr>
<tr>
<td>Born abroad, year entry missing</td>
<td>3185</td>
<td>5773</td>
<td>2.54 (2.38 to 2.70)</td>
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### Ethnic group

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>Number</th>
<th>Univariable</th>
<th>Multivariable*</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>3871</td>
<td>14042</td>
<td>Reference</td>
</tr>
<tr>
<td>Black African</td>
<td>6095</td>
<td>11412</td>
<td>3.04 (2.89 to 3.20)</td>
</tr>
<tr>
<td>Indian, Pakistani, Bangladeshi</td>
<td>12395</td>
<td>20212</td>
<td>4.24 (4.05 to 4.45)</td>
</tr>
<tr>
<td>Other</td>
<td>3646</td>
<td>7269</td>
<td>2.67 (2.52 to 2.83)</td>
</tr>
</tbody>
</table>

### Region of reporting

<table>
<thead>
<tr>
<th>Region of reporting</th>
<th>Number</th>
<th>Univariable</th>
<th>Multivariable*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other</td>
<td>14983</td>
<td>31936</td>
<td>Reference</td>
</tr>
<tr>
<td>London</td>
<td>12291</td>
<td>23671</td>
<td>1.22 (1.18 to 1.26)</td>
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</tbody>
</table>

### Previous TB diagnosis

<table>
<thead>
<tr>
<th>Previous TB diagnosis</th>
<th>Number</th>
<th>Univariable</th>
<th>Multivariable*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>20163</td>
<td>40287</td>
<td>Reference</td>
</tr>
<tr>
<td>Yes</td>
<td>1568</td>
<td>3985</td>
<td>0.65 (0.60 to 0.69)</td>
</tr>
<tr>
<td>HIV co-infection†</td>
<td></td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>No/unknown</td>
<td>26015</td>
<td>53005</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1259</td>
<td>2602</td>
<td>1.00 (0.92 to 1.08)</td>
</tr>
</tbody>
</table>

*Overall p value for categorical variables.
†For cases reported between 1999 and 2005.
EP, extrapulmonary; OR, odds ratio; TB, tuberculosis.

Miliary tuberculosis

Although most of the risk factors for extrapulmonary tuberculosis were also found to be associated with miliary tuberculosis, they could not explain the observed increase. In line with
previous studies, cases with miliary disease were more likely to be co-infected with HIV. As there has been an increase in HIV co-infected tuberculosis cases in the UK, one might have expected that this explains part of the increase seen. The lack of an association between HIV co-infection and the observed rise in miliary tuberculosis could be due to the small numbers of co-infected cases, especially among south Asians. Additional reasons for this large increase remain unclear and other factors, such as increases in immunosuppressive disorders other than HIV, may have contributed to the rise. For instance, nutritional and environmental factors such as vitamin D deficiency have been associated with an increased risk of tuberculosis. In contrast to all extrapulmonary cases, place of birth/time since entry was not a strong risk factor for miliary disease. Miliary cases were also found to be older, which could suggest a role for reactivation disease.

Despite the large increase in miliary tuberculosis, the total number of cases remains low and comprises only around 2% of all cases each. This trend therefore does not explain the overall increase in extrapulmonary disease. Molecular epidemiological analysis may throw further light on these changing trends.

