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Explaining risk factors for drug-resistant tuberculosis in England and Wales: contribution of primary and secondary drug resistance

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SUMMARY

Drug-resistant tuberculosis can be transmitted (primary) or develop during the course of treatment (secondary). We investigated risk factors for each type of resistance. We compared all patients in England and Wales with isoniazid- and multidrug-resistant tuberculosis in two time-periods (1993–1994 and 1998–2000) with patients with fully sensitive tuberculosis, examining separately patients without and with previous tuberculosis (a proxy for primary and secondary drug-resistant tuberculosis). Patients with previous tuberculosis smear positivity and arrival in the United Kingdom <5 years were strongly associated with multidrug resistance and isoniazid resistance. In patients with no previous tuberculosis HIV infection, residence in London and foreign birth were risk factors for multidrug resistance, and non-white ethnicity, residence in London and HIV infection for isoniazid resistance. Risk factors for each type of resistance differ. Elevated risks associated with London residence, HIV positivity, and ethnicity were mainly seen in those without previous tuberculosis (presumed transmission).

INTRODUCTION

Drug-resistant tuberculosis is a threat to tuberculosis control worldwide [1]. In England and Wales multidrug resistant isolates (resistant to at least isoniazid and rifampicin) have remained uncommon with >2% of isolates multidrug resistant [2, 3]. However, these cases are important because they are difficult to treat and consume valuable health resources [4]. Approximately 6% of isolates in England and Wales are isoniazid resistant [2, 3].

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It is important to distinguish between drug resistance due to treatment failure (acquired or secondary resistance) and drug resistance due to transmission of resistant strains (initial or primary resistance). Most (but not all) patients who have drug-resistant disease and have been treated for tuberculosis in the past have acquired resistance as a result of inadequate treatment; conversely most patients with resistant strains at the beginning of treatment who have no prior history of tuberculosis treatment have primary resistance as a result of transmission of a resistant strain. Risk factors for the two pathways to drug-resistant tuberculosis are likely to differ.

Internationally, studies have consistently found resistance to be strongly related to previous treatment [5, 6]. HIV has been found to be a risk factor

for resistance in the United States [5, 7–9] but not in Africa [10]. Some studies have found resistance to be associated with cavitatory pulmonary disease [11], and most studies from developed countries (particularly the United States) have found relationships with ethnic groupings [5, 7], foreign birth [7, 12–14] and urban centres [13]. In the United Kingdom surveillance data from England and Wales have generally shown an excess of drug-resistant cases in London, in HIV-positive cases, those not born in the United Kingdom and sometimes in non-white ethnic groups [2, 3, 15].

We aimed to investigate the previously found associations in the United Kingdom between ethnic groups, foreign born, HIV infected, London residents and drug-resistant tuberculosis by stratifying tuberculosis patients by a previously recorded episode of tuberculosis as a proxy for primary (transmitted) and secondary (through treatment) pathways to drug resistance. To maximize power, and investigate any differences in risk factors over time, we combined data for two periods with linked laboratory and surveillance data: 1993–1994 and 1998–2000.

METHODS

During 1993–1994 a national surveillance scheme for drug sensitivity results was established (Mycobnet) [16]. In 1995 clinicians were asked to provide more detailed risk factor information on all drug-resistant cases and a random sample of age-matched (<40 years, $\geqslant 40$ years) fully sensitive controls identified through the 1993 National Tuberculosis Survey (NTS) and Mycobnet. Since the 1998 NTS [17] a system of enhanced tuberculosis surveillance has operated with routine linking to Mycobnet. For this analysis tuberculosis patients with isolate information for 1993–1994 were identified from the 1993 NTS, the newly established Mycobnet laboratory surveillance system and the 1995 questionnaire. Tuberculosis patients with isolate information for 1998–2000 were identified from enhanced tuberculosis surveillance for England and Wales and Mycobnet. Resistance was determined using the resistance ratio method on Lowenstein–Jensen media or modified proportion method on liquid media (Bactec 460; Becton Dickinson, Sparks, MD, USA) [18, 19]. To optimize information available for analysis of risk factors and to remove possible duplicate information (from multiple isolates on the same individual), isolates in Mycobnet for which there was no corresponding surveillance record were deleted. Where there was more than one isolate available for an individual the first was used. HIV status for both 1993–1994 data and 1998–2000 data was ascertained by matching with the Public Health Laboratory Service HIV and AIDS register using Soundex codes and dates of birth. At analysis subjects with no recorded HIV status were classified as HIV negative, subjects with no recorded history of tuberculosis were classified as 'no previous tuberculosis', and subjects with no smear result recorded were assumed to be smear negative. World region of origin was examined using World Bank/Global Burden of Disease categorizations [20].

