# Risk factors for recurrent tuberculosis in England and Wales, 1998–2005

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## ABSTRACT

**Background** Information on recurrent tuberculosis can provide an indication of the effectiveness of tuberculosis services and identify patients who are most vulnerable. The objective of this study was to estimate the incidence of, and investigate risk factors for, recurrent episodes of tuberculosis in England and Wales.

**Methods** Episodes of recurrent tuberculosis were identified among prospectively collected records of tuberculosis cases reported to the Health Protection Agency between 1998 and 2005. An episode of recurrent tuberculosis was defined as a re-notified case in the same patient after at least 12 months from the date of the initial notification. To estimate incidence, follow-up time was calculated for all cases until re-notification or censure. Multivariable Cox proportionate hazard models were used to determine hazard ratios (HR) for recurrence of tuberculosis and investigate the risk associated with clinical, demographic and microbiological factors.

**Results** Five hundred and eighty-eight recurrent tuberculosis events were identified among 53 214 cases reported between 1998 and 2005, a rate of 4.1 (95% CI 3.8 to 4.5) episodes per 1000 person years of follow-up. Factors independently associated with a greater risk of recurrent tuberculosis were HIV co-infection (HR 1.64, 95% CI 1.13 to 2.38) and belonging to a South Asian ethnic group (HR 1.54, 95% CI 1.23 to 1.93).

**Conclusion** Tuberculosis recurrence is uncommon in England and Wales despite the absence of a universal directly observed treatment policy. The identification of HIV co-infection as a risk factor for recurrent tuberculosis is consistent with findings elsewhere. The higher risk among South Asians, however, requires further investigation.

## INTRODUCTION

Recurrent tuberculosis can be the result of a new infection (exogenous re-infection) or the reactivation of the tuberculosis strain responsible for the original episode of disease (endogenous reactivation). A host of factors can influence the likelihood of recurrent tuberculosis including the level of adherence to treatment, the severity of the original episode, the patient's immune status and the risk of re-infection.[1]

In a low incidence setting, the risk of re-infection and subsequent disease is generally considered to be small and the majority of cases of recurrent tuberculosis would be expected to be due to reactivation.[1–3] In contrast, in high incidence settings the proportion of recurrent tuberculosis cases due to re-infection is higher because of the increased risk of exposure.[4 5]

England and Wales is considered to be a low incidence setting with a rate of 13 cases per 100 000 population in 2007. However, rates >50 per 100 000 exist in some inner city areas and rates >100 per 100 000 occur in certain ethnic minority groups, especially among new entrants.[6] Rates are also high among elderly subjects, homeless people and persons with a history of prison detention.[7] The proportion of cases co-infected with HIV has also significantly increased in recent years.[8]

Very few data have been published on recurrent tuberculosis in the UK,[9] and no national investigation has so far been conducted. An understanding of recurrent tuberculosis can inform about the effectiveness of tuberculosis control services and help identify those who are most vulnerable. The objective of this study was to investigate the incidence of, and risk factors for, recurrent episodes of tuberculosis in England and Wales.

## METHODS

This study was undertaken using all tuberculosis cases reported to Enhanced Tuberculosis Surveillance between 1998 and 2005 in England and Wales and information on HIV status obtained from matched data with the national HIV database (1982–2005).

An episode of recurrent tuberculosis was defined as a case re-notified at least 12 months from the date of the initial notification. This is based on the reporting criteria of Enhanced Tuberculosis Surveillance that a year has to elapse before a case in the same patient can be notified again, and that any case reported from the same patient twice within a year is considered a single episode. The underlying assumption is that most cases would be expected to have completed their treatment within 12 months of commencement, which is also why 12 months is the standard cut-off time at which treatment outcomes are recorded.[10]

The case definition for Enhanced Tuberculosis Surveillance includes culture-confirmed disease due to *Mycobacterium tuberculosis* complex and, in the absence of culture confirmation, any patient with a clinical diagnosis and a decision to treat with a full course of antituberculosis therapy. Multidrug-resistant tuberculosis (MDR-TB) refers to resistance to at least isoniazid and rifampicin.

