

Vitamin D deficiency and tuberculosis disease phenotype

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What is the key question?

What are the factors which result in extrapulmonary tuberculosis phenotype?

What is the bottom line?

Vitamin D deficiency is strongly and independently associated with extrapulmonary tuberculosis (TB) at the time of TB diagnosis.

Why read on?

Our data provide the first evidence for vitamin D determining TB disease phenotype and help to explain the longstanding yet unexplained association of extrapulmonary TB with ethnicity and geographic origin.

Abstract

Background: Extrapulmonary tuberculosis is increasingly common yet the determinants of the wide clinical spectrum of tuberculosis are poorly understood.

Methods: We examined surveillance data (Birmingham, UK; 1980-2009, and USA CDC; 1993-2008) to identify demographic factors associated with extrapulmonary tuberculosis. We then directly tested association of these factors and serum 25-hydroxycholecalciferol (25(OH)D) concentration with extrapulmonary tuberculosis by multivariable analysis in a separate UK cohort.

Results: Data were available for 10,152 and 277,013 tuberculosis cases for Birmingham and US respectively. Local-born individuals of White ethnicity had a lower proportion of extrapulmonary disease compared to local-born Non-Whites ($p < 0.0001$); both groups had a lower proportion of extrapulmonary disease compared to foreign-born Non-Whites ($p < 0.0001$). In a separate UK cohort ($n = 462$), individuals with extrapulmonary tuberculosis had lower mean serum 25(OH)D concentration than those with pulmonary tuberculosis (11.4 nmol/L vs. 15.2 nmol/L respectively, $p = 0.0001$). On multivariable analysis, vitamin D deficiency was strongly associated with extrapulmonary tuberculosis independently of ethnicity, gender and other factors. Doubling in serum 25(OH)D concentration conferred substantially reduced risk of extrapulmonary disease (OR 0.55, 95% CI 0.41-0.73).

Conclusions: We identify vitamin D deficiency as a probable risk factor for extrapulmonary dissemination in tuberculosis which may account for the associations of dark-skinned ethnicity and female gender with extrapulmonary disease. Our findings implicate vitamin D status in *M. tuberculosis* containment *in vivo* and, given the high prevalence of deficiency, may inform development of novel tuberculosis prevention strategies.

Introduction

Although tuberculosis (TB) presents as a broad spectrum of clinical phenotypes, clinically categorised as pulmonary and extrapulmonary disease, little is known about the determinants of this clinical spectrum. Although pulmonary TB is the commonest presentation, extrapulmonary TB accounts for a large and growing proportion.^{1 2}

The most important known risk factors for extrapulmonary TB are untreated HIV infection, iatrogenic immunosuppression (especially anti-TNF-alpha therapy) and infancy.^{3 4} This association with impaired cellular immunity suggests that extrapulmonary disease in immunocompetent adults may reflect a more subtle impairment of host responses that mediate bacterial containment *in vivo*. Genetic factors associated with extrapulmonary TB include polymorphisms in vitamin D receptor (VDR),^{5 6} IL-1 β ,^{6 7} Toll-like receptor 2 (TLR2/1)⁶ and the P2X7 gene, suggesting a role for innate immunity in containment versus extrapulmonary dissemination.⁸ Pathogen-related factors may also influence disease phenotype and certain mycobacterial lineages are associated with extrapulmonary TB,⁹ although these associations have been inconsistent.^{9 10}

Recent epidemiological studies in high-income low-burden northern hemisphere countries (including the US, UK and Germany) have revealed a disproportionate incidence of extrapulmonary TB in ethnic minority populations from high-burden regions.^{1 2 11} Indeed, ethnicity appears to be strongly associated with extrapulmonary TB independently of mycobacterial lineage.¹² We postulated that a detailed international epidemiological analysis of clinical disease phenotype encompassing diverse ethnic groups and immigrants from high-burden to low-burden regions might delineate hitherto unrecognised host or environmental factors that influence extrapulmonary dissemination and clinical disease spectrum.

Methods

Study design and description of data sources

We utilised routine anonymous TB surveillance data prospectively notified in two independent high-income settings: Birmingham/Solihull, UK and US Centers for Disease Control (CDC).

Birmingham/Solihull has a population of 1.22 million¹³ and between 2007-09 (for Birmingham and Solihull respectively) the 3-year average TB notifications were 441 and 12, whilst incidence was 42 and 6 (per 100,000 population per year) respectively.¹⁴ All TB cases are recorded in a centralised chest clinic database allowing ascertainment of all notified cases since 1980.

To confirm that patterns found during the study were not purely UK-specific, we analysed data from an independent US dataset - the publicly-available US TB surveillance dataset (Online Tuberculosis Information System – OTIS; <http://wonder.cdc.gov/tb.html>) which holds aggregate data (individual level information is not publicly available) for all verified cases of active TB in the US from 1993-2008.¹⁵

Study populations and data collection

We included all cases of active TB diagnosed between January 1st 1980-December 31st 2009 (Birmingham/Solihull) and January 1st 1993-December 31st 2008 (US CDC) with complete data on age, sex, country of birth (whether local- or foreign-born), ethnicity and site of disease; patients with missing information for one or more of these variables were excluded from analysis. Further information gathered from the datasets is presented in the supplementary methods (SI Appendix).

