1 Appendix D: Evidence tables – RQ S: Risk factors for drug resistance

Table 1: Conaty, 2004

Bibliographic reference	**Conaty SJ, Hayward AC, Story A, Glynn JR, Drobniewski FA and Watson JM (2004) Explaining risk factors for drug-resistant tuberculosis in England and Wales: contribution of primary and secondary drug resistance. Epidemiology and Infection 132(6): 1099-108**
Study type	Unmatched case-control
Study quality	Sample sufficiently represents the population of interest with regard to key characteristics? *yes* Loss to follow-up sufficiently unrelated to key characteristics? *yes* Prognostic factor of interest adequately measured? *yes, although blinding not reported* Outcome of interest adequately measured? *yes, although blinding not reported* Important potential confounders appropriately accounted for? *multivariate analysis used, although effect estimates only adjusted for age and two periods of analysis (1993–1994 and 1998–2000)* Statistical analysis appropriate? *not all factors that underwent univariate analysis were entered into the multivariate analyses; unclear how factors were selected for the multivariate analyses*
Number of patients	n = 9541 • isoniazid-resistant tuberculosis = 701 – previous history of disease = 63 – no history of disease = 638 • multidrug-resistant tuberculosis = 140 – previous history of disease = 54 – no history of disease = 86 • fully sensitive tuberculosis = 8700 – previous history of disease = 576 – no history of disease = 8124
Patient characteristics	*Study group(s)* All patients in England and Wales with isoniazid- and multidrug-resistant tuberculosis in two time-periods (linked laboratory and surveillance data from 1993–1994 and 1998–2000)[1,2] Isoniazid resistance was defined as resistance to isoniazid without resistance to rifampicin, pyrazinamide or ethambutol Multidrug resistance was defined as resistance to at least isoniazid and rifampicin *Comparator* All patients in England and Wales with fully sensitive tuberculosis in two time-periods (linked laboratory and surveillance data from 1993–1994 and 1998–2000)[1,2] Fully sensitive tuberculosis was defined as sensitivity to isoniazid, rifampicin, pyrazinamide and ethambutol

Bibliographic reference	**Conaty SJ, Hayward AC, Story A, Glynn JR, Drobniewski FA and Watson JM (2004) Explaining risk factors for drug-resistant tuberculosis in England and Wales: contribution of primary and secondary drug resistance. Epidemiology and Infection 132(6): 1099-108**

Drug susceptibility testing
Resistance ratio method on Lowenstein-Jensen media or modified proportion method on liquid media (BACTEC 460)

Exclusion
Other resistance patterns, such as isolated rifampicin resistance

Population characteristics
Patients with no history of disease

	Isoniazid-resistant	*Multidrug-resistant*	*Fully sensitive*
Age group, n(%)			
0-19 years	44(10)	5(9)	604(8)
20-39 years	244(57)	36(64)	3464(44)
40-59 years	99(23)	7(13)	1832(23)
60-79 years	29(7)	7(13)	1549(20)
≥80 years	10(2)	1(2)	390(5)
Sex, n(%)			
Male	368(58)	52(60)	4587(57)
Female	268(42)	34(40)	3519(43)
Site, n(%)			
Pulmonary	376(62)	55(66)	5345(66)
Extrapulmonary	231(38)	28(34)	2726(34)
HIV status, n(%)			
Positive	39(6)	10(12)	264(3)
Negative[3]	599(94)	76(88)	7860(97)
London, n(%)			
Resident	336(53)	54(64)	3227(40)
Non-resident	296(47)	31(36)	4889(60)
Smear status, n(%)			

Bibliographic reference	Conaty SJ, Hayward AC, Story A, Glynn JR, Drobniewski FA and Watson JM (2004) Explaining risk factors for drug-resistant tuberculosis in England and Wales: contribution of primary and secondary drug resistance. Epidemiology and Infection 132(6): 1099-108

Positive	209(33)	33(38)	2730(34)
Negative[4]	429(67)	53(62)	5394(66)
Ethnic group, n(%)			
White	133(22)	25(31)	2673(34)
Indian subcontinent	239(40)	30(38)	2966(38)
African	156(27)	22(28)	1492(19)
Other	67(11)	3(4)	634(8)
Origin, n(%)			
Non-UK born	393(72)	59(80)	4411(62)
UK born	155(28)	15(20)	2742(38)
Years in the UK, n(%)			
Born in the UK	155(28)	15(20)	2742(38)
0-1 years	70(13)	14(19)	715(10)
2-4 years	74(14)	6(8)	763(10)
5-9 years	57(10)	7(9)	605(8)
10-19 years	35(6)	3(4)	488(7)
20-99 years	42(7)	2(3)	809(11)
Unknown	115(21)	27(36)	1031(14)