### Table 4 Univariable and multivariable analysis for miliary tuberculosis among tuberculosis cases

<table>
<thead>
<tr>
<th>Number</th>
<th>Univariable OR (95% CI)</th>
<th>Multivariable* OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miliary All</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>38</td>
<td>2.40 (1.65 to 3.50)</td>
<td>2.75 (1.69 to 4.47)</td>
</tr>
<tr>
<td>2000</td>
<td>100</td>
<td>2.43 (1.68 to 3.53)</td>
<td>3.11 (1.93 to 5.01)</td>
</tr>
<tr>
<td>2001</td>
<td>106</td>
<td>2.88 (2.00 to 4.14)</td>
<td>3.33 (2.08 to 5.33)</td>
</tr>
<tr>
<td>2002</td>
<td>128</td>
<td>2.78 (1.93 to 4.00)</td>
<td>3.54 (2.21 to 5.65)</td>
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<tr>
<td>2003</td>
<td>127</td>
<td>3.24 (2.27 to 4.62)</td>
<td>4.19 (2.65 to 6.65)</td>
</tr>
<tr>
<td>2004</td>
<td>154</td>
<td>3.08 (2.16 to 4.39)</td>
<td>3.47 (2.19 to 5.51)</td>
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<tr>
<td>2005</td>
<td>163</td>
<td>3.42 (2.40 to 4.86)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>506</td>
<td>1.18 (1.04 to 1.33)</td>
<td>1.13 (0.95 to 1.33)</td>
</tr>
<tr>
<td>Female</td>
<td>490</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age group</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0–14</td>
<td>40</td>
<td>0.85 (0.61 to 1.19)</td>
<td>1.04 (0.66 to 1.65)</td>
</tr>
<tr>
<td>15–29</td>
<td>44</td>
<td>1.33 (1.12 to 1.57)</td>
<td>1.12 (0.90 to 1.41)</td>
</tr>
<tr>
<td>30–44</td>
<td>309</td>
<td>1.13 (0.92 to 1.40)</td>
<td>1.14 (0.85 to 1.53)</td>
</tr>
<tr>
<td>45–59</td>
<td>144</td>
<td>1.50 (1.26 to 1.79)</td>
<td>1.71 (1.30 to 2.25)</td>
</tr>
<tr>
<td>60+</td>
<td>259</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Place of birth</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Born in UK</td>
<td>161</td>
<td>2.03 (1.50 to 2.76)</td>
<td>1.22 (0.78 to 1.92)</td>
</tr>
<tr>
<td>Born abroad, entry &lt;1 year ago</td>
<td>57</td>
<td>2.10 (1.61 to 2.75)</td>
<td>1.49 (1.00 to 2.23)</td>
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<tr>
<td>Born abroad, entry 1–2 years ago</td>
<td>82</td>
<td>2.06 (1.65 to 2.56)</td>
<td>1.43 (1.00 to 2.05)</td>
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<tr>
<td>Born abroad, entry 2–5 years ago</td>
<td>159</td>
<td>1.65 (1.26 to 2.18)</td>
<td>1.19 (0.79 to 1.80)</td>
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<tr>
<td>Born abroad, entry 5–10 years ago</td>
<td>76</td>
<td>2.22 (1.80 to 2.73)</td>
<td>1.59 (1.13 to 2.24)</td>
</tr>
<tr>
<td>Born abroad, entry &gt;10 years ago</td>
<td>205</td>
<td>2.44 (1.94 to 3.07)</td>
<td>1.63 (1.13 to 2.35)</td>
</tr>
<tr>
<td>Born abroad, year entry missing</td>
<td>142</td>
<td></td>
<td></td>
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<tr>
<td>Ethnic group</td>
<td></td>
<td></td>
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<tr>
<td>White</td>
<td>143</td>
<td>2.30 (1.87 to 2.82)</td>
<td>1.34 (0.90 to 1.99)</td>
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<tr>
<td>Black African</td>
<td>263</td>
<td>2.05 (1.69 to 2.48)</td>
<td>1.92 (1.36 to 2.71)</td>
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<td>Indian, Pakistani, Bangladeshi</td>
<td>415</td>
<td>1.71 (1.34 to 2.17)</td>
<td>1.34 (0.90 to 2.00)</td>
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<td></td>
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<tr>
<td>Region of reporting</td>
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<td></td>
<td></td>
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<tr>
<td>Other</td>
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<td>1.88 (0.78 to 1.00)</td>
<td>0.88 (0.78 to 1.00)</td>
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<td>London</td>
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<td></td>
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<td>Previous TB diagnosis</td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>712</td>
<td>0.58 (0.42 to 0.79)</td>
<td>0.60 (0.42 to 0.86)</td>
</tr>
<tr>
<td>Yes</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV co-infection†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Known</td>
<td>670</td>
<td>3.94 (3.28 to 4.73)</td>
<td>4.48 (3.43 to 5.84)</td>
</tr>
<tr>
<td>Yes</td>
<td>146</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Because data on HIV were only available for cases reported between 1999 and 2005, the full multivariable analysis does not include 2006 cases. For categorical values overall p values are reported.
†For cases reported between 1999 and 2005.
Strengths and limitations
The analysis was based on 8 consecutive years of national surveillance data, providing a large and representative dataset. As with other observational studies, the effect of residual and unmeasured confounding cannot be excluded. One of the main limitations of the study is the inability to adjust for the effects of social risk factors, causes of immunosuppression other than HIV and time since infection. Interactions between various risk factors were found on multivariable analyses, making their effects difficult to interpret. These interactions, however, did not affect the results for the trend in extrapulmonary disease. HIV co-infection status was obtained by matching tuberculosis cases to HIV/AIDS reports, with a potential for misclassification of cases, and was not available for cases reported in 2006 and those aged <15 years of age, reducing the power and extrapolation of the results. As negative test results are not reported, HIV status also includes a certain extent of misclassification, and its association with extrapulmonary tuberculosis may therefore be underestimated.

CONCLUSION
In the UK the clinical presentation of tuberculosis is changing with an increasing proportion of patients now presenting with extrapulmonary manifestations. This study shows that this is related to the increasing numbers of non-UK born cases who came into the country many years before developing disease. Although the absolute numbers remain small, the increase in miliary tuberculosis was particularly large; the reasons for this remain unclear. Clinicians need to be aware of this increasing trend and have a higher index of suspicion of extrapulmonary tuberculosis, especially among cases from the Indian subcontinent. Improvements in obtaining culture confirmation for extrapulmonary tuberculosis should be an objective.

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Competing interests: None.

Ethics approval: This study was carried out with national surveillance data. The Health Protection Agency has Patient Information Advisory Group approval to hold and analyse national surveillance data for public health purposes under Section 60 of the Health and Social Care Act 2001. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the paper for publication.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Increase in extrapulmonary tuberculosis in England and Wales 1999–2006

M E Kruijshaar and I Abubakar

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