Increase in extra pulmonary tuberculosis in England and Wales 1999 - 2006
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Abstract
Background: Extra pulmonary tuberculosis appears to be increasing in England and Wales. We examined trends in extra pulmonary tuberculosis and factors associated with these trends.

Methods: We used national tuberculosis surveillance data from 1999-2006 for England and Wales, including demographic, clinical and laboratory information. Trends in the proportion of tuberculosis cases with extra pulmonary disease were investigated using the chi-square trend test and associated factors using logistic regression.

Results: Amongst all tuberculosis cases, the proportion with extra pulmonary disease increased from 48% in 1999 (2,717 cases) to 53% in 2006 (4,205 cases, p<0.001). Regression analysis showed that the rise in extra pulmonary disease was associated with an increase in the proportion of non-UK born cases (odds ratio 2.7 [2.6-2.8]). A more than three-fold 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 nor in any of the other risk factors identified.

Conclusions: The proportion of cases with extra pulmonary 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 extra pulmonary tuberculosis in non-UK born cases.
Introduction
Tuberculosis remains a major global public health issue. 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 joint, genitourinary tract, central nervous system and may affect multiple organs. Miliary disease and meningitis are associated with particularly poor outcomes.

The diagnosis and management of extra pulmonary tuberculosis poses particular challenges. The diagnosis is often difficult due to the wide spectrum of clinical presentations, the limited specificity of the manifestations and difficulties in obtaining specimens for culture. It is frequently made using histological or radiological evidence in combination with signs or symptoms, but can only be confirmed by microbiological culture. Managing cases with extra pulmonary tuberculosis is complicated due to the sometimes longer course of treatment 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 extra pulmonary tuberculosis. In the United States the proportion increased from 16% in 1993 to 21% in 2006. Recent reports from the Netherlands and Canada suggest that it now affects nearly 40% of tuberculosis cases. Changes in the demographic characteristics of tuberculosis cases and the HIV epidemic are thought to be responsible for this increase. Factors associated with extra pulmonary tuberculosis include female gender, young age, Asian and African origin and HIV infection.

In the UK, more than 40% of cases reported currently have extra pulmonary tuberculosis (without pulmonary involvement). 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 extra pulmonary 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 1st January 1999 and 31st December 2006 were included in the analysis. Treatment outcome is collected for cases reported to ETS one 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.

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: (i) clinician’s judgement that the patient’s clinical and/or radiological signs and/or symptoms are compatible with tuberculosis, and (ii) decision to treat the patient with a full course of anti-tuberculosis treatment.
The following sites of disease are distinguished in ETS: pulmonary (tuberculosis affecting the lung parenchyma), bone/joint, cryptic disseminated, extra thoracic lymph nodes, gastrointestinal, genitourinary, intra-thoracic lymph nodes, meningitis, miliary, pleural, spinal tuberculosis, other extra pulmonary, and unknown. If any site other than pulmonary or unknown was involved, cases were considered to have “extra pulmonary 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

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-square 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% due to missing information.

Factors associated with extra pulmonary tuberculosis were investigated using univariable and multivariable logistic regression models comparing all cases with extra pulmonary 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 sites with substantial increases compared to all cases without the respective site of disease.

Results

Study population

A total of 55607 cases of tuberculosis were reported in England and Wales between 1999 and 2006. Of these, 50% (27,762) had exclusive pulmonary and 41% (22,933) exclusive extra pulmonary disease. In 8% (4341) of cases both sites were involved and in 1% (571) the site was unknown. Common extra pulmonary sites included extra-thoracic lymph nodes, the pleura and intra-thoracic 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 extra pulmonary disease was 35 years, 51% were male, 19% were UK born, 13% 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 extra pulmonary and pulmonary tuberculosis increased between 1999 and 2006 (Table 2). The proportion of all cases that had extra pulmonary disease (with and without pulmonary involvement) rose from 48% in 1999 to 53% in 2006 (p<0.001)
The largest increase was seen in miliary tuberculosis, where the proportion rose three-fold from 0.7% to 2.2% (p<0.001). Tuberculosis meningitis, gastro-intestinal and spinal tuberculosis also rose considerably compared to 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).

Table 1. Demographic and clinical characteristics of tuberculosis cases reported in England and Wales, 1999-2006.