Patients with a history of disease

	Isoniazid-resistant	*Multidrug-resistant*	*Fully sensitive*
Age group, n(%)			
0-19 years	0(0)	2(7)	37(7)
20-39 years	12(44)	16(57)	181(33)
40-59 years	5(19)	6(21)	129(24)
60-79 years	9(33)	4(14)	161(29)
≥80 years	1(4)	0(0)	39(7)
Sex, n(%)			
Male	32(51)	39(72)	323(56)

Bibliographic reference	Conaty SJ, Hayward AC, Story A, Glynn JR, Drobniewski FA and Watson JM (2004) Explaining risk factors for drug-resistant tuberculosis in England and Wales: contribution of primary and secondary drug resistance. Epidemiology and Infection 132(6): 1099-108			
	Female	31(49)	15(28)	253(44)
	Site, n(%)			
	Pulmonary	37(62)	43(83)	444(77)
	Extrapulmonary	23(38)	9(17)	29(23)
	HIV status, n(%)			
	Positive	3(5)	4(7)	15(3)
	Negative[3]	60(95)	50(93)	561(97)
	London, n(%)			
	Resident	33(52)	24(46)	191(33)
	Non-resident	30(48)	28(54)	385(67)
	Smear status, n(%)			
	Positive	27(43)	35(65)	249(43)
	Negative[4]	36(57)	19(35)	327(57)
	Ethnic group, n(%)			
	White	21(33)	13(25)	248(44)
	Indian subcontinent	24(38)	24(45)	215(38)
	African	11(17)	10(19)	71(12)
	Other	6(10)	6(11)	36(6)
	Origin, n(%)			
	Non-UK born	37(64)	39(76)	279(51)
	UK born	21(36)	12(24)	266(49)
	Years in the UK, n(%)			
	Born in the UK	21(36)	12(24)	266(49)
	0-1 years	5(9)	12(24)	46(8)
	2-4 years	7(12)	7(14)	24(5)
	5-9 years	5(9)	4(8)	33(6)
	10-19 years	5(9)	3(6)	30(6)
	20-99 years	1(2)	3(6)	71(13)
	Unknown	14(24)	10(20)	75(14)

<table>
<tr><th>Bibliographic reference</th><th>Conaty SJ, Hayward AC, Story A, Glynn JR, Drobniewski FA and Watson JM (2004) Explaining risk factors for drug-resistant tuberculosis in England and Wales: contribution of primary and secondary drug resistance. Epidemiology and Infection 132(6): 1099-108</th></tr>
<tr><td>Location</td><td>England and Wales</td></tr>
<tr><td>Approach to analysis</td><td>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 and fully sensitive tuberculosis, and between multidrug-resistant tuberculosis and fully sensitive tuberculosis
Individuals with other resistance patterns were excluded from analysis
Final multivariate models were selected by backward elimination of variables from full models
All odds ratios adjusted for age and two periods of analysis (1993–1994 and 1998–2000)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Risk factors for isoniazid resistance in patients with a history of tuberculosis
<table>
<tr><th>Risk factor</th><th>Adjusted OR (95% CI)</th><th>P-value</th></tr>
<tr><td>HIV-positive[3]</td><td>0.6 (0.1 to 4.6)</td><td>0.59</td></tr>
<tr><td>London residence</td><td>1.8 (0.9 to 3.7)</td><td>0.11</td></tr>
<tr><td>Smear-positive[4]</td><td>3.2 (1.1 to 9.2)</td><td>0.03</td></tr>
<tr><td>Length of time in the UK</td><td></td><td></td></tr>
<tr><td>Born in the UK</td><td>1.0 (reference)</td><td></td></tr>
<tr><td>In the UK <5 years</td><td>2.8 (0.8 to 9.7)</td><td>0.13</td></tr>
<tr><td>In the UK 5-9 years</td><td>5.3 (1.2 to 23.5)</td><td>0.03</td></tr>
<tr><td>In the UK ≥10 years</td><td>0.9 (0.3 to 3.8)</td><td>0.91</td></tr>
<tr><td>Ethnic group</td><td></td><td></td></tr>
<tr><td>White</td><td>1.0 (reference)</td><td></td></tr>
<tr><td>Indian subcontinent</td><td>1.2 (0.4 to 3.7)</td><td>0.72</td></tr>
<tr><td>Black African</td><td>0.9 (0.2 to 3.8)</td><td>0.94</td></tr>
<tr><td>Other</td><td>0.5 (0.1 to 2.6)</td><td>0.42</td></tr>
</table>
Risk factors for isoniazid resistance in patients with no history of tuberculosis
<table>
<tr><th>Risk factor</th><th>Adjusted OR (95% CI)</th><th>P-value</th></tr>
<tr><td>HIV-positive[3]</td><td>1.3 (0.8 to 1.9)</td><td>0.25</td></tr>
<tr><td>London residence</td><td>1.4 (1.1 to 1.7)</td><td>0.001</td></tr>
<tr><td>Smear-positive[4]</td><td>1.1 (0.8 to 1.4)</td><td>0.55</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Conaty SJ, Hayward AC, Story A, Glynn JR, Drobniewski FA and Watson JM (2004) Explaining risk factors for drug-resistant tuberculosis in England and Wales: contribution of primary and secondary drug resistance. Epidemiology and Infection 132(6): 1099-108