The minimum dataset of Enhanced Tuberculosis Surveillance includes demographic, clinical and microbiological information on all cases of tuberculosis reported by clinicians. The implementation of continuous monitoring of treatment outcome began for tuberculosis cases reported in 2001. Patients are categorised as completed treatment, died (including cases identified post mortem), still

on treatment, treatment stopped, transferred out or lost to follow-up.

Data linkage was used to identify re-notifications among all tuberculosis cases reported between 1998 and 2005. Using in-house software, potential matches between cases were ranked by a scoring system based on the degree of similarity across personal identifiers (soundex of forename, soundex of surname, date of birth, NHS number and post code). High scores above an agreed level were considered automatically matched, and scores below this were operator-assessed until no further matches were likely to be found.

Using the same methodology as above, records in the national tuberculosis database were linked with the national HIV database for the years 1985–2005 to estimate the number of tuberculosis cases co-infected with HIV.[8] Identifiers on HIV/AIDS cases, however, are only available for patients aged over 15 years and are limited to soundex of the surname, sex and date of birth.

To calculate the incidence of recurrent tuberculosis among all reported cases, follow-up time in days was calculated for all cases from 12 months after they were notified until an event (re-notification) or censure (31 December 2005). The estimate of incidence and hazard analysis effectively covered cases reported between 1 January 1998 and 31 December 2004, followed until censure. Information from treatment outcome monitoring was used to account for losses to follow-up attributable to death. To aid comparison with other published studies, we also looked at the incidence of re-notification among a subset of all pulmonary cases (with or without extrapulmonary disease), culture-confirmed pulmonary cases and sputum-positive cases who completed treatment.

### Statistical analysis

Cox proportionate hazard models were used to investigate risk factors associated with a tuberculosis case being re-notified. Unadjusted hazard ratios (HR) for demographic, microbiological and clinical factors were calculated from univariable analysis. Adjusted hazard ratios were estimated by multivariable analysis. The final model controlled for sex and those variables with p values $<0.2$ from the univariable analysis. Results with a p value $<0.05$ were considered significant. Significance of interactions between explanatory variables was tested using likelihood ratio tests. Interactions with a p value $<0.01$ were considered significant. Cases of MDR-TB (identified at the start of treatment) were excluded from the survival analysis (n=268). The minimum recommended period of treatment for MDR-TB is 18 months and such cases would not be considered recurrent tuberculosis if reported again after 12 months. Hazard analyses were also performed looking specifically at the subset of cases known to have completed treatment.

All analyses were performed using STATA V.9.

## RESULTS

A total of 588 re-notifications were identified among the 53 214 cases reported from 1998 to 2005 in England and Wales. Five hundred and seventy-seven of these re-notifications were second episodes and 11 were third episodes. After accounting for mortality, 42 558 cases were followed for a total of 142 507 person years, an incidence of 4.1 (95% CI 3.8 to 4.5) re-notifications per 1000 person years of follow-up. The median follow-up time was 3.3 years (IQR 1.6–5.1), with a median time from start of follow-up to re-notification of 1.1 years (IQR 0.5–2.3). Table 1 presents the number of re-notifications by year since follow-up. The majority (46%) of re-notifications occurred within 1 year of follow-up, and the number of re-notifications declined with length of follow-up time.

**Table 1** Time to re-notification by year since follow-up, England and Wales 1998–2005

| Follow-up (years) | No of events | % of total re-notifications |
|---|---|---|
| 0–1 | 273 | 46% |
| 1–2 | 141 | 24% |
| 2–3 | 79 | 13% |
| 3–4 | 46 | 8% |
| 4–5 | 26 | 4% |
| 5–6 | 16 | 3% |
| 6–7 | 7 | 1% |
| Total | 588 | 100% |

Event = re-notification.

Compared with all reported cases, re-notified cases had a similar demographic, clinical and microbiological profile except that a higher proportion of re-notified cases were from a South Asian ethnic group (Indian, Pakistani or Bangladeshi) (46% vs 38%). Higher levels of isoniazid resistance (9.2% vs 6.6%), multidrug resistance (3% vs 0.9%) and HIV co-infection (6.3% vs 4.9%) were also observed for re-notified cases than for all cases.