Measurement of 25(OH)D in a separate UK TB cohort

We included all consecutively diagnosed cases of active TB recruited between November 1st 2007 and 30th June 2011 (London) and January 1st 2010 and July 10th 2012 (Leicester) (with

complete demographic and clinical data). We included those patients where, depending on the treating physician's practice, a serum 25(OH)D sample had been drawn up to 90 days prior to diagnosis or within 30 days of treatment initiation.

Definitions of patterns of tuberculous disease

Active TB cases were defined by the major sites of disease into three distinct clinical patterns: pulmonary only (only lung parenchyma involved), extrapulmonary only (only one/more extrapulmonary site(s) involved) and both pulmonary and extrapulmonary (pulmonary disease and one/more extrapulmonary sites involved concurrently). Further details of the definitions of different patterns of disease are outlined in the supplementary methods (SI Appendix).

Data analysis

Data analysis was conducted in several steps. Continuous data were summarised with median and interquartile range (IQR), and compared using the non-parametric Mann-Whitney U-test. Categorical responses were expressed as a percentage and comparisons made using Pearson's chi-square test (or Fisher's exact test if appropriate).

For the Birmingham and CDC datasets, we assessed temporal trends in extrapulmonary tuberculosis diagnosis (using χ^2 test for trend) and compared the numbers (and proportion) of cases of each disease type stratified by local/Foreign-birth and White/Non-White ethnicity (using Fisher's exact test). Univariable analysis of factors associated with extrapulmonary tuberculosis only was assessed using logistic regression and reported as crude odds ratios (OR) and 95% confidence intervals (CI). To calculate adjusted OR (and 95% CI) we mutually adjusted for: year, and season, of notification, age, gender, ethnicity, country of birth, time since arrival and HIV status (see SI Appendix for details of regression modelling).

For the London and Leicester datasets we compared individuals with pulmonary and extrapulmonary disease using a one-way analysis of variance (on the log-transformed concentrations) with Bonferroni correction, if appropriate. The proportions of subjects who were severely vitamin D deficient [serum 25(OH)D <20nmol/L] were compared between groups using Fisher's exact test. We further assessed the factors associated with extrapulmonary TB in this dataset using logistic regression and reported results as odds ratios (with 95% confidence intervals). In the multivariable model we adjusted for centre (ie. London or Leicester), year, and season, of notification, age, gender, ethnic group, location of birth, time since arrival, HIV status and serum 25(OH)D concentration. Serum 25(OH)D was used as a continuous variable transformed by \log_2 ; each unit change in \log_2 serum 25(OH)D corresponds to a doubling in serum 25(OH)D on the original scale which thereby allows a more clinically relevant, and intuitive, interpretation of the odds ratios (see SI appendix for further details of logistic regression modelling).

Details of analytical methods are presented in the supplementary methods (SI Appendix). All analyses used STATA 9.2 (StataCorp, TX). All tests were two tailed; p-values ≤ 0.05 were considered significant.

Results

Description of cohorts

Study population flow-charts for the Birmingham and US CDC cohorts are outlined in supplementary figures S1A and S1B respectively (SI Appendix).

Demographic characteristics of the Birmingham and US CDC cohort are set out in table 1. During the Birmingham study period (1980-2009) pulmonary only disease decreased by 26.1% whilst extrapulmonary only disease increased by 96.6% ($p < 0.001$); the proportion of

cases that were exclusively extrapulmonary (compared to pulmonary only) therefore increased from 31.6% to 52.9% (χ^2 for trend <0.001). During the CDC study period (between 1993-1996 and 2005-2008) overall TB notifications decreased by 43.2% but the decrease in pulmonary only cases (46.5%) was greater than for extrapulmonary only cases (27.8%). Consequently, the proportion of cases that were exclusively extrapulmonary (as compared to pulmonary only) increased from 17.8% to 22.6% (χ^2 for trend $p<0.001$).

Relationship of clinical disease phenotype with foreign-birth and ethnicity

Figure 1 outlines, for the Birmingham and US datasets, the proportion of cases that are pulmonary and extrapulmonary in different demographic groups.

Individuals of UK-born White ethnicity had a significantly lower proportion of extrapulmonary only disease (18.1%) as compared to individuals of UK-born Non-White ethnicity (34.3%)($p<0.001$) and both had a significantly lower proportion of extrapulmonary disease compared to individuals of foreign-born Non-White ethnicity (49.9%)($p<0.001$ for UK-born White and UK-born Non-White). Similarly in the US, US-born individuals of White ethnicity had a lower proportion of extrapulmonary-only disease (14.7%) compared to individuals of US-born Non-White ethnicity (18.9%)($p<0.001$) and both groups had a lower proportion of extrapulmonary disease compared to foreign-born Non-White cases (24.1%)($p<0.001$ for US-born White and US-born Non-White).

Other factors associated with extrapulmonary tuberculosis

In the UK (table 2), multivariable analysis revealed that extrapulmonary TB was associated with increasing age up to 45 yrs and female gender. In a sensitivity analysis of the UK data, including cases with concurrent pulmonary and extrapulmonary TB as extrapulmonary TB did not change

the outcomes of the multivariable analysis (data not shown). Univariable analysis of the US population (SI Appendix - table S1) revealed extrapulmonary TB was associated with increasing age up to 45 yrs, female gender, employment status, HIV status (HIV-seropositivity), no past history of TB and drug sensitive disease.