Risk factors for multidrug-resistant tuberculosis and isolated isoniazid resistance were first examined in a univariate analysis (controlling for the stratum matching for age for 1993–1994). Risk factors were then examined by multiple logistic regression to control for other confounding variables. In both univariate and multivariate analysis comparisons were between isolated isoniazid resistance (resistance to isoniazid without resistance to rifampicin, pyrazinamide or ethambutol) and fully sensitive tuberculosis (sensitive to isoniazid, rifampicin, pyrazinamide and ethambutol) and between multidrug-resistant tuberculosis (resistance to at least isoniazid and rifampicin) and fully sensitive tuberculosis (as above). Individuals with other resistance patterns were excluded from analysis. Final multivariate models were selected by backward elimination of variables from full models. An age term was fitted in all models to allow valid comparison between age-frequency matched and non-matched data from the two time-periods. Time-period interaction terms were fitted to examine differences in effects in the two time-periods for the following variables: sex, HIV infection, foreign birth, ethnicity and London residence. To allow comparison of the importance of potential risk factors for drug resistance in the four analyses (multidrug or isolated isoniazid resistance, and primary or acquired resistance) factors that were statistically significant in at least one model are included in all the multivariate models presented. All analyses were performed in STATA version 7.0 [21].

RESULTS

In total there were 9541 subjects with either multidrug-resistant, isolated isoniazid-resistant or fully sensitive initial isolates included in the analysis.

Thirty patients were excluded from analysis because of another resistance pattern (mostly isolated rifampicin resistance). From the 1993–1994 period there were 615 subjects: 56 with multidrug resistance, 248 with isolated isoniazid resistance and 311 age-matched controls with fully sensitive isolates. From the 1998–2000 period there were 8926 subjects: 84 with multidrug resistance, 453 with isolated isoniazid resistance and 8389 with fully sensitive isolates. Overall 693 (7·3%) were recorded as having had tuberculosis previously. In the unmatched prevalent data from 1998–2000 the proportion of previous tuberculosis patients with multidrug resistance was 4·9% and with isolated isoniazid resistance 4·7%. In patients with no previous tuberculosis the proportion with multidrug resistance was 0·7% and with isolated isoniazid resistance 5·1%.

Univariate associations

There was a strong association between previous treatment and multidrug resistance (OR 9·1, 95% CI 6·3–13·2). This overall relationship was weaker for isolated isoniazid resistance (OR 1·6, 95% CI 1·2–2·1).

Risk factors for isolated isoniazid-resistant tuberculosis compared with fully sensitive tuberculosis for subjects with previous tuberculosis and with no previous tuberculosis are given in Table 1. Risk factors for multidrug-resistant tuberculosis compared with fully sensitive tuberculosis for subjects with previous tuberculosis and with no previous tuberculosis are given in Table 2.

Multivariate analysis

Risk factors for multidrug-resistant tuberculosis and isoniazid-resistant tuberculosis did not vary greatly by individual World Bank region, and numbers in some regions were small (or zero) so we took forward to multivariate analysis a variable measuring length of time since arrival in the country with a base category of born in the United Kingdom rather than region of origin.

Risk factors for isoniazid-resistant tuberculosis

Risk factors for isoniazid resistance in patients with previous tuberculosis and no previous tuberculosis are presented in Table 3.

No previous tuberculosis

In patients with no history of tuberculosis the most important risk factor for isoniazid resistance was ethnicity. Compared with the white ethnic group adjusted odds ratios were similar in ethnic groups from the Indian sub-continent (OR 1·6, 95% CI 1·2–2·1), Black Africans (OR 1·7, 95% CI 1·2–2·4) and other non-white ethnic groups combined (OR 1·9, 95% CI 1·3–2·8). London residence was also associated (OR 1·4, 95% CI 1·1–1·7). There was interaction between time-period and HIV infection ($P = 0{\cdot}026$). HIV infection was a significant risk factor (OR 2·4, 95% CI 1·1–5·2) in 1993–1994 but not in 1998–2000 (OR 1·0, 95% CI 0·6–1·6).