Length of time in the UK		
Born in the UK	1.0 (reference)	
In the UK <5 years	1.1 (0.8 to 1.5)	0.65
In the UK 5-9 years	1.2 (0.8 to 1.7)	0.34
In the UK ≥10 years	0.9 (0.7 to 1.3)	0.70
Ethnic group		
White	1.0 (reference)	
Indian subcontinent	1.6 (1.2 to 2.1)	0.003
Black African	1.7 (1.2 to 2.4)	0.002
Other	1.9 (1.3 to 2.8)	0.001

Risk factors for multidrug resistance in patients with a history of tuberculosis

Risk factor	*Adjusted OR (95% CI)*	*P-value*
HIV-positive[3]	2.8 (0.6 to 11.9)	0.17
London residence	1.2 (0.6 to 2.4)	0.67
Smear-positive[4]	5.9 (1.8 to 19.0)	0.003
Length of time in the UK		
Born in the UK	1.0 (reference)	
In the UK <5 years	5.8 (1.8 to 18.5)	0.003
In the UK 5-9 years	2.2 (0.4 to 11.6)	0.34
In the UK ≥10 years	1.7 (0.4 to 6.9)	0.46
Ethnic group		
White	1.0 (reference)	
Indian subcontinent	1.5 (0.5 to 5.1)	0.48
Black African	1.1 (0.3 to 4.6)	0.91
Other	1.5 (0.3 to 6.8)	0.56

Risk factors for multidrug resistance in patients with no history of tuberculosis

Risk factor	*Adjusted OR (95% CI)*	*P-value*
HIV-positive[3]	2.5 (1.2 to 5.2)	0.02

Bibliographic reference	Conaty SJ, Hayward AC, Story A, Glynn JR, Drobniewski FA and Watson JM (2004) Explaining risk factors for drug-resistant tuberculosis in England and Wales: contribution of primary and secondary drug resistance. Epidemiology and Infection 132(6): 1099-108		
	London residence	2.0 (1.2 to 3.3)	0.006
	Smear-positive[4]	1.4 (0.7 to 2.5)	0.32
	Length of time in the UK		
	Born in the UK	1.0 (reference)	
	In the UK <5 years	3.2 (1.4 to 7.4)	0.006
	In the UK 5-9 years	3.0 (1.1 to 8.5)	0.04
	In the UK ≥10 years	1.2 (0.4 to 3.7)	0.76
	Ethnic group		
	White	1.0 (reference)	
	Indian subcontinent	0.8 (0.4 to 1.5)	0.41
	Black African	0.6 (0.3 to 1.2)	0.16
	Other	0.3 (0.1 to 0.9)	0.04
Source of funding	1 author supported by the United Kingdom's Department for International Development and the Department of Health; 1 author supported by Camden Primary Care Trust		
Comments			

[1] Reason provided for 2 time periods: to maximise power and investigate any differences in risk factors over time