In both the UK and the US, as time between arrival and development of active TB increased, the proportion of foreign-born cases that were extrapulmonary doubled and then stabilised (from 24.9% at <1-year to 51.8% at >1-year in Birmingham and from 13.3% at <1-year to 26.8% at >1-year in the US; $p < 0.001$ for both Birmingham and the US). Interestingly, foreign-born Non-White individuals developing active TB within 12 months of arrival actually had a lower proportion of extrapulmonary TB (24.9% in Birmingham and 13.3% in the US) than local-born Non-Whites (34.4% in Birmingham and 18.9% in the US; $p = 0.001$ and $p < 0.001$ for Birmingham and US CDC respectively).

Association of serum 25(OH)D level with tuberculosis disease phenotype

Given the associations we found between disease pattern and different demographic and ethnic groups, we postulated that vitamin D deficiency may be a key factor determining clinical phenotype. We therefore tested this hypothesis in a clinically precisely-defined, ethnically diverse, cohort of 462 TB patients from London and Leicester, UK (figure S2 - SI Appendix). Demographic details of the cohort are presented in table S2 (SI Appendix). Subjects included in the vitamin D cohort were younger and less likely to have HIV co-infection than those subjects excluded from the study due to lack of vitamin D data at diagnosis but were similar in all other respects (table S2).

Overall, mean serum 25(OH)D levels in the cohort were 12.6 nmol/L (95% CI 11.8-13.5 nmol/L); 70.4% and 97.8% of the cohort had serum 25(OH)D levels <20 nmol/L and <75

nmol/L respectively. Individuals with purely extrapulmonary TB (11.4 nmol/L; 95% CI 10.5-12.5 nmol/L) and any extrapulmonary TB (11.4 nmol/L; 95% CI 10.6-12.3 nmol/L) had significantly lower serum 25(OH)D levels as compared to individuals with pulmonary TB only (15.2 nmol/L; 95% CI 13.5-17.2nmol/L) ($p<0.001$ and $p<0.001$ respectively). Severe vitamin D deficiency [serum 25(OH)D <20 nmol/L]¹⁶ was significantly more common in individuals with purely extrapulmonary TB (74.7%; $p=0.005$) and individuals with any extrapulmonary involvement (75.4%; $p=0.001$) than in subjects with purely pulmonary TB (60.9%; figure S3 - SI Appendix). Among foreign-born non-White individuals who were UK-resident for more than one year, those who presented with purely extrapulmonary (10.7 nmol/L; 95% CI 9.8-11.6 nmol/L) or any extrapulmonary TB (10.7 nmol/L; 95% CI 9.9-11.5 nmol/L) had lower mean serum 25(OH)D levels than those with purely pulmonary TB (12.7 nmol/L; 95% CI 14.7-24.5 nmol/L) ($p=0.030$ and $p=0.020$ respectively).

On multivariable analysis (table 3), a doubling in serum 25(OH)D was associated with a reduced risk of purely extrapulmonary (OR 0.55, 95% CI 0.41-0.73) and any extrapulmonary TB (OR 0.66, 95% CI 0.51-0.84). Additional factors independently associated with extrapulmonary disease included season of notification (highest in winter/spring when 25(OH)D levels are usually lowest^{16 17}), increasing age and, for the foreign-born, increasing time since arrival in the UK. Notably, whilst on univariable analysis Non-White ethnicity was associated with extrapulmonary disease, on multivariable analysis, when taking serum 25(OH)D into account, the association with ethnicity disappeared. In a further sensitivity analysis, results remained quantitatively unchanged when analyses were restricted to those individuals who had had a vitamin D level measured within 30 days of commencing anti-tuberculous therapy (either before or after).

Discussion

In two independent Northern hemisphere settings, clinical patterns of TB significantly and consistently differed by demographic and ethnic group in northern latitudes. Collectively, these findings suggest an environmental factor influencing clinical phenotype. The inter- and intra-nationally reproducible relationship of disease phenotype with foreign birth and non-white ethnicity potentially implicates vitamin D status. To directly test this possibility we analysed serum 25(OH)D concentrations in an independent UK cohort and found that vitamin D deficiency, after adjusting for ethnicity and migration, was significantly associated with extrapulmonary TB. Our data potentially implicate an environmental factor (vitamin D) other than HIV-induced or iatrogenic immunosuppression influencing TB disease phenotype. Previous studies have found associations between sun exposure,¹⁸ seasonality^{19 20} and TB incidence as well as between vitamin D deficiency and prevalence of latent²¹ and active TB⁵. However, vitamin D deficiency has not hitherto been implicated in determining clinical phenotype. Despite vitamin D's pivotal role in antimycobacterial host defence²²⁻²⁶ and the augmentation of antimycobacterial immunity with vitamin D supplementation,²⁷ the clinical effects of vitamin D deficiency in TB are unknown. We identify extrapulmonary TB as a potential clinical correlate of vitamin D deficiency.

The known associations between certain phylogenetic mycobacterial lineages and particular ethnic groups and disease sites might in theory have confounded our observations as the lineages of the infecting strains in our study populations were not known. However, in a subset of over 1,000 TB patients in the Birmingham cohort where the lineages of the infecting strains were known, non-white ethnicity was strongly and independently associated with extrapulmonary TB on multivariable analysis after taking mycobacterial lineage into account.¹² In the current study, the fact that vitamin D deficiency was associated with extrapulmonary TB independently of non-white ethnicity (which was not associated with extrapulmonary disease

after taking vitamin D status into account) suggests that vitamin D deficiency may mediate the widely-recognised association of non-white ethnicity with extrapulmonary dissemination.