Previous tuberculosis

Smear-positive status was the most important risk factor for isoniazid-resistant disease in subjects with a history of tuberculosis (OR 3·2, 95% CI 1·1–9·2). Those of non-UK origin arriving in the last 10 years were at increased risk of isoniazid resistance compared with those born in the United Kingdom (OR 3·2, 95% CI 1·4–7·0) and this was particularly marked for those arriving in the United Kingdom 5–9 years prior to diagnosis (OR 5·3, 95% CI 1·2–23·5). There was a non-significant association between London residence and isoniazid resistance. Other variables such as HIV status, ethnicity and gender were not predictors of isoniazid drug resistance.

Risk factors for multidrug resistance

Risk factors for multidrug resistant tuberculosis in patients with previous tuberculosis and no previous tuberculosis are presented in Table 4.

No previous tuberculosis

Important risk factors for multidrug resistance in subjects without a history of previous tuberculosis included being HIV positive (OR 2·5, 95% CI 1·2–5·2), and London residence (OR 2·0, 95% CI 1·2–3·3). Non-UK origin was also important with the risk of multidrug-resistant disease higher for those arriving in the last 5 years (OR 3·2, 95% CI 1·4–7·3) and decreasing with duration of residence in the United Kingdom. There were no significant associations between multidrug resistance and ethnicity, gender and smear-positive disease. There was strong interaction between time-period and foreign birth

Table 1. *Risk factors for isolated isoniazid drug-resistant tuberculosis 1993–1994 and 1998–2000 by previous tuberculosis: univariate analysis*