[2] Drug sensitivity results obtained from MycobNet, the UK Mycobacterial Surveillane Network; linked risk factor information obtained from the National Tuberculosis Survey and the Enhanced Tuberculosis Surveillance data

[3] At analysis subjects with no recorded HIV status were classified as HIV negative

[4] At analysis subjects with no smear result recorded were assumed to be smear negative

[5] At analysis subjects with no recorded history of tuberculosis were classified as 'no previous tuberculosis'

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio

Table 2: French, 2008

Bibliographic reference	French CE, Glynn JR, Kruijshaar ME, Ditah IC, Delpech V and Abubakar I (2008) The association between HIV and antituberculosis drug resistance. European Respiratory Journal 32(3): 718-25
Study type	Unmatched case-control

<table>
<tr><th>Bibliographic reference</th><th>French CE, Glynn JR, Kruijshaar ME, Ditah IC, Delpech V and Abubakar I (2008) The association between HIV and antituberculosis drug resistance. European Respiratory Journal 32(3): 718-25</th></tr>
<tr><td>Study quality</td><td>Sample sufficiently represents the population of interest with regard to key characteristics? yes
Loss to follow-up sufficiently unrelated to key characteristics? yes
Prognostic factor of interest adequately measured? yes, although blinding not reported
Outcome of interest adequately measured? yes, although blinding not reported
Important potential confounders appropriately accounted for? cases and controls unmatched; multivariate analysis used, although it was unclear which confounders were accounted for
Statistical analysis appropriate? a number of factors reported in the univariate analyses were not reported as multivariate analyses</td></tr>
<tr><td>Number of patients</td><td>n = 18130
• isoniazid-resistant tuberculosis = 1195
• multidrug-resistant tuberculosis = 125
• fully sensitive tuberculosis = 16810</td></tr>
<tr><td>Patient characteristics</td><td>Study group(s)
All new cases of isoniazid- and multidrug-resistant tuberculosis in England and Wales between 1999 and 2005[1]

Comparator
All new cases of fully sensitive tuberculosis in England and Wales between 1999 and 2005[1]

Drug susceptibility testing
Isolates are tested for resistance to the four firstline drugs (isoniazid, rifampicin, ethambutol and pyrazinamide), and some second-line drugs
Reference laboratories used the resistance ratio or the proportion method, and are subject to quality assurance systems

Exclusion
Cases with M. bovis were excluded from calculations of pyrazinamide resistance since they are usually intrinsically resistant to it

Population characteristics
<table>
<tr><th></th><th>Isoniazid-resistant</th><th>Multidrug-resistant</th><th>Fully sensitive</th></tr>
<tr><td>HIV status[2], n
Negative</td><td>1108</td><td>111</td><td>15755</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	French CE, Glynn JR, Kruijshaar ME, Ditah IC, Delpech V and Abubakar I (2008) The association between HIV and antituberculosis drug resistance. European Respiratory Journal 32(3): 718-25			
	Positive	87	14	1055
	Age, n			
	15-44 years	957	108	11017
	45-64 years	177	12	3235
	≥65 years	61	5	2558
	Sex, n			
	Male	704	66	9488
	Female	490	59	7296
	Missing data	1 (0.1%)	0 (0.0%)	26 (0.2%)
	Place of reporting, n			
	Outside London	534	58	9914
	London	661	67	6896
	Ethnic group, n			
	White	193	13	4438
	Black Caribbean	91	3	474
	Black African	324	51	3736
	Indian/Pakistani/Bangladeshi	400	39	6133
	Other	168	16	1825
	Missing data	19 (1.3%)	3 (2.4%)	204 (1.2%)
	Place of birth and time since entry into the UK, n			
	UK born	275	19	4705
	Non-UK born (<2 years)	182	37	2250
	Non-UK born (≥2 years)	562	53	7359
	Non-UK born (unknown)	116	11	1654
	Missing data	60 (5.0%)	5 (4.0%)	842 (5.0%)
	Site, n			
	Extrapulmonary	427	35	5708
	Smear-positive pulmonary	415	46	5826
	Other pulmonary	350	44	5234