Although males are more likely to present with TB per se we found that extrapulmonary TB was associated with female gender, as previously observed.^{2 11} Vitamin D deficiency is more common in women¹⁷ and, interestingly, the association of female gender with extrapulmonary TB disappeared after taking vitamin D status into account on multivariable analysis.

Although seasonality of TB incidence has previously been reported,¹⁹ this is the first study to assess TB seasonality in a population with known 25(OH)D status, enabling us to independently assess the influence of these two factors on disease phenotype. The proportion of extrapulmonary to pulmonary TB was highly seasonal, being highest in winter and spring (when 25(OH)D status is lowest in northern hemisphere residents) and lowest in the autumn (when 25(OH)D status is highest). However, after controlling for 25(OH)D status, extrapulmonary TB incidence remained independently associated with seasonality, suggesting that an additional, as yet undetermined, seasonal factor may influence clinical phenotype.

The intermediate prevalence of extrapulmonary TB in local-born Non-Whites (between UK-born Whites and foreign-born Non-Whites) is consistent with a role for vitamin D deficiency since UK-born Non-Whites have intermediate levels of 25(OH)D compared to UK-born Whites and foreign-born Non-Whites.²⁸ Interestingly, the increasing prevalence of extrapulmonary TB in the US, especially in Non-White individuals, corresponds to the increasing prevalence of vitamin D deficiency in the US over time which is also most marked in Non-White individuals.²⁹ Such changes might also explain the temporal trend in Birmingham although there may be increasing ascertainment with wider use of cross-sectional radiology.

The large sample size, independent northern latitude settings and multiple diverse ethnic groups in this study suggest that our findings are generalisable. Moreover, the size of effect for

the association between vitamin D deficiency and extrapulmonary disease is not inconsequential, being higher than, or in line with, odds ratios associated with pathogen⁹ and host genetic^{6,8} factors predisposing to extrapulmonary TB.

How vitamin D deficiency preferentially favours development of extrapulmonary TB is unclear and may depend on whether or not haematogenous spread to extrapulmonary sites occurs after primary infection. If following initial infection, *M. tuberculosis* is contained within the lungs, then vitamin D deficiency may cause T-cell immunosuppression or upregulated matrix metalloproteinase activity promoting basement membrane penetration,³⁰ resulting in impaired bacillary containment predisposing to extrathoracic dissemination and seeding. This would then increase the likelihood of extrapulmonary disease upon subsequent reactivation. Alternatively, if bacilli routinely spread haematogenously after initial pulmonary infection and are then contained by host responses in peripheral extrapulmonary sites as well as in the lung, the mechanisms of peripheral containment may be more vitamin D-dependent than those in the lung. Regardless of which model is correct, our patient-based data support a role for vitamin D in bacillary containment suggesting that the potent downstream vitamin D-dependent anti-mycobacterial macrophage effector mechanisms elucidated *in vitro* might also mediate mycobacterial containment *in vivo*.^{22 25 26}

Our work has several limitations. Data were obtained from surveillance systems limiting our analysis to routinely collected variables. HIV status was incompletely recorded in the surveillance datasets;² however, in the separate UK cohort where 25(OH)D were measured, HIV status was known for most patients. Given the US CDC aggregate data, regression modelling was univariable rather than multivariable. In the vitamin D cohort not all patients had vitamin D levels checked or checked in the eligible time-period and it is possible that physicians only selected specific patients for testing meaning that we could not completely exclude the possibility of selection bias. We did not have data on possible use of vitamin D supplements.

Also, it is possible that serum 25(OH)D concentrations may have been affected by anti-tuberculous treatment in those individuals who had already commenced treatment but any such effect was mitigated by including only patients whose levels were measured within 30 days of treatment initiation. In any event, both these latter factors would have affected all TB phenotypes equally, not specifically extrapulmonary TB. It is possible that the extrapulmonary phenotype was related to some other unmeasured factor (such as socio-economic or nutritional status) which was in turn correlated both with ethnicity and vitamin D status. Furthermore it is possible, although unproven, that patients with extrapulmonary TB might behave differently to patients with pulmonary TB (for example spending more time indoors) consequently resulting in lower vitamin D levels.

Our classification of TB disease was based on exclusively pulmonary or extrapulmonary involvement. Since extrapulmonary disease is more likely to be culture-negative it might theoretically have been clinically over-diagnosed in certain demographic groups. However, this is unlikely as our findings were based on complete surveillance datasets and were unaffected by changes in classification of extrapulmonary TB (where extrapulmonary was defined as pulmonary plus extrapulmonary) and by limiting analysis to culture-positive cases only.

Whilst vitamin D deficiency appears to be a risk factor for extrapulmonary TB, our findings do not confirm causality. It is theoretically possible that deficiency is a consequence of unrelated immunological changes that predispose to extrapulmonary TB or instead caused by an extrapulmonary disease phenotype or dissemination (ie reverse causality). If vitamin D deficiency does play a causal role, the implications for international public health, particularly migrant health, as well as for mechanisms of *in vivo* containment of *M. tuberculosis* could be considerable.

Conflict of Interest Statement

AL is Non-Executive Director of a nutraceutical company several of whose products contain vitamin D.

MP, JI, SS, LG, DC, GW, MW, ARM, OMK and MD declare that they have no conflict of interest.

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Ethical Approval

No patient-specific data or personal identifiers were used in the preparation of this report which was an analysis of routinely-collected clinical service data.