	Previous tuberculosis			No previous tuberculosis		
Risk factor	Isoniazid resistance ($N=63$) n (n/N%)*	Fully sensitive ($N=576$) N (n/N%)	OR† (95% CI)	Isoniazid resistance ($N=638$) n (n/N%)	Fully sensitive ($N=8124$) n (n/N%)	OR† (95% CI)
Age group‡						
0–19 years	0 (0)	37 (7)	0·0	44 (10)	604 (8)	1·0 (0·7–1·4)
20–39 years	12 (44)	181 (33)	1·0 (ref.)	244 (57)	3464 (44)	1·0 (ref.)
40–59 years	5 (19)	129 (24)	0·5 (0·2–1·7)	99 (23)	1832 (23)	0·8 (0·6–1·0)
60–79 years	9 (33)	161 (29)	0·8 (0·3–2·0)	29 (7)	1549 (20)	0·3 (0·2–0·4)
⩾80 years	1 (4)	39 (7)	0·4 (0·0–3·1)	10 (2)	390 (5)	0·4 (0·2–0·7)
Sex						
Male	32 (51)	323 (56)	0·8 (0·5–1·4)	368 (58)	4587 (57)	1·1 (0·9–1·3)
Female	31 (49)	253 (44)		268 (42)	3519 (43)	
Site						
Pulmonary	37 (62)	444 (77)	0·5 (0·3–0·8)	376 (62)	5345 (66)	0·8 (0·7–1·0)
Extrapulmonary	23 (38)	129 (23)		231 (38)	2726 (34)	
HIV status						
Positive	3 (5)	15 (3)	1·6 (0·4–6·0)	39 (6)	264 (3)	1·7 (1·2–2·4)
Negative (or unrecorded)	60 (95)	561 (97)		599 (94)	7860 (97)	
London						
Resident	33 (52)	191 (33)	2·2 (1·3–3·9)	336 (53)	3227 (40)	1·5 (1·3–1·8)
Non-resident	30 (48)	385 (67)		296 (47)	4889 (60)	
Smear status						
Positive	27 (43)	249 (43)	1·0 (0·6–1·7)	209 (33)	2730 (34)	1·0 (0·8–1·2)
Negative or unrecorded	36 (57)	327 (57)		429 (67)	5394 (66)	
Ethnic group						
White	21 (33)	248 (44)	1·0 (ref.)	133 (22)	2673 (34)	1·0 (ref.)
Indian sub-continent	24 (38)	215 (38)	1·4 (0·7–2·7)	239 (40)	2966 (38)	1·4 (1·1–1·8)
African	11 (17)	71 (12)	1·5 (0·5–4·5)	156 (27)	1492 (19)	1·5 (1·2–2·0)
Other	6 (10)	36 (6)	1·5 (0·4–5·3)	67 (11)	634 (8)	1·6 (1·2–2·2)
Origin						
Non UK-born	37 (64)	279 (51)	1·6 (0·9–2·9)	393 (72)	4411 (62)	1·4 (1·2–1·7)
UK-born	21 (36)	266 (49)		155 (28)	2742 (38)	
Global region of origin						
Established market economies§	22 (40)	282 (55)	1·0 (ref.)	168 (32)	2948 (44)	1·0 (ref.)
Former socialist	1 (2)	6 (1)	2·4 (0·3–21·4)	6 (1)	66 (1)	1·5 (0·6–3·4)
India	9 (16)	62 (12)	1·9 (0·8–4·4)	72 (14)	920 (14)	1·3 (1·0–1·8)
China	1 (2)	5 (1)	2·5 (0·3–20·5)	5 (1)	65 (1)	1·3 (0·5–3·3)
Other Asia and Islands	2 (4)	17 (3)	1·7 (0·4–8·0)	52 (10)	422 (6)	1·9 (1·3–2·6)
Sub-Saharan Africa	9 (16)	69 (13)	1·9 (0·7–5·2)	123 (24)	1212 (18)	1·5 (1·1–1·9)
Latin America & Caribbean	0 (0)	4 (1)	0·0	7 (1)	106 (2)	1·2 (0·6–2·7)
Middle Eastern Crescent	11 (20)	71 (14)	2·0 (0·8–4·6)	87 (17)	981 (15)	1·4 (1·1–1·9)
Years in the UK						
Born in UK	21 (36)	266 (49)	1·0 (ref.)	155 (28)	2742 (38)	1·0 (ref.)
0–1 years	5 (9)	46 (8)	1·6 (0·5–5·3)	70 (13)	715 (10)	1·3 (1·0–1·8)
2–4 years	7 (12)	24 (5)	5·0 (1·3–18·2)	74 (14)	763 (10)	1·3 (1·0–1·8)
5–9 years	5 (9)	33 (6)	2·7 (0·8–8·5)	57 (10)	605 (8)	1·3 (1·0–1·8)
10–19 years	5 (9)	30 (6)	2·5 (0·8–7·3)	35 (6)	488 (7)	1·2 (0·8–1·7)
20–99 years	1 (2)	71 (13)	0·2 (0·0–1·3)	42 (7)	809 (11)	1·2 (0·8–1·7)
Unknown period	14 (24)	75 (14)	2·3 (1·1–5·0)	115 (21)	1031 (14)	1·8 (1·4–2·4)

* n/N% = percentage of resistant (or fully sensitive) exposed to risk factor.
† All odds ratios adjusted for age (<40, ⩾40 years) to allow for age-matching in 1993–1994 data.
‡ Excludes 1993–1994 data because of frequency matching.
§ Includes UK-born.

Table 2. *Risk factors for multidrug-resistant (MDR) tuberculosis 1993–1994 and 1998–2000 by previous tuberculosis: univariate analysis*