<table>
<thead>
<tr>
<th></th>
<th>All cases</th>
<th>Extra Pulmonary Site</th>
<th>Only Pulmonary Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>55,607</td>
<td>27,274</td>
<td>27,762</td>
</tr>
<tr>
<td>Gender - male</td>
<td>30,380</td>
<td>13,877</td>
<td>16,220</td>
</tr>
<tr>
<td>Median age (IQR)</td>
<td>36 (IQR 26-55)</td>
<td>35 (IQR 26-50)</td>
<td>37 (IQR 26-60)</td>
</tr>
<tr>
<td>UK born (11% unknown)</td>
<td>15,658</td>
<td>5,176</td>
<td>10,358</td>
</tr>
<tr>
<td>Ethnic group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>14,042</td>
<td>3,871</td>
<td>10,171</td>
</tr>
<tr>
<td>Black African</td>
<td>11,412</td>
<td>6,095</td>
<td>5,225</td>
</tr>
<tr>
<td>Indian, Pakistani, Bangladeshi</td>
<td>20,212</td>
<td>12,395</td>
<td>7,617</td>
</tr>
<tr>
<td>Other</td>
<td>7,269</td>
<td>3,646</td>
<td>3,623</td>
</tr>
<tr>
<td>Reported in London</td>
<td>23,671</td>
<td>12,291</td>
<td>11,156</td>
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<tr>
<td>Previous TB diagnosis*</td>
<td>3,985</td>
<td>1,568</td>
<td>2,384</td>
</tr>
<tr>
<td>HIV co-infection**</td>
<td>2,602</td>
<td>1,259</td>
<td>1,314</td>
</tr>
<tr>
<td>Culture confirmation</td>
<td>32,804</td>
<td>14,351</td>
<td>18,453</td>
</tr>
</tbody>
</table>

N: number of cases; % proportion of cases, IQR: inter-quartile range; * 20% unknown; **for cases reported between 1999-2005.

Table 2. Number and proportion of tuberculosis cases reported with pulmonary and extra pulmonary tuberculosis, England and Wales 1999 and 2006.

<table>
<thead>
<tr>
<th></th>
<th>1999</th>
<th>2006</th>
<th>% Increase in Numbers</th>
<th>p-value</th>
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<tbody>
<tr>
<td>ET Lymph Nodes</td>
<td>1066</td>
<td>1575</td>
<td>47.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pleural</td>
<td>436</td>
<td>641</td>
<td>47.0%</td>
<td>0.041</td>
</tr>
<tr>
<td>IT Lymph Nodes</td>
<td>371</td>
<td>591</td>
<td>59.3%</td>
<td>0.001</td>
</tr>
<tr>
<td>Gastro intestinal</td>
<td>175</td>
<td>315</td>
<td>80.0%</td>
<td>0.002</td>
</tr>
<tr>
<td>Spine</td>
<td>145</td>
<td>268</td>
<td>84.8%</td>
<td>0.007</td>
</tr>
<tr>
<td>Bone (not spine)</td>
<td>140</td>
<td>161</td>
<td>15.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>111</td>
<td>135</td>
<td>21.6%</td>
<td>0.008</td>
</tr>
<tr>
<td>Military TB</td>
<td>38</td>
<td>180</td>
<td>373.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TB Meningitis</td>
<td>86</td>
<td>165</td>
<td>91.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CNS other</td>
<td>41</td>
<td>70</td>
<td>70.7%</td>
<td>0.240</td>
</tr>
<tr>
<td>Cryptic disseminated</td>
<td>31</td>
<td>38</td>
<td>22.6%</td>
<td>0.075</td>
</tr>
<tr>
<td>Laryngeal</td>
<td>15</td>
<td>13</td>
<td>13.3%</td>
<td>0.005</td>
</tr>
</tbody>
</table>

% proportion of cases; 95% CI: 95% confidence interval for proportions using Wilson procedure; X2 trend*: chi-square trend test with 1 degree of freedom for changes across each year; ET: extra-thoracic; IT: intra-thoracic; TB: tuberculosis; Extra pulmonary only: all extra pulmonary tuberculosis sites without pulmonary involvement; Pulmonary only: pulmonary tuberculosis without extra pulmonary involvement; All TB: all tuberculosis cases including those with unknown or other extra pulmonary sites of disease; REF reference group.
Factors associated with the increase in extra pulmonary disease