Contributors

AL, MP and SS conceived of the idea for the study. JI, MD, MJW and GW collected the clinical data as part of routine care. LG extracted data for the London cohort. MP undertook the data analysis. MP and AL wrote the first draft of the manuscript with subsequent revisions made by all other co-authors. All co-authors had sight of the submitted paper. AL is guarantor for the paper.

Tables

Table 1. Demographic characteristics of individuals with active tuberculosis in the Birmingham and US CDC datasets

Variable	Birmingham (n=10,152)	Variable	CDC USA (n=277013)
Age (median, interquartile range)	35.0 (23.0-55.0)		
Age categories		Age categories	
Under 16	1264 (12.5%)	Under 5	10217 (3.7%)
16-25	1960 (19.3%)	5-14	7123 (2.6%)
26-35	1990 (19.6%)	15-24	25534 (9.2%)
36-45	1358 (13.4%)	25-44	97349 (35.1%)
46-55	1101 (10.6%)	45-64	76262 (27.5%)
over 55	2479 (24.4%)	>64	60528 (21.9%)
Gender		Gender	
Female	4902 (48.3%)	Male	173621 (62.7%)
Male	5250 (51.7%)	Female	103392 (37.3%)
Ethnicity		Ethnicity	
White	1991 (19.6%)	American Indian or Alaska Native	3532 (1.3%)
Indian Subcontinent	6233 (61.4%)	Asian or Pacific Islander	56962 (20.6%)
Afro-Caribbean	1484 (14.6%)	Black or African American	86697 (31.3%)
Oriental/Other Asia	220 (2.2%)	Hispanic or Latino	66934 (24.2%)
Other	224 (2.2%)	White, Non-Hispanic	62888 (22.7%)
Place of birth		Place of birth	
United Kingdom	3612 (35.6%)	United States of America	153598 (55.4%)
Foreign-born	6540 (64.4%)	Foreign-born	123415 (44.6%)
Time since entry to the UK (years)¹		Time since entry to the US (years)⁷	
<1	331 (5.7%)	< 1 year	23897 (23.7%)
1 - 5	1943 (33.3%)	1-4 years	24990 (24.8%)
6-10	818 (14.0%)	5-14 years	27467 (27.3%)
>10	2740 (47.0%)	15+ years	24280 (24.1%)
Employment status²		Employment status⁸	
Unemployed	447 (11.4%)	Unemployed	144308 (59.0%)
Retired	334 (8.5%)	Employed	100345 (41.0%)
Employed/housewife	1670 (42.4%)		
Student/child	1486 (37.7%)		
HIV status³		HIV status⁹	
Negative	171 (88.6%)	Negative	101606 (77.9%)
Positive	22 (11.4%)	Positive	28836 (22.1%)
Previous TB⁴		Previous TB¹⁰	
No	4777 (95.3%)	No	260527 (94.8%)
Yes	236 (4.7%)	Yes	14350 (5.2%)
Type of disease		Type of disease	
Pulmonary only	5590 (55.1%)	Pulmonary only	203449 (73.4%)
Pulmonary and extrapulmonary	763 (7.5%)	Pulmonary and extrapulmonary	21524 (7.8%)
Extrapulmonary only	3799 (37.4%)	Extrapulmonary only	52040 (18.8%)
Site of extrapulmonary disease			
Intrathoracic lymph node	525 (11.5%)		
Extrathoracic lymph node	1907 (41.8%)		
Bone and joint	461 (10.1%)		
Central nervous system	169 (3.7%)		
Pleura	505 (11.7%)		
Peritoneum	108 (2.4%)		
Genitourinary	180 (4.0%)		
Intestinal	212 (4.7%)		
Miliary	198 (4.3%)		
Pericardial	51 (1.1%)		
Soft tissue	101 (2.2%)		
Other	538 (11.8%)		
Culture positive⁵		Culture positive¹¹	
No	5398 (53.2%)	No	56072 (20.2%)
Yes	4754 (46.8%)	Yes	220941 (79.8%)
Drug sensitivity⁶		Drug sensitivity¹²	
Fully sensitive	1634 (91.8%)	Not multi-drug resistant	206274 (98.5%)
Mono-drug resistant	116 (6.5%)	Multi-drug resistant	3154 (1.5%)
Multi-drug resistant	30 (1.7%)		

Resident in correctional facility¹³

No	264422 (96.3%)
Yes	10237 (3.7%)

Footnotes

¹Only applies to foreign-born individuals; data available for 5832 individuals

²Data available for 3937 individuals

³Data available for 193 individuals

⁴Data available for 5013 individuals

⁵Culture positive for 3134/5590 (56.1%) pulmonary only cases, 1246/2553 (32.8%) extrapulmonary only cases and 374/763 (49.0%) pulmonary and extrapulmonary cases

⁶Data available for 1780 individuals

⁷Only applies to foreign-born individuals; unknown for 22781

⁸Unknown for 32360

⁹Unknown for 146571

¹⁰Unknown for 2136

¹¹Culture positive for 165319/203449 (81.3%) pulmonary only cases, 36994/52040 (71.1%) extrapulmonary only cases and 18628/21524 (86.5%) pulmonary and extrapulmonary cases

¹²Only relevant to culture positive cases; unknown for 11513

¹³Unknown for 2354

Table 2. Demographic, clinical and temporal variables associated with different patterns of tuberculosis for Birmingham dataset