	Previous tuberculosis			No previous tuberculosis		
Risk factor	MDR ($N=54$) n (n/N%)*	Fully sensitive ($N=576$) n (n/N%)	OR† (95% CI)	MDR ($N=86$) n (n/N%)	Fully sensitive ($N=8124$) n (n/N%)	OR† (95% CI)
Age group‡						
0–19 years	2 (7)	37 (7)	0·6 (0·1–2·8)	5 (9)	604 (8)	0·8 (0·3–2·0)
20–39 years	16 (57)	181 (33)	1·0 (ref.)	36 (64)	3464 (44)	1·0 (ref.)
40–59 years	6 (21)	129 (24)	0·5 (0·2–1·4)	7 (13)	1832 (23)	0·4 (0·2–0·8)
60–79 years	4 (14)	161 (29)	0·3 (0·1–0·9)	7 (13)	1549 (20)	0·4 (0·2–1·0)
⩾80 years	0 (0)	39 (7)	0·0	1 (2)	390 (5)	0·2 (0·0–1·8)
Sex						
Male	39 (72)	323 (56)	2·2 (1·2–4·1)	52 (60)	4587 (57)	1·2 (0·8–1·8)
Female	15 (28)	253 (44)		34 (40)	3519 (43)	
Site						
Pulmonary	43 (83)	444 (77)	1·5 (0·7–3·1)	55 (66)	5345 (66)	1·0 (0·6–1·6)
Extrapulmonary	9 (17)	129 (23)		28 (34)	2726 (34)	
HIV status						
Positive	4 (7)	15 (3)	2·2 (0·7–6·9)	10 (12)	264 (3)	3·6 (1·8–7·0)
Negative (or unrecorded)	50 (93)	561 (97)		76 (88)	7860 (97)	
London						
Resident	24 (46)	191 (33)	1·5 (0·8–2·7)	54 (64)	3227 (40)	2·4 (1·5–3·8)
Non-resident	28 (54)	385 (67)		31 (36)	4889 (60)	
Smear status						
Positive	35 (65)	249 (43)	2·6 (1·4–4·7)	33 (38)	2730 (34)	1·2 (0·8–1·9)
Negative or unrecorded	19 (35)	327 (57)		53 (62)	5394 (66)	
Ethnic group						
White	13 (25)	248 (44)	1·0 (ref.)	25 (31)	2673 (34)	1·0 (ref.)
Indian sub-continent	24 (45)	215 (38)	1·7 (0·7–4·1)	30 (38)	2966 (38)	0·9 (0·5–1·6)
African	10 (19)	71 (12)	3·3 (0·9–12·6)	22 (28)	1492 (19)	0·1 (0·6–2·3)
Other	6 (11)	36 (6)	3·1 (0·8–13·0)	3 (4)	634 (8)	0·4 (0·1–1·4)
Origin						
Non UK-born	39 (76)	279 (51)	2·7 (1·4–5·5)	59 (80)	4411 (62)	2·3 (1·3–4·2)
UK-born	12 (24)	266 (49)		15 (20)	2742 (38)	
Global region of origin						
Established market economies§	14 (29)	282 (55)	1·0 (ref.)	20 (29)	2948 (44)	1·0 (ref.)
Former socialist economies	0 (0)	6 (1)	0·0	2 (3)	66 (1)	4·6 (1·0–20·8)
India	12 (25)	62 (12)	3·7 (1·5–8·9)	12 (17)	920 (14)	1·7 (0·8–3·6)
China	2 (4)	5 (1)	7·7 (1·4–43·6)	0 (0)	65 (1)	0·0
Other Asia and Islands	0 (0)	17 (3)	0·0	4 (6)	422 (6)	1·5 (0·5–4·4)
Sub-Saharan Africa	10 (21)	69 (13)	3·2 (1·1–9·1)	20 (29)	1212 (18)	2·5 (1·2–5·1)
Latin America & Caribbean	0 (0)	4 (1)	0·0	5 (7)	106 (2)	6·8 (2·5–18·3)
Middle Eastern Crescent	10 (21)	71 (14)	2·9 (1·1–7·3)	7 (10)	981 (15)	1·0 (0·4–2·5)
Years in the UK						
Born in UK	12 (24)	266 (49)	1·0 (ref.)	15 (20)	2742 (38)	1·0 (ref.)
0–1 years	12 (24)	46 (8)	5·9 (2·0–17·5)	14 (19)	715 (10)	5·5 (2·0–14·8)
2–4 years	7 (14)	24 (5)	6·9 (1·6–29·4)	6 (8)	763 (10)	2·1 (0·7–6·5)
5–9 years	4 (8)	33 (6)	3·2 (0·9–11·3)	7 (9)	605 (8)	2·6 (0·9–7·4)
10–19 years	3 (6)	30 (6)	2·5 (0·6–9·3)	3 (4)	488 (7)	1·2 (0·3–4·5)
20–99 years	3 (6)	71 (13)	0·9 (0·2–3·3)	2 (3)	809 (11)	0·3 (0·1–1·5)
Unknown period	10 (20)	75 (14)	2·7 (1·1–7·1)	27 (36)	1031 (14)	4·7 (2·4–9·3)

* n/N% = percentage of resistant (or fully sensitive) exposed to risk factor.
† All odds ratios adjusted for age (<40, ⩾40 years) to allow for age-matching in 1993–1994 data.
‡ Excludes 1993–1994 data because of frequency matching.
§ Includes UK-born.