Table 2 describes the clinical characteristics of initial and re-notified cases. The proportion of re-notified cases with pulmonary disease was lower than the initial notifications. The proportion of re-notified cases with lymph node disease was higher than the initial notifications. Among South Asians, 55% of initial cases had pulmonary disease and 25% had lymph node disease. Among re-notified cases in South Asians, the proportion of pulmonary disease was 45% while lymph node disease increased to 31%. The mean CD4 count among co-infected cases was also low, although it was not possible to relate this to the time of the diagnosis of tuberculosis. Among cases in whom a treatment outcome was reported, 78% of initial cases completed treatment compared with 75% of re-notified cases; 7% of re-notified cases died during treatment.

**Table 2** Clinical factors associated with initial and re-notified cases, England and Wales 1998–2005

| Category | Level | Initial cases n=588 | Re-notified cases n=588 |
|---|---|---|---|
| Site of disease | Pulmonary | 349 (59.4) | 324 (55.1) |
| | Lymph node | 104 (17.7) | 126 (21.4) |
| | Pulmonary +extrapulmonary | 49 (8.3) | 19 (3.2) |
| | Other | 30 (5.1) | 48 (8.2) |
| | Pleural | 15 (2.6) | 11 (1.9) |
| | Miliary | 14 (2.4) | 10 (1.7) |
| | >2 extrapulmonary sites | 10 (1.7) | 12 (2) |
| | Bone | 9 (1.5) | 19 (3.2) |
| | CNS | 8 (1.4) | 19 (3.2) |
| HIV | HIV +ve | 34 (5.8) | 37 (6.3) |
| | Not known +ve | 554 (94.2) | 551 (93.7) |
| | Mean CD4 count ($mm^3$)* | 168.1 | |
| Treatment outcome | Treatment completed | 165 (28.1) | 331 (56.3) |
| | Treatment not completed | 46 (7.8) | 109 (18.5) |
| | Outcome unknown | 377 (64.1) | 148 (25.2) |

*CD4 count only available for 12 cases and relates to earliest known report and not the time of tuberculosis diagnosis.
Treatment not completed includes: died, lost to follow-up, still on treatment, treatment stopped and transferred out.

Table 3 describes the incidence of re-notified tuberculosis and the results of the hazard analysis. The highest incidence of recurrent tuberculosis was observed among cases co-infected with HIV.

Factors independently associated with a greater risk of re-notification relative to each baseline group were belonging to a South Asian or unknown ethnic group and HIV co-infection (table 3). Children aged <15 years and elderly subjects (age ≥65 years) were at lower risk of having a recurrent episode than young adults. Cases of extrapulmonary disease (pleural, lymph node or bone) were also significantly less likely to be re-notified than cases of pulmonary disease.

Among pulmonary, culture-confirmed pulmonary and sputum smear-positive cases who completed treatment, the incidence of re-notification was 5.5 (95% CI 4.6 to 6.6), 6.6 (95% CI 5.3 to 8.1) and 7.9 (95% CI 6.1 to 10.2) per 1000 years of follow-up, respectively.

In the analysis of cases that completed treatment, the adjusted HR was significantly lower for children (HR 0.19, 95% CI 0.05 to 0.79) and significantly higher for patients from a South Asian ethnic group (HR 1.57, 95% CI 1.01 to 2.44), those with culture-confirmed disease (HR 1.41, 95% CI 1.00 to 1.99) and those with HIV co-infection (HR 1.86, 95% CI 1.01 to 3.43). Among pulmonary cases who completed treatment, the adjusted HR remained significantly higher for patients from a South Asian ethnic group (HR 1.72, 95% CI 1.03 to 2.86) and patients with HIV co-infection (HR 2.47, 95% CI 1.27 to 4.81).

## DISCUSSION

The findings from this study estimated the overall incidence of recurrent tuberculosis in England and Wales to be 4 cases per 1000 person years of follow-up. This equates to 400 cases per 100 000 tuberculosis cases, which is much higher than the incidence of tuberculosis in the general population of England and Wales (13 cases per 100 000 in 2007). This study also found that HIV co-infection and belonging to a South Asian ethnic group were significantly associated with re-notification, including among cases who completed a full course of treatment.