<table>
<tr><th>Bibliographic reference</th><td colspan="4">French CE, Glynn JR, Kruijshaar ME, Ditah IC, Delpech V and Abubakar I (2008) The association between HIV and antituberculosis drug resistance. European Respiratory Journal 32(3): 718-25</td></tr>
<tr><td></td><td colspan="4">
<table>
<tr><td>Missing data</td><td>3 (0.3%)</td><td>0 (0.0%)</td><td>42 (0.2%)</td></tr>
</table>
</td></tr>
<tr><td>Location</td><td colspan="4">England and Wales</td></tr>
<tr><td>Approach to analysis</td><td colspan="4">Multivariate models were built using a forward-fitting approach, and interactions were assessed using the likelihood ratio test
In both univariate and multivariate analysis comparisons were between isolated isoniazid resistance and fully sensitive tuberculosis, and between multidrug-resistant tuberculosis and fully sensitive tuberculosis</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="4">Risk factors for isoniazid resistance in patients with no history of tuberculosis
<table>
<tr><th>Risk factor</th><th>Adjusted OR (95% CI)</th><th>P-value</th></tr>
<tr><td>HIV status[2]
Negative
Positive</td><td>
1.0 (reference)
1.02 (0.80 to 1.30)</td><td>0.895</td></tr>
<tr><td>Age
15-44 years
45-64 years
≥65 years</td><td>
1.0 (reference)
0.70 (0.59 to 0.83)
0.34 (0.26 to 0.44)</td><td><0.001</td></tr>
<tr><td>Place of reporting
Outside London
London</td><td>
1.0 (reference)
1.52 (1.34 to 1.72)</td><td><0.001</td></tr>
<tr><td>Ethnic group
White
Black Caribbean
Black African
Indian/Pakistani/Bangladeshi
Other</td><td>
1.0 (reference)
3.11 (2.36 to 4.08)
1.22 (1.00 to 1.50)
1.18 (0.99 to 1.42)
1.40 (1.12 to 1.76)</td><td><0.001</td></tr>
</table>
Risk factors for multidrug resistance in patients with no history of tuberculosis
<table>
<tr><th>Risk factor</th><th>Adjusted OR (95% CI)</th><th>P-value</th></tr>
<tr><td>HIV status[2]
Negative
Positive</td><td>
1.0 (reference)
0.91 (0.47 to 1.76)</td><td>0.775</td></tr>
<tr><td>Age</td><td></td><td></td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	French CE, Glynn JR, Kruijshaar ME, Ditah IC, Delpech V and Abubakar I (2008) The association between HIV and antituberculosis drug resistance. European Respiratory Journal 32(3): 718-25		
	15-44 years	1.0 (reference)	0.010
	45-64 years	0.52 (0.27 to 0.99)	
	≥65 years	0.35 (0.14 to 0.90)	
	Ethnic group		
	White	1.0 (reference)	0.323
	Black Caribbean	1.40 (0.39 to 5.01)	
	Black African	2.02 (0.88 to 4.64)	
	Indian/Pakistani/Bangladeshi	1.33 (0.61 to 2.90)	
	Other	1.39 (0.56 to 3.45)	
	Place of birth and time since entry into the UK		
	UK born	1.0 (reference)	0.028
	Non-UK born (<2 years)	2.23 (1.08 to 4.63)	
	Non-UK born (≥2 years)	1.19 (0.59 to 2.38)	
	Non-UK born (unknown)	1.24 (0.53 to 2.91)	
Source of funding	No details provided		
Comments			

[1] Drug sensitivity results obtained from MycobNet, the UK Mycobacterial Surveillane Network; linked risk factor information obtained from Enhanced Tuberculosis Surveillance data

[2] The Enhanced Tuberculosis Surveillance system does not collect information on HIV status, so this information was obtained by matching case reports (for 1999–2005) with the national HIV/AIDS reports database (for 1979–2006) using in-house matching software; matching was not carried out on cases aged <15 years as HIV in children is reported separately; tuberculosis cases that were not matched to HIV/ AIDS reports were considered to be HIV-negative (although it is recognised that they are more accurately described as 'not known to be HIV-positive'); cases that were diagnosed with HIV >1 year after the date of tuberculosis diagnosis were excluded, since it was unknown whether they were infected with HIV at the time of tuberculosis diagnosis

Abbreviations: AIDS, autoimmune deficiency syndrome; HIV, human immunodeficiency virus

Table 3: Kruijshaar, 2008

Bibliographic reference	Kruijshaar ME, Watson JM, Drobniewski F, Anderson C, Brown TJ, Magee JG, Smith EG, Story A and Abubakar I (2008) Increasing antituberculosis drug resistance in the United Kingdom: analysis of National Surveillance Data. BMJ 336(7655): 1231-4