Table 3. *Risk factors for isolated isoniazid resistance by history of tuberculosis: multivariate analysis**

	Previous tuberculosis ($n=639$)			No previous tuberculosis ($n=8762$)		
Risk factor	OR	95% CI	*P* value	OR	95% CI	*P* value
HIV positive	0·6	0·1–4·6	0·59	1·3	0·8–1·9	0·25
London residence	1·8	0·9–3·7	0·11	1·4	1·1–1·7	0·001
Smear-positive disease	3·2	1·1–9·2	0·03	1·1	0·8–1·4	0·55
Length of time the in UK						
Born in UK	1·0 (ref.)			1·0 (ref.)		
In UK <5 years	2·8	0·8–9·7	0·13	1·1	0·8–1·5	0·65
In UK 5–9 years	5·3	1·2–23·5	0·03	1·2	0·8–1·7	0·34
In UK ⩾10 years	0·9	0·3–3·8	0·91	0·9	0·7–1·3	0·70
Ethnic group						
White	1·0 (ref.)			1·0 (ref.)		
Indian sub-continent	1·2	0·4–3·7	0·72	1·6	1·2–2·1	0·003
Black African	0·9	0·2–3·8	0·94	1·7	1·2–2·4	0·002
Other	0·5	0·1–2·6	0·42	1·9	1·3–2·8	0·001

* All odds ratios adjusted for age and two periods of analysis (1993–1994 and 1998–2000).

Table 4. *Risk factors for multidrug resistance by history of tuberculosis: multivariate analysis**

	Previous tuberculosis ($n=630$)			No previous tuberculosis ($n=8210$)		
Risk factor	OR	95% CI	*P* value	OR	95% CI	*P* value
HIV positive	2·8	0·6–11·9	0·17	2·5	1·2–5·2	0·02
London residence	1·2	0·6–2·4	0·67	2·0	1·2–3·3	0·006
Smear-positive disease	5·9	1·8–19·0	0·003	1·4	0·7–2·5	0·32
Length of time in UK						
Born in UK	1·0 (ref.)			1·0 (ref.)		
In UK <5 years	5·8	1·8–18·5	0·003	3·2	1·4–7·4	0·006
In UK 5–9 years	2·2	0·4–11·6	0·34	3·0	1·1–8·5	0·04
In UK ⩾10 years	1·7	0·4–6·9	0·46	1·2	0·4–3·7	0·76
Ethnic group						
White	1·0 (ref.)			1·0 (ref.)		
Indian sub-continent	1·5	0·5–5·1	0·48	0·8	0·4–1·5	0·41
Black African	1·1	0·3–4·6	0·91	0·6	0·3–1·2	0·16
Other	1·5	0·3–6·8	0·56	0·3	0·1–0·9	0·04

* All odds ratios adjusted for age and two periods of analysis (1993–1994 and 1998–2000).

($P=0·016$). Foreign birth was a non-significant risk factor for multidrug resistance during 1993–1994 (OR 1·5, 95% CI 0·6–4·1) but a strong risk factor for multidrug resistance during 1998–2000 (OR 8·0, 95% CI 2·6–25·4).

Previous tuberculosis

Important risk factors for multidrug resistance in subjects with a history of previous tuberculosis included smear-positive disease (OR 5·8, 95% CI 1·8–18·5), and non-UK origin – particularly those who had arrived within the last 5 years in whom the risk compared with UK-born was approximately six-fold (OR 5·8, 95% CI 1·8–18·5). This risk appeared to decrease with duration of residence in the United Kingdom. Being HIV positive was a modest predictor of multidrug resistance (OR 2·8) but was not statistically significant. Other variables including London residence, ethnic group and gender were not important predictors of multidrug resistance.