A systematic review of prospective cohort studies and randomised clinical trials calculated a mean recurrence rate of 18 (95% CI 10 to 40) episodes per 1000 person years of follow-up for low incidence countries and 79 episodes per 1000 person years for high incidence countries.[11] This review only included patients with sputum-positive pulmonary tuberculosis followed at cure for 12 months. In comparison, our estimate for sputum-positive cases who completed treatment was 7.9 episodes per

**Table 3** Incidence and hazard ratios for recurrent tuberculosis, England and Wales, 1998–2005

| | | | | | Univariable | | | Multivariable (N=42 473) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Category** | **Level** | **Subjects** | **Events** | **Incidence per 1000 years** | **HR** | **95% CI** | **p Value** | **HR** | **95% CI** | **p Value** |
| All | | 42 558 | 588 | 4.1 (3.8–4.5) | – | – | – | – | – | – |
| Sex | Female | 19 387 | 274 | 4.2 (3.8–4.7) | Ref | | 0.64 | Ref | | 0.57 |
| | Male | 23 102 | 314 | 4.1 (3.6–4.5) | 0.96 | 0.82 to 1.13 | | 0.95 | 0.81 to 1.12 | |
| Age group | 0–14 | 2700 | 15 | 1.6 (1.0–2.7) | 0.33 | 0.2 to 0.56 | <0.001 | 0.37 | 0.22 to 0.62 | <0.001 |
| | 15–44 | 24 493 | 377 | 4.8 (4.4–5.4) | Ref | | | Ref | | |
| | 45–64 | 8606 | 125 | 4.2 (3.5–5.0) | 0.89 | 0.72 to 1.09 | | 0.94 | 0.76 to 1.16 | |
| | 65+ | 6742 | 71 | 2.8 (2.2–3.5) | 0.60 | 0.47 to 0.78 | | 0.66 | 0.50 to 0.86 | |
| Region | London | 18 260 | 270 | 4.5 (4.0–5.1) | Ref | | 0.07 | Ref | | 0.07 |
| | Not London | 24 298 | 318 | 3.8 (3.4–4.3) | 0.86 | 0.73 to 1.01 | | 0.85 | 0.71 to 1.01 | |
| Country of birth | UK born | 12 801 | 175 | 3.7 (3.2–4.3) | Ref | | 0.49 | – | – | – |
| | Non-UK born | 25 042 | 343 | 4.3 (3.9–4.8) | 0.90 | 0.75 to 1.08 | | – | – | – |
| | Unknown | 4715 | 70 | 4.3 (3.4–5.4) | 1.00 | 0.77 to 1.30 | | – | – | – |
| Ethnic group | White | 11 255 | 133 | 3.1 (2.6–3.7) | Ref | | 0.02 | Ref | | <0.001 |
| | Black Caribbean | 1111 | 16 | 4.2 (2.6–6.9) | 1.29 | 0.77 to 2.17 | | 1.17 | 0.69 to 1.99 | |
| | Black African | 8024 | 95 | 4.1 (3.4–5.0) | 1.20 | 0.93 to 1.57 | | 0.99 | 0.73 to 1.34 | |
| | South Asian | 15 720 | 255 | 4.8 (4.2–5.4) | 1.48 | 1.12 to 1.82 | | 1.54 | 1.23 to 1.93 | |
| | Chinese | 611 | 10 | 4.9 (2.6–9.2) | 1.52 | 0.80 to 2.90 | | 1.44 | 0.75 to 2.75 | |
| | Other | 3789 | 44 | 3.9 (2.9–5.3) | 1.16 | 0.82 to 1.63 | | 1.07 | 0.77 to 1.54 | |
| | Unknown | 2048 | 35 | 5.0 (3.6–7.0) | 1.51 | 1.04 to 2.19 | | 1.60 | 1.09 to 2.34 | |
| Site of disease | Pulmonary | 21 539 | 348 | 4.8 (4.3–5.3) | 1.24 | 1.00 to 1.55 | <0.001 | Ref | | <0.001 |
| | Pulmonary+ extrapulmonary | 2645 | 50 | 5.5 (4.2–7.3) | 1.45 | 1.04 to 2.04 | | 1.07 | 0.79 to 1.44 | |
| | Pleural | 2107 | 15 | 2.2 (1.3–3.7) | 0.57 | 0.33 to 0.98 | | 0.42 | 0.25 to 0.72 | |
| | Lymph node | 8208 | 104 | 3.9 (3.2–4.7) | Ref | | | 0.72 | 0.57 to 0.91 | |
| | Bone | 1505 | 9 | 1.8 (0.9–3.4) | 0.46 | 0.23 to 0.90 | | 0.34 | 0.17 to 0.65 | |
| | CNS | 807 | 8 | 3.0 (1.5–6.0) | 0.78 | 0.38 to 1.60 | | 0.59 | 0.29 to 1.19 | |
| | Miliary | 929 | 14 | 4.7 (2.8–7.9) | 1.2 | 0.69 to 2.10 | | 0.86 | 0.50 to 1.48 | |
| | >2 extrapulmonary sites | 1072 | 10 | 2.8 (1.5–5.3) | 0.74 | 0.38 to 1.40 | | 0.51 | 0.27 to 0.96 | |
| | Other extrapulmonary | 3746 | 30 | 2.5 (1.7–3.5) | 0.64 | 0.42 to 0.96 | | 0.48 | 0.33 to 0.70 | |
| Culture | Not positive | 17 694 | 208 | 3.4 (3.0–3.9) | Ref | | <0.001 | 0.87 | 0.72 to 1.03 | 0.11 |
| | Positive | 24 864 | 380 | 4.6 (4.2–5.1) | 1.34 | 1.12 to 1.58 | | Ref | | |
| Isoniazid* | Sensitive | 21 502 | 338 | 4.8 (4.3–5.3) | Ref | | 0.52 | - | – | – |
| | Resistant | 1328 | 17 | 4.2 (2.6–6.7) | 0.85 | 0.52 to 1.39 | | - | – | – |
| HIV | Not known +ve | 40 637 | 554 | 4.0 (3.7–4.3) | Ref | | <0.01 | Ref | | 0.01 |
| | Positive | 1921 | 34 | 7.6 (5.4–10.7) | 1.65 | 1.17 to 2.34 | | 1.64 | 1.13 to 2.38 | |