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

On multivariable analysis, extra pulmonary cases were more likely to be female (OR 1.27 [95% CI 1.21-1.32), 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 to pulmonary cases (Table 3). They were also less likely to have had a previous diagnosis of tuberculosis (0.72 [0.67-0.78]), while HIV co-infection was not associated with extra pulmonary 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 extra pulmonary disease in any year compared to 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 extra pulmonary 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 into 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 extra pulmonary cases did not increase in most sub-groups such as the UK born, the non-UK born, recent entrants and the black African ethnic group. There was, however, a significantly increase in the Indian, Pakistani, Bangladeshi ethnic group and in cases that entered the UK 5-10 year prior to being diagnosed with tuberculosis.

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

Miliary tuberculosis and tuberculosis meningitis

Due 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 (1.71 [1.30-2.25]), born abroad with entry into the UK more than a year prior to diagnosis (p= 0.008 - 0.050), of Indian, Pakistani, Bangladeshi ethnic group (1.92 [1.36-2.71]), and co-infected with HIV (4.48 [3.43-5.84]); and less likely to have had a previous diagnosis of tuberculosis (0.60 [0.42-0.86]) compared to all other tuberculosis cases. 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.
Table 3. Univariable and multivariable analysis for the association between characteristics of tuberculosis cases and extra pulmonary site of disease.

<table>
<thead>
<tr>
<th></th>
<th>Number (EP / all cases)</th>
<th>Univariable OR (95% CI)</th>
<th>Multivariable analysis* OR (95% CI)</th>
<th>p-value</th>
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<tr>
<td><strong>Year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>2717 / 5704</td>
<td>Reference</td>
<td>Reference</td>
<td>0.001</td>
</tr>
<tr>
<td>2000</td>
<td>2966 / 6271</td>
<td>0.98 (0.91-1.05)</td>
<td>1.00 (0.92-1.09)</td>
<td></td>
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<tr>
<td>2001</td>
<td>3058 / 6597</td>
<td>0.95 (0.88-1.02)</td>
<td>0.95 (0.87-1.03)</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>3181 / 6794</td>
<td>0.98 (0.91-1.05)</td>
<td>0.89 (0.81-0.97)</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>3359 / 6913</td>
<td>1.03 (0.96-1.11)</td>
<td>0.95 (0.87-1.03)</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>3600 / 7240</td>
<td>1.09 (1.01-1.16)</td>
<td>1.01 (0.92-1.10)</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>4188 / 8037</td>
<td>1.19 (1.11-1.27)</td>
<td>1.03 (0.95-1.12)</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>4205 / 8051</td>
<td>1.21 (1.13-1.29)</td>
<td>1.06 (0.97-1.15)</td>
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<tr>
<td><strong>Gender</strong></td>
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<td></td>
<td></td>
<td></td>
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<td>Male</td>
<td>13877 / 30380</td>
<td>Reference</td>
<td>Reference</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>13343 / 25121</td>
<td>1.36 (1.31-1.40)</td>
<td>1.27 (1.21-1.32)</td>
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<tr>
<td><strong>Age group</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0-14</td>
<td>1502 / 3209</td>
<td>0.90 (0.84-0.97)</td>
<td>1.18 (1.08-1.30)</td>
<td></td>
</tr>
<tr>
<td>15-29</td>
<td>8219 / 16391</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>30-44</td>
<td>8730 / 15732</td>
<td>1.25 (1.19-1.30)</td>
<td>1.39 (1.32-1.47)</td>
<td></td>
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<tr>
<td>45-59</td>
<td>4212 / 8570</td>
<td>0.97 (0.92-1.02)</td>
<td>1.32 (1.23-1.42)</td>
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<tr>
<td>60+</td>
<td>4602 / 11690</td>
<td>0.64 (0.61-0.68)</td>
<td>1.06 (0.99-1.14)</td>
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<tr>
<td><strong>Place of birth</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Born in UK</td>
<td>5176 / 15658</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Born abroad, entry &lt;1 year ago</td>
<td>1006 / 2757</td>
<td>1.17 (1.07-1.27)</td>
<td>0.74 (0.67-0.83)</td>
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<tr>
<td>Born abroad, entry 1-2 years ago</td>
<td>2191 / 3818</td>
<td>2.72 (2.53-2.92)</td>
<td>1.67 (1.52-1.83)</td>
<td></td>
</tr>
<tr>
<td>Born abroad, entry 2-5 years ago</td>
<td>4644 / 7583</td>
<td>3.21 (3.03-3.40)</td>
<td>1.90 (1.75-2.05)</td>
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<tr>
<td>Born abroad, entry 5-10 years ago</td>
<td>2719 / 4497</td>
<td>3.11 (2.91-3.34)</td>
<td>1.75 (1.60-1.92)</td>
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<tr>
<td>Born abroad, entry 10+ years ago</td>
<td>5350 / 9134</td>
<td>2.90 (2.75-3.06)</td>
<td>1.48 (1.37-1.60)</td>
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<tr>
<td>Born abroad, year entry missing</td>
<td>3185 / 5773</td>
<td>2.54 (2.38-2.70)</td>
<td>1.43 (1.32-1.56)</td>
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<td><strong>Ethnic group</strong></td>
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<td>&lt;0.001</td>
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<tr>
<td>White</td>
<td>3871 / 14042</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Black African</td>
<td>6095 / 11412</td>
<td>3.04 (2.89-3.20)</td>
<td>1.99 (1.83-2.17)</td>
<td></td>
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<tr>
<td>Indian, Pakistani, Bangladeshi</td>
<td>12395 / 20212</td>
<td>4.24 (4.05-4.45)</td>
<td>3.09 (2.87-3.32)</td>
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<tr>
<td>Other</td>
<td>3646 / 7269</td>
<td>2.67 (2.52-2.83)</td>
<td>1.88 (1.73-2.05)</td>
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<td><strong>Region of reporting</strong></td>
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<td>London</td>
<td>12291 / 23671</td>
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<td>Other</td>
<td>20163 / 40287</td>
<td>Reference</td>
<td>Reference</td>
<td>&lt;0.001</td>
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<td><strong>Previous TB diagnosis</strong></td>
<td>1568 / 3985</td>
<td>0.65 (0.60-0.69)</td>
<td>0.72 (0.67-0.78)</td>
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<tr>
<td>No</td>
<td>26015 / 53005</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1259 / 2602</td>
<td>1.00 (0.92-1.08)</td>
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</table>