DISCUSSION

In this analysis of surveillance data we found that recent migration and smear positivity were strong

risk factors for drug-resistant tuberculosis partly because they were strong risk factors in patients with presumed secondary drug resistance (from treatment failure). Elevated risks associated with London residence, HIV infection, and ethnicity were mainly, but not wholly, attributable to transmission. In the presumed primary drug resistance (transmission) group two risk factors varied by period: foreign birth was an important risk factor for multi-drug resistant diseases during 1998–2000, and HIV infection was a risk factor for isoniazid resistance during 1993–1994.

The main strength of this study was the use of large and representative combined microbiological and surveillance datasets allowing adjustment for a number of risk factors. In particular combining data over two periods significantly increased power (one third of the drug-resistant cases were from the 1993–1994 period), and also allowed us to observe changes in risk factors between periods.

The main weaknesses of our study relate to the nature of surveillance data. For example, despite matching with a central HIV register under-ascertainment of HIV is likely. Testing for HIV on diagnosis of tuberculosis has only recently been strongly recommended in the United Kingdom and recent data from two centres in London have provided estimates of prevalence of 11% [22] and 13% [23]; higher than the 5·6% prevalence amongst London residents in our dataset. In general under-ascertainment of HIV and for other risk factors should, if it is not differential as described above, cause bias towards the null; we would expect a strengthening of the association if ascertainment were improved. The use of age-matched case-control data also restricted some analyses and specifically made it difficult to examine age effects. The use of surveillance data also did not permit us to examine treatment compliance and other risk factors important for understanding resistance.

It has been increasingly recognized that at least in areas of high transmission acquisition of new strains can be mistaken for relapse [24, 25]. However, this is probably less important in the United Kingdom where recent transmission is relatively infrequent [26]. Our findings suggest that the pathways to drug-resistant disease are not simple and, for some risk factors, change over time. As can be viewed in Tables 3 and 4 for several of these risk factors the differences between the associations (odds ratios) for those with previous tuberculosis and those without is not great, although because of the much higher numbers of subjects without previous tuberculosis the estimates (odds ratios) for those without previous tuberculosis are more precise. The failure to find clear differences between these two groups could either be because the same risk factors are important for both pathways to resistant disease or possibly because of misclassification (the previous tuberculosis group including subjects with transmitted drug resistance).

Foreign birth

The association between drug resistance and foreign birth was particularly strong for previously treated patients recently arriving in the United Kingdom. A similar observation that risk of drug-resistant disease was higher in recent arrivals to the United Kingdom was made 40 years ago in the 1963 National Survey [27]. However, foreign-born now constitute 63% of patients reported with tuberculosis in England, Wales and Northern Ireland [28], compared with 26% in 1963.

Because of the relationship with recent arrival it is probable that in part this is measuring a higher risk of relapse with multidrug-resistant disease in those with a history of recent treatment abroad and so is at least partly due to interrupted treatment or inadequate treatment in country of origin. It may also be that this indicates a change in the pattern of migration and less adequate treatment in groups that have come to the United Kingdom more recently than those who have migrated in the past.

Foreign birth was also a risk factor for multidrug resistance without any previous tuberculosis (presumed transmission). The increased risk of multidrug-resistant tuberculosis in patients from outside the United Kingdom compared to those UK-born probably reflects higher resistance rates elsewhere [29]; i.e. transmission of multi-resistant strain has occurred in the country of origin (or in transit). However, transmission within the United Kingdom within foreign-born groups cannot be excluded. The much stronger relationship between foreign birth and multidrug resistance in the 1998–2000 period may reflect increased prevalence of multidrug resistance in the countries of origin of immigrant groups in this later period. Unfortunately we were not able to explore the effect of individual countries and regions of origin in great detail because of lack of power, however, the unadjusted data in Table 2 suggest

problems with drug resistance are not confined to any single world region with elevated odds ratios for Former Socialist Economies, Latin America and the Caribbean, and Sub-Saharan Africa.

Ethnicity

For most of the analyses there was little association between multidrug-resistant tuberculosis and non-white ethnicity, therefore, after allowing for migration/foreign birth, ethnicity in itself is no risk factor. However, non-white ethnicity remains a risk factor for primary isoniazid-resistant tuberculosis (from presumed transmission). This indicates modest increased exposure to isoniazid-resistant strains in non-white ethnic groups. There has been a major outbreak of isoniazid-resistant tuberculosis in the London area covering the latter period of this study and it may be that risk factors for isoniazid resistance partly reflect the specific risk factors associated with this outbreak [29].