<table>
<tr><th>Bibliographic reference</th><th>Kruijshaar ME, Watson JM, Drobniewski F, Anderson C, Brown TJ, Magee JG, Smith EG, Story A and Abubakar I (2008) Increasing antituberculosis drug resistance in the United Kingdom: analysis of National Surveillance Data. BMJ 336(7655): 1231-4</th></tr>
<tr><td>Study type</td><td>Observational</td></tr>
<tr><td>Study quality</td><td>Sample sufficiently represents the population of interest with regard to key characteristics?
Loss to follow-up sufficiently unrelated to key characteristics? unclear; loss to follow-up, its reasons and the characteristics of those lost not reported
Prognostic factor of interest adequately measured? yes, although blinding not reported
Outcome of interest adequately measured? Approach to drug susceptibility testing not reported; blinding not reported
Important potential confounders appropriately accounted for? yes
Statistical analysis appropriate? yes</td></tr>
<tr><td>Number of patients</td><td>n = 28485</td></tr>
<tr><td>Patient characteristics</td><td>Study group(s)
All cases of isoniazid-, rifampicin- and multidrug-resistant tuberculosis in England, Wales and Northern Ireland between 1998 and 2005[1]
Multidrug resistant tuberculosis is defined as resistance to at least isoniazid and rifampicin

Comparator
All cases of fully sensitive tuberculosis in England, Wales and Northern Ireland between 1998 and 2005[1]

Tuberculosis diagnosis
Tuberculosis cases were either confirmed by culture to be caused by M tuberculosis complex or met the following criteria: a clinician’s judgment that the patient’s clinical or radiological signs are compatible with tuberculosis and clinician’s decision to treat the patient with a full course of antituberculosis treatment

Exclusion
Most M. bovis isolates are resistant to pyrazinamide and were therefore excluded these from analyses of pyrazinamide resistance

Population characteristics
<table>
<tr><th></th><th>Culture confirmed cases (tested for isoniazid and rifampicin)</th></tr>
<tr><td>All cases</td><td>28 485</td></tr>
<tr><td>Median (IQR) age (years)</td><td>35 (26-54)</td></tr>
<tr><td>Male</td><td>16 164 (56.8)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td colspan="4">Kruijshaar ME, Watson JM, Drobniewski F, Anderson C, Brown TJ, Magee JG, Smith EG, Story A and Abubakar I (2008) Increasing antituberculosis drug resistance in the United Kingdom: analysis of National Surveillance Data. BMJ 336(7655): 1231-4</td></tr>
<tr><td></td><td colspan="4">
<table>
<tr><td>Born in UK</td><td>8035 (31.4)</td></tr>
<tr><td>Median (IQR) time since entry to UK (years)</td><td>4 (2-13)</td></tr>
<tr><td>Ethnic group:
White
Black Caribbean
Black African
Black other
Indian, Pakistani, Bangladeshi
Chinese
Other</td><td>
7541 (27.7)
770 (2.8)
5967 (21.9)
241 (0.9)
9963 (36.6)
448 (1.6)
2327 (8.5)</td></tr>
<tr><td>Reported in London</td><td>11 851 (41.6)</td></tr>
<tr><td>Pulmonary disease</td><td>18 997 (67.0)</td></tr>
<tr><td>Previous diagnosis</td><td>1889 (8.3)</td></tr>
<tr><td>M. tuberculosis</td><td>27884 (99.4)</td></tr>
<tr><td>M. bovis</td><td>123 (0.4)</td></tr>
<tr><td>M. africanum</td><td>33 (0.1)</td></tr>
<tr><td>Sputum smear positive</td><td>9909 (60.6)</td></tr>
</table>
</td></tr>
<tr><td>Location</td><td colspan="4">England, Wales, and Northern Ireland</td></tr>
<tr><td>Approach to analysis</td><td colspan="4">Multivariable models adjusted for age, sex, place of birth (born in the UK or elsewhere), ethnic group (white, black Caribbean, black African, black other, Indian/Pakistani/Bangladeshi, Chinese, other including mixed), region (London versus outside London), previous diagnosis, and site of disease (pulmonary z</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="4">Risk factors for isoniazid resistance in patients with tuberculosis living in London
<table>
<tr><th>Risk factor</th><th>n</th><th>% resistant</th><th>Adjusted OR (95% CI)</th></tr>
<tr><td>Age (linear)</td><td>11 848</td><td>8.5</td><td>0.99 (0.98 to 0.99)</td></tr>
<tr><td>Sex:
Female
Male</td><td>
5056
6783</td><td>
8.1
8.8</td><td>
0.92 (0.79 to 1.08)
Reference</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Kruijshaar ME, Watson JM, Drobniewski F, Anderson C, Brown TJ, Magee JG, Smith EG, Story A and Abubakar I (2008) Increasing antituberculosis drug resistance in the United Kingdom: analysis of National Surveillance Data. BMJ 336(7655): 1231-4