*overall p-value for categorical variables; **for cases reported between 1999-2005;
Table 4. Univariable and multivariable analysis for miliary tuberculosis among tuberculosis cases.

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Univariable</th>
<th>Multivariable*</th>
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<tbody>
<tr>
<td></td>
<td>Miliary</td>
<td>All</td>
<td>OR</td>
</tr>
<tr>
<td><strong>Year</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>38</td>
<td>5704</td>
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<td>2000</td>
<td>100</td>
<td>6271</td>
<td>2.40 (1.65-3.50)</td>
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<td>2001</td>
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<td>6597</td>
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<td>2002</td>
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<td>6794</td>
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<td>2003</td>
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<td>6913</td>
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<td>2004</td>
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<td>7240</td>
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<td>2005</td>
<td>163</td>
<td>8037</td>
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<td>2006</td>
<td>180</td>
<td>8051</td>
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<td><strong>Gender</strong></td>
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<td>Female</td>
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<td>15-29</td>
<td>244</td>
<td>16931</td>
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<tr>
<td>30-44</td>
<td>309</td>
<td>15732</td>
<td>1.33 (1.12-1.57)</td>
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<tr>
<td>45-59</td>
<td>144</td>
<td>8570</td>
<td>1.13 (0.92-1.40)</td>
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<tr>
<td>60+</td>
<td>259</td>
<td>11690</td>
<td>1.50 (1.26-1.79)</td>
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<tr>
<td><strong>Place of birth</strong></td>
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<td>Born in UK</td>
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<td>15658</td>
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<td>Born abroad, entry &lt;1 year ago</td>
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<td>2757</td>
<td>2.03 (1.50-2.76)</td>
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<tr>
<td>Born abroad, entry 1-2 years ago</td>
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<td>2.10 (1.61-2.75)</td>
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<td>Born abroad, entry 2-5 years ago</td>
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<td>14042</td>
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<td>Black African</td>
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<td>Indian, Pakistani, Bangladeshi</td>
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<td>2.05 (1.69-2.48)</td>
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<td>Other</td>
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<td>Other</td>
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<td>London</td>
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</tr>
<tr>
<td>No</td>
<td>712</td>
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<td>Yes</td>
<td>41</td>
<td>3985</td>
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<td><strong>HIV co-infection</strong></td>
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<td>No / unknown</td>
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<td>Yes</td>
<td>146</td>
<td>2602</td>
<td>3.94 (3.28-4.73)</td>
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</table>