Whole cohort (n=9389) ¹					Non-White ethnic groups (n=7478) ¹				
Variable	Extrapulmonary TB only ¹ (n=3799)	Unadjusted OR (95% CI)	Adjusted OR ² (95% CI)	p-value	Variable	Extrapulmonary TB only ¹ (n=3460)	Unadjusted OR (95% CI)	Adjusted OR ³ (95% CI)	p-value
Period					Period				<0.001
1980-1984	568/1798 (31.6)	1	1	<0.001	1980-1984	487/1291 (37.7)	1	1	
1985-1989	487/1345 (36.2)	1.23 (1.06-1.43)	1.24 (1.06-1.46)		1985-1989	426/1005 (42.4)	1.21 (1.03-1.44)	1.28 (1.08-1.53)	
1990-1994	494/1471 (33.6)	1.09 (0.95-1.27)	1.09 (0.94-1.28)		1990-1994	431/1120 (38.5)	1.03 (0.88-1.22)	1.09 (0.92-1.3)	
1995-1999	475/1242 (38.2)	1.34 (1.15-1.56)	1.28 (1.09-1.50)		1995-1999	444/1001 (44.4)	1.32 (1.11-1.56)	1.41 (1.18-1.68)	
2000-2004	755/1604 (47.1)	1.93 (1.67-2.21)	1.85 (1.60-2.15)		2000-2004	696/1348 (51.6)	1.76 (1.51-2.06)	1.96 (1.67-2.31)	
2005-2009	1020/1929 (52.9)	2.43 (2.13-2.78)	2.24 (1.94-2.59)		2005-2009	976/1713 (57.0)	2.19 (1.89-2.53)	2.34 (2.01-2.74)	
Season					Season				
Winter	818/2118 (38.6)	1	1	0.370	Winter	732/1661 (44.1)	1	1	0.170
Spring	956/2404 (39.8)	1.05 (0.93-1.18)	0.99 (0.87-1.12)		Spring	876/1908 (45.9)	1.08 (0.94-1.23)	1.01 (0.88-1.16)	
Summer	1062/2581 (41.2)	1.11 (0.99-1.25)	1.04 (0.92-1.18)		Summer	979/2075 (47.2)	1.13 (1.00-1.29)	1.11 (0.97-1.27)	
Autumn	963/2286 (42.1)	1.16 (1.03-1.31)	1.09 (0.96-1.24)		Autumn	873/1834 (47.6)	1.15 (1.01-1.32)	1.14 (0.99-1.31)	
Age categories					Age categories				
Under 16	383/1167 (32.8)	1	1	<0.001	Under 16	334/958 (34.9)	1	1	<0.001
16-25	652/1828 (35.7)	1.13 (0.97-1.33)	0.80 (0.68-0.94)		16-25	634/1678 (37.8)	1.13 (0.96-1.34)	0.86 (0.72-1.03)	
26-35	923/1840 (50.2)	2.06 (1.77-2.40)	1.34 (1.13-1.60)		26-35	889/1651 (53.8)	2.18 (1.85-2.57)	1.42 (1.18-1.72)	
36-45	623/1240 (50.2)	2.07 (1.75-2.44)	1.49 (1.23-1.80)		36-45	579/999 (58.0)	2.58 (2.15-3.09)	1.70 (1.37-2.10)	
46-55	468/1022 (45.8)	1.73 (1.45-2.06)	1.31 (1.07-1.60)		46-55	419/770 (54.4)	2.23 (1.84-2.71)	1.47 (1.17-1.85)	
Over 55	750/2292 (32.7)	1.00 (0.86-1.16)	0.81 (0.68-0.98)		Over 55	605/1422 (42.5)	1.38 (1.17-1.64)	0.83 (0.67-1.03)	
Gender					Gender				
Male	1716/4831 (35.5)	1	1	<0.001	Male	1541/3622 (42.6)	1	1	<0.001
Female	2083/4558 (45.7)	1.53 (1.41-1.66)	1.43 (1.31-1.56)		Female	1919/3856 (46.0)	1.34 (1.22-1.47)	1.37 (1.24-1.50)	
Country of birth/Ethnicity					Country of birth/time since entry				
UK-born White	301/1663 (18.1)	1	1	<0.001	UK-born	598/1741 (34.3)	1	1	<0.001
UK-born Indian Subcontinent	421/1180 (35.7)	2.51 (2.11-2.98)	2.29 (1.89-2.78)		Foreign-born/<1 year	77/309 (24.9)	0.63 (0.48-0.84)	0.61 (0.45-0.81)	
UK-born Afro-Caribbean	156/505 (30.9)	2.02 (1.61-2.54)	1.81 (1.43-2.30)		Foreign-born/1-5 years	931/1763 (52.8)	2.14 (1.87-2.45)	1.87 (1.61-2.18)	
UK-born Oriental/Other Asia	3/13 (23.1)	1.36 (0.37-4.96)	1.10 (0.30-4.10)		Foreign-born/6-10 years	405/733 (55.3)	2.36 (1.98-2.81)	1.98 (1.63-2.42)	
UK-born Other	18/43 (41.9)	3.26 (1.76-6.05)	2.91 (1.54-5.50)		Foreign-born/>10 years	1169/2340 (50.0)	1.91 (1.68-2.17)	1.64 (1.39-1.94)	
Foreign-born White	38/248 (15.3)	0.82 (0.57-1.18)	0.94 (0.65-1.36)		Foreign-born/time not known	280/592 (47.3)	1.72 (1.42-2.07)	1.67 (1.34-2.07)	
Foreign-born Indian Subcontinent	2308/4544 (50.8)	4.67 (4.07-5.36)	4.10 (3.56-4.73)						
Foreign-born Afro-Caribbean	390/836 (46.7)	3.96 (3.29-4.76)	2.78 (2.29-3.38)						
Foreign-born Oriental/Other Asia	80/194 (41.2)	3.18 (2.32-4.34)	2.78 (2.01-3.83)						
Foreign-born Other	84/163 (51.5)	4.81 (3.45-6.70)	3.82 (2.72-5.37)						