*Isolates with known susceptibility results.
Event=re-notification, South Asian, Indian, Pakistani and Bangladeshi ethnic groups.

1000 person years, just within the lower confidence interval of the estimate in the review.

A retrospective study of surveillance data and clinical records in New South Wales (NSW) Australia (annual incidence of tuberculosis 6.5 per 100 000 population) estimated a very low incidence of recurrent tuberculosis for culture-confirmed pulmonary disease at 0.7 cases per 1000 years of follow-up.[12] In comparison, our estimate for culture-confirmed pulmonary cases who completed treatment was almost 10 times higher at 6.6 per 1000 years of follow-up. The Australian study, however, only looked at patients reported cured after their initial episode and who were culture confirmed in both the initial and the recurrent episode. Furthermore, the NSW study had a longer mean follow-up (5 years), did not adjust for mortality or take into account the possible migration of patients to other parts of the country. Despite this, our estimate may also be higher because of real differences in the risk of recurrent tuberculosis in the two settings.

Tuberculosis/HIV co-infection is a recognised risk factor for recurrence of tuberculosis.[11 13] A low CD4 count is also associated with recurrence[11] and indicates late diagnosis of HIV—for example, in Black Africans[14]—and/or the absence of antiretroviral therapy. Furthermore, although 6 months is the recommended treatment duration, there is some evidence to suggest that this may be insufficient to prevent relapse.[15 16] The more common less severe extrapulmonary sites of disease have a lower risk of relapse than pulmonary cases. The latter may be a proxy marker for disease severity and are likely to include cases with disease cavitations which are thought to be harder to cure fully.[11] Children may be at lower risk than adults because of lower bacterial load and increased supervision and attention to care, as indicated by their high rates of treatment completion.[17]

Over 40% of tuberculosis cases reported in England and Wales occur in patients belonging to a South Asian ethnic group. With rates greater than 100 cases per 100 000 population, the risk of further exposure and therefore re-infection is likely to be higher within South Asian communities than in the general population, possibly explaining the observed higher risk of recurrence. Frequent travel to high incidence countries by South Asians visiting friends and relatives may also raise the risk of re-infection,[18 19] especially among longer term travellers.[20] An alternative explanation for the higher recurrence rate observed in this group may relate to the previously observed link between vitamin D deficiency and tuberculosis among South Asians in the UK.[21–24] Vitamin D deficiency reduces immunocompetence and may increase the risk of recurrent tuberculosis from re-infection or reactivation.