* Please note that because data on HIV were only available for cases reported between 1999-2005, the full multivariable analysis does not include 2006 cases. For categorical values overall p-value are reported. **for cases reported between 1999-2005.

Discussion

The rise in extra pulmonary tuberculosis cases between 1999 to 2006 exceeded the increase in the number of cases with pulmonary disease. With 43% of cases presenting with exclusive extra pulmonary disease in 2006, England now has one of the highest proportions of extra pulmonary disease among Western countries. 5,8-10

The proportion of cases with miliary tuberculosis increased more than three-fold.

**Extra pulmonary disease**

Multivariable analysis showed that the increasing proportion of extra pulmonary cases could be explained by the growing proportion of non-UK born cases, a finding that is consistent with previous studies. 7,11,16 One possible explanation for the increasing risk of extra pulmonary 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 extra pulmonary disease was more likely to develop five or more years after contact, while pulmonary disease was more likely to develop early. In our study, the odds ratios for extra pulmonary disease among the non-UK born increased with time since arrival, indicating that recent entrants, who are likely to have been infected more recently compared to those who arrived in the country a longer time ago, presented less often with extra pulmonary disease. This supports the notion that reactivation disease is more likely to present at an extra pulmonary site. The subgroup analysis showing a rise in extra pulmonary 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 extra pulmonary 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 extra pulmonary 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 extra pulmonary 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 extra pulmonary disease, as it could result in more clinical diagnoses being made in absence of culture confirmation. This is, however, unlikely, as an increasing trend was observed amongst culture-confirmed cases.

Miliary tuberculosis

Although most of the risk factors for extra pulmonary 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 immune-suppressive 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 extra pulmonary 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 extra pulmonary disease. Molecular epidemiological analysis may throw a further light on these changing trends.
**Clinical implications**

Extra pulmonary cases are not infectious to others, but they are more difficult to recognise and diagnose. Clinicians need to be aware of the observed increase, and have a higher index of clinical suspicion, especially amongst the non-UK born population. Culture is the only way to confirm the disease, and at around 53% there is still room for improvement. Clinicians should ensure that samples from patients with suspected extra-pulmonary tuberculosis, in general, and from biopsy specimens in particular, are sent for mycobacterial culture. The increase in miliary tuberculosis is particularly worrisome, as cases with this form of tuberculosis are known to have particularly poor outcomes. ³

**Strengths and limitations**

The analysis was based on eight consecutive years of national surveillance data, providing a large and representative dataset. As with other observational studies, the effect of residual and unmeasured confounding can not be excluded. One of the main limitations of the study is the inability to adjust for the effects of social risk factors, causes of immune-suppression 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 extra pulmonary 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 under 15 years of age, reducing power and extrapolation of results. As negative test results are not reported, HIV status also includes a certain extent of misclassification, and its association with extra pulmonary 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 extra pulmonary manifestations. This study shows that this is related to the increasing numbers of non-UK born cases, that came into the country many years prior to developing disease. Although absolute numbers remain small, the increase in miliary tuberculosis was particularly large, and reasons for this remain unclear. Clinicians need to be aware of this increasing trend, and have a higher index of suspicion of extra pulmonary tuberculosis, especially amongst cases from the Indian subcontinent. Improvements in obtaining culture confirmation for extra pulmonary tuberculosis should be an objective.
Acknowledgements
We would like to acknowledge all those who provide information on tuberculosis and HIV/AIDS diagnoses in England and Wales. Many thanks to David Quinn for preparing the Enhanced Tuberculosis Surveillance dataset for analysis and for his role in the data matching processes and to Dr Oscar Franco for his extensive comments on this document.

Ethical 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.

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Competing interests
All authors declare that the answer to the questions on your competing interest form are all No and therefore have nothing to declare.

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