				Ethnicity⁴				
				Indian Subcontinent	2729/5724 (47.7)	1	1	<0.001
				Afro-Caribbean	546/1341 (40.7)	0.75 (0.67-0.85)	0.69 (0.60-0.78)	
				Oriental/Other Asia/Other	185/413 (44.8)	0.89 (0.73-1.09)	0.83 (0.67-1.02)	
Employment status				Employment status				
Unemployed	167/401 (41.6)	1		Unemployed	161/325 (49.5)	1		
Retired	106/292 (36.3)	0.80 (0.59-1.09)		Retired	86/210 (41.0)	0.71 (0.50-1.00)		
Employed/housewife	819/1528 (53.6)	1.62 (1.30-2.02)		Employed/housewife	795/1393 (57.1)	1.35 (1.06-1.72)		
Student/child	459/1365 (33.6)	0.71 (0.57-0.89)		Student/child	410/1149 (35.7)	0.57 (0.44-0.72)		
Previous TB				Previous TB				
No	2092/4321 (48.4)	1		No	1971/3700 (53.3)	1		
Yes	81/215 (37.7)	0.64 (0.49-0.85)		Yes	76/181 (42.0)	0.63 (0.47-0.86)		
HIV status				HIV status				
Negative/Unknown	3793/9375 (40.5)	1	1	Negative/Unknown	3454/7464 (46.3)	1	1	0.230
Positive	6/14 (42.9)	1.10 (0.38-3.18)	0.54 (0.18-1.59)	Positive	6/14 (42.9)	0.87 (0.30-2.51)	0.51 (0.17-1.52)	
Drug sensitivity				Drug sensitivity				
Fully sensitive	585/1452 (40.3)	1		Fully sensitive	566/1244 (45.5)	1		
Mono-resistant	44/110 (40.0)	0.99 (0.67-1.47)		Mono-resistant	44/100 (44.0)	0.94 (0.62-1.42)		
Multi-drug resistant	7/26 (26.9)	0.55 (0.23-1.31)		Multi-drug resistant	7/19 (36.8)	0.70 (0.27-1.79)		

Footnotes

¹Comparison of extrapulmonary TB cases only versus pulmonary TB only (concurrent pulmonary-extrapulmonary cases excluded)

²Models mutually adjusted for year of notification, season of notification, age, gender, country of birth, ethnicity and HIV status

³Model mutually adjusted for year of notification, season of notification, age, gender, country of birth, time since arrival, ethnicity and HIV status

⁴For the model restricted to non-White individuals, due to small numbers of individuals in the Other category we collapsed together Oriental/Other Asian with the Other category

Table 3. Demographic, clinical and temporal variables associated with different patterns of tuberculosis for the London and Leicester (vitamin D) cohort (n=462)