It is not clear, however, why other minority ethnic groups such as Black Africans who have high rates of tuberculosis[25] in England and Wales do not have an increased risk compared with the white ethnic group. One reason may be that the increase in cases and rates in Black Africans has occurred relatively recently, with insufficient numbers followed for a long enough time to give statistically significant results in this study. In comparison, communities of South Asian decent have been long established in the UK with continued and sustained levels of immigration since the 1960s and consistently high rates of tuberculosis over the last 10 years. An independent risk was also observed for an 'unknown' ethnic group. Many of these cases also had an unknown country of birth recorded, which has previously been associated with poor treatment outcome.[26]

This study used re-notification as a proxy for recurrent tuberculosis in an analysis of retrospective surveillance data. It is therefore possible that some re-notifications were 'false new episodes'. For example, enlarged lymph nodes can occur after successful treatment and be wrongly re-notified. Indeed, an increase in lymph node tuberculosis was observed between the initial and re-notified cases, and this increase was slightly higher among south Asians (results not shown). Such false positives, however, would be unlikely as there was a potential gap of at least 4 months from the end of a standard course of therapy before re-notification was possible. Furthermore, it is not clear why such a phenomenon would be specific to one ethnic group and why clinicians would not be aware of this, especially in areas with a large case load among South Asians.

The lack of mortality data prior to 2001, except for cases diagnosed at post mortem examination, will lead to an underestimate of the recurrence rate. From 2001 onwards, treatment outcome reporting collected mortality information, although this information is not complete for all cases.[27] Incomplete mortality information inflates the denominator of person years at risk by erroneously assuming a longer follow-up time for some patients. This may in part explain why the incidence appeared as high for cases completing treatment as for all cases. The estimate for cases that completed treatment is therefore likely to be more robust because of a lower subsequent risk of death compared with cases with indeterminate outcomes. Incomplete mortality information may also be the reason why elderly subjects appear to be at a significantly lower risk of recurrent tuberculosis than young adults since the former are at much greater risk of death.

The absence of strain typing information meant that this study was not able to distinguish between recurrent cases due to reactivation and those due to re-infection, or to investigate their respective risk factors. Although it would be reasonable to assume that the majority of recurrent cases in England and Wales are due to reactivation, we cannot exclude a contribution of cases caused by re-infection. The latter could be implied by the increased risk among South Asians in the cohort of cases that completed treatment. Moreover, investigations of recurrent tuberculosis in other low incident countries have yielded results ranging from 4% to 33% of re-infections among recurrent cases.[1–3 28–30]

Nevertheless, despite some limitations in using surveillance data, the results of the analysis in finding recognised risk or protective factors indicates that our methods had a good specificity for identifying recurrent cases. Furthermore, this is the first national investigation of recurrent tuberculosis in the UK and it raises some important questions for further research. Our paper also highlights the difficulty in making inter-country comparisons, and some internationally agreed definitions[30] and standards for measuring the incidence of recurrent tuberculosis would be useful.

Although the incidence appears low and reflects well on tuberculosis services in England and Wales, there remain opportunities to reduce the incidence further by targeting those most at risk. Improving the proportion of patients that fully complete treatment is one obvious starting point. For HIV-infected patients, the early diagnosis of HIV and treatment with antiretroviral therapy will reduce the likelihood of recurrent tuberculosis. Prolonging treatment for HIV co-infected cases is also an option to consider but requires expert guidance. Raising awareness about vitamin D deficiency has recently been advocated, and may also impact on the incidence of tuberculosis and its recurrence among South Asians.[31]

In conclusion, tuberculosis recurrence appears to be uncommon in England and Wales despite the absence of a universal policy of directly observed treatment. There are, however, patients who are at greater risk. The increased risk among South Asians requires further investigation. Strain typing

information on isolates is becoming more widely available and national surveillance is now collecting risk factor information on homelessness, history of incarceration, alcoholism and drug abuse. The former will be especially crucial to our understanding of recurrent tuberculosis in the UK and subsequent interventions to improve tuberculosis control.

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