HIV infection

HIV infection was more clearly a risk factor for (primary) drug resistance associated with transmission. HIV infection was significantly associated with multidrug resistance in those with no previous tuberculosis. For isoniazid resistance it was a risk factor in 1993–1994 but not for 1998–2000. The estimate for the odds ratio (2·8) in those in the 'previous tuberculosis' group suggests that it may be a risk factor for multidrug resistance but this relationship did not reach significance. In New York in the late 1980s and early 1990s much drug resistance in HIV-positive patients was the result of transmission in institutional settings such as hospitals, prisons and residential facilities [30]. Hospital outbreaks of multidrug-resistant tuberculosis involving several HIV-positive patients occurred in London in 1995 [31] and 1997 [32] however, to our knowledge there were no reported institutional outbreaks of multidrug-resistant tuberculosis in the United Kingdom during the two study periods. Therefore, increased risks of multidrug-resistant disease associated with HIV infection may be due to exposure in non health-care settings associated with other lifestyle features associated with HIV infection. Plausibly the finding that HIV is not a risk factor for isoniazid-resistant tuberculosis in 1998–2000 is an early indication that the advent of highly active anti-retroviral treatment has decreased risk of exposure to drug-resistant strains.

Alternatively the association may be a cohort effect. Since people with HIV infection progress from tuberculosis infection to active disease faster than immunocompetent people, the prevalence of drug resistance in HIV-positive patients largely depends on recently circulating strains, and so will be greater than in HIV-negative patients when drug resistance is increasing. However, the proportion of multidrug-resistant isolates has been stable in the United Kingdom for many years, although this may not be the case in other countries. It has also been postulated that HIV-infected individuals could be more susceptible to drug-resistant strains that may have reduced virulence. However, the lack of association between HIV and drug resistance in African studies suggests that differences in exposure are a more important explanation [10].

London residence

Measures of association between drug-resistant tuberculosis and London residence were modestly elevated in all categories, that is for those with drug-resistant tuberculosis from presumed transmission and treatment failure for both isoniazid- and multidrug-resistant tuberculosis, although associations only reach significance for primary drug-resistant tuberculosis (transmission). The simplest interpretation of these data is that residence in London is an independent risk factor for exposure to drug-resistant tuberculosis. There is no evidence that residence in London is a strong independent predictor of treatment failure.

Smear positivity

The strength of the association between smear positivity and presumed secondary drug-resistant tuberculosis was notable. We speculate that smear positivity indirectly measures high bacillary load in a previous episode of tuberculosis and this contributed to the development of drug resistance. Subsequent presentation with smear-positive disease therefore becomes a marker of possible acquired drug resistance. This finding has not to our knowledge been reported before, however, the association with cavitatory disease (also associated with high bacillary load) has been reported [11, 33]. This finding should be interpreted cautiously. It may be that smear positivity

is a consequence of drug resistance rather than a cause. However, if notification data is being received correctly then smear-positive status should reflect status at the beginning of treatment rather than part way into treatment. Also this relationship is much stronger in those with previous tuberculosis than those without, which we would not expect if the relationship was simply due to mistaken direction of causation.

Implications for treatment and control

Recent arrivals to the United Kingdom are more likely to have multidrug-resistant tuberculosis than those born in the United Kingdom and this risk is most marked in those with a history of tuberculosis. This may constitute an additional reason both to support international measures to ensure effective treatment in the country of origin and improve procedures at the port of entry. However, it should be emphasized that multidrug resistance is uncommon. Whilst it is true that the history of tuberculosis is a very strong predictor of multidrug resistance and within this group recent arrival in the United Kingdom and smear-positive disease are strong predictors of multidrug resistance, the great majority of subjects with a history of tuberculosis do not have multidrug- or isoniazid-resistant isolates.

Among those with no previous tuberculosis, certain subgroups – London residents, HIV positive, non-white ethnic groups (isoniazid) and foreign born (multidrug resistance) – appear to be at elevated risk of being infected with drug-resistant strains and special efforts to diagnose early, manage effectively and rigorously follow-up contacts in these groups may be needed to reduce the risk of transmission of resistant strains.

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