Variable	Extrapulmonary TB only ¹ (n=217)	Unadjusted OR (95% CI)	Adjusted OR ² (95% CI)	p-value	Variable	Any extrapulmonary involvement (n=301)	Unadjusted OR (95% CI)	Adjusted OR ³ (95% CI)	p-value
Centre					Centre				
London	63/102 (61.8)	1	1	0.050	London	82/121 (67.8)	1	1	0.140
Leicester	154/276 (55.8)	0.78 (0.49-1.24)	0.42 (0.18-0.99)		Leicester	219/341 (64.2)	0.85 (0.55-1.33)	0.54 (0.24-1.21)	
Period of notification					Period of notification				
2007-2009	37/64 (57.8)	1	1	0.590	2007-2009	48/75 (64.0)	1	1	0.600
2010-2012	180/314 (57.3)	0.98 (0.57-1.69)	1.31 (0.49-3.51)		2010-2012	253/387 (65.4)	1.06 (0.63-1.78)	1.28 (0.51-3.24)	
Season					Season				
Winter	51/82 (62.3)	1	1	<0.001	Winter	72/103 (69.9)	1	1	0.003
Spring	76/124 (61.3)	0.96 (0.54-1.71)	0.88 (0.44-1.75)		Spring	104/152 (68.4)	0.93 (0.54-1.60)	0.81 (0.43-1.52)	
Summer	68/115 (59.1)	0.88 (0.49-1.57)	1.11 (0.55-2.25)		Summer	94/141 (66.7)	0.86 (0.50-1.49)	1.00 (0.52-1.93)	
Autumn	22/57 (38.6)	0.38 (0.19-0.77)	0.24 (0.10-0.55)		Autumn	31/65 (47.0)	0.38 (0.20-0.72)	0.30 (0.14-0.62)	
Age categories n (%)					Age categories n (%)				
16-25	32/79 (40.5)	1	1	0.005	16-25	54/101 (53.5)	1	1	0.040
26-35	64/115 (55.7)	1.84 (1.03-3.29)	1.90 (0.95-3.78)		26-35	93/144 (64.6)	1.59 (0.94-2.67)	1.53 (0.83-2.81)	
36-45	54/77 (70.1)	3.44 (1.77-6.69)	4.28 (1.87-9.81)		36-45	64/87 (73.6)	2.42 (1.31-4.49)	2.81 (1.32-5.99)	
46-55	31/50 (62.0)	2.40 (1.16-4.96)	4.08 (1.59-10.47)		46-55	44/63 (69.8)	2.02 (1.04-3.92)	2.64 (1.14-6.08)	
Over 55	36/57 (63.2)	2.52 (1.25-5.08)	4.14 (1.56-11.02)		Over 55	46/67 (68.7)	1.91 (0.99-3.64)	3.06 (1.26-7.43)	
Gender					Gender				
Male	110/208 (52.9)	1	1	0.063	Male	165/263 (62.7)	1	1	0.160
Female	107/170 (62.9)	1.51 (1.00-2.29)	1.62 (0.97-2.69)		Female	136/199 (68.3)	1.28 (0.87-1.89)	1.40 (0.88-2.24)	
Country of birth/time since entry					Country of birth/time since entry				
UK-born	21/62 (33.9)	1	1	0.003	UK-born	24/65 (36.9)	1	1	0.001
Foreign-born/<1 year	4/13 (30.8)	0.87 (0.24-3.15)	0.88 (0.19-4.13)		Foreign-born/<1 year	5/14 (35.7)	0.95 (0.28-3.16)	0.68 (0.15-2.95)	
Foreign-born/1-5 years	59/101 (58.4)	2.74 (1.42-5.30)	2.71 (1.19-6.14)		Foreign-born/1-5 years	99/141 (70.2)	4.03 (2.17-7.48)	3.75 (1.77-7.95)	
Foreign-born/6-10 years	50/71 (66.3)	4.65 (2.23-9.67)	4.76 (1.95-11.64)		Foreign-born/6-10 years	58/79 (73.4)	4.72 (2.32-9.59)	4.07 (1.75-9.45)	
Foreign-born/>10 years	73/107 (68.2)	4.19 (2.16-8.15)	2.42 (1.04-5.66)		Foreign-born/>10 years	99/133 (74.4)	4.97 (2.63-9.40)	2.84 (1.28-6.30)	
Foreign-born/time not known	3/11 (27.3)	0.73 (0.18-3.05)	0.51 (0.11-2.90)		Foreign-born/time not known	8/16 (50.0)	1.71 (0.57-5.14)	1.53 (0.43-5.46)	

Ethnicity					Ethnicity				
White	18/51 (35.3)	1	1	0.650	White	19/52 (36.5)	1	1	0.170
Indian Subcontinent	136/224 (60.7)	2.83 (1.50-5.34)	1.53 (0.64-3.67)		Indian Subcontinent	188/276 (68.1)	3.71 (2.00-6.89)	2.21 (0.97-5.02)	
Afro-Caribbean	33/52 (63.5)	3.18 (1.42-7.12)	1.43 (0.51-4.02)		Afro-Caribbean	46/65 (70.8)	4.20 (1.93-9.15)	1.99 (0.76-5.22)	
Oriental/Other Asia/Other	30/51 (58.8)	2.62 (1.18-5.83)	1.94 (0.69-5.39)		Oriental/Other Asia/Other	48/69 (69.6)	3.97 (1.85-8.51)	2.88 (1.11-7.45)	
Vitamin D status					Vitamin D				
25(OH)D level (log ₂ nmol/L) ⁴		0.68 (0.55-0.83)	0.55 (0.41-0.73)	<0.001	Vitamin D level (log ₂ nmol/L)		0.68 (0.56-0.82)	0.66 (0.51-0.84)	0.001
HIV status					HIV status				
Negative	198/354 (55.9)	1	1	0.350	Negative	274/430 (63.7)	1	1	0.520
Positive	5/7 (71.4)	1.97 (0.38-10.29)	2.59 (0.36-18.69)		Positive	6/8 (75.0)	1.71 (0.34-8.56)	1.87 (0.28-12.74)	

Footnotes

¹Comparison of extrapulmonary TB cases only versus pulmonary TB only (concurrent pulmonary-extrapulmonary cases excluded)

²Models mutually adjusted for period of notification, season of notification, age, gender, country of birth/time since entry, ethnicity, 25(OH)D level and HIV status

³Models mutually adjusted for period of notification, season of notification, age, gender, country of birth/time since entry, ethnicity, 25(OH)D level and HIV status

⁴Refers to the odds ratio associated with an increase in continuous log-transformed 25(OH)D levels by log 2 (which corresponds to a doubling in 25(OH)D levels)

Figure

Figure 1. Patterns of tuberculosis stratified by location of birth (local or foreign) and ethnic group (White versus Non-White) for Birmingham and US CDC datasets

Footnotes

¹Proportions are calculated on purely pulmonary and extrapulmonary cases only (i.e. concurrent pulmonary and extrapulmonary cases are excluded for the purposes of this figure)

²For the Birmingham dataset concurrent pulmonary and extrapulmonary case numbers (and proportions) were: local-born white 72 (4.1%), local-born non-white 136 (7.2%) and foreign-born non-white 547 (8.7%)

³For the US CDC dataset concurrent pulmonary and extrapulmonary case numbers (and proportions) were: local-born white 3075 (5.6%), local-born non-white 8939 (9.1%) and foreign-born non-white 9009 (7.8%)

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