Born in UK:			
No	8822	7.9	0.76 (0.60 to 0.95)
Yes	1806	11.1	Reference
Ethnic group:			
White	1747	7.7	Reference
Black Caribbean	470	21.5	2.93 (2.11 to 4.09)
Black African	3877	8.7	1.08 (0.80 to 1.45)
Black other	174	10.9	1.38 (0.75 to 2.55)
Indian, Pakistani, Bangladeshi	3606	6.8	0.89 (0.66 to 1.19)
Chinese	174	9.8	1.41 (0.75 to 2.64)
Other	1464	8.4	1.04 (0.74 to 1.46)
Year (linear)	11 851	8.5	1.04 (1.00 to 1.07)
Previous diagnosis:			
Yes	655	10.2	1.35 (1.02 to 1.78)
No	8504	8.5	Reference
Site of disease:			
Pulmonary	7556	9	1.06 (0.89 to 1.25)
Extrapulmonary	4247	7.7	Reference

Risk factors for isoniazid resistance in patients with tuberculosis living outside of London

Risk factor	*n*	*% resistant*	*Adjusted OR (95% CI)*
Age (linear)	16 633	3.0	0.98 (0.98 to 0.99)
Sex:			
Female	7227	2.9	0.81 (0.69 to 0.96)
Male	9381	3.1	Reference
Born in UK:			

Bibliographic reference	Kruijshaar ME, Watson JM, Drobniewski F, Anderson C, Brown TJ, Magee JG, Smith EG, Story A and Abubakar I (2008) Increasing antituberculosis drug resistance in the United Kingdom: analysis of National Surveillance Data. BMJ 336(7655): 1231-4

No	8700	3.2	1.49 (1.16 to 1.92)
Yes	6229	2.7	Reference
Ethnic group:			
White	5794	2.3	Reference
Black Caribbean	300	2.1	1.35 (0.77 to 2.36)
Black African	2090	2.1	0.99 (0.68 to 1.43)
Black other	67	1.2	0.99 (0.30 to 3.28)
Indian, Pakistani, Bangladeshi	6357	4.0	1.26 (0.94 to 1.69)
Chinese	274	5.1	1.71 (0.99 to 2.95)
Other	863	3.2	1.65 (1.11 to 2.44)
Year (linear)	16 634	3.0	1.01 (0.98 to 1.05)
Previous diagnosis:			
Yes	1234	3.2	1.80 (1.40 to 2.32)
No	12 278	0.7	Reference
Site of disease:			
Pulmonary	11 441	2.8	0.82 (0.69 to 0.98)
Extrapulmonary	5097	3.4	Reference

Risk factors for rifampicin resistance in patients with tuberculosis

Risk factor	*n*	*% resistant*	*Adjusted OR (95% CI)*
Age (linear)	28481	1.2	0.98 (0.97 to 0.99)
Sex:			
Female	12283	1.2	0.83 (0.64 to 1.08)
Male	16164	1.3	Reference
Born in UK:			
No	17522	1.4	1.88 (1.24 to 2.86)

Bibliographic reference	Kruijshaar ME, Watson JM, Drobniewski F, Anderson C, Brown TJ, Magee JG, Smith EG, Story A and Abubakar I (2008) Increasing antituberculosis drug resistance in the United Kingdom: analysis of National Surveillance Data. BMJ 336(7655): 1231-4

Yes	8035	0.7	Reference
Ethnic group:			
White	7541	0.7	Reference
Black Caribbean	770	9.1	1.28 (0.59 to 2.79)
Black African	5967	1.7	0.98 (0.59 to 1.64)
Black other	241	2.5	1.87 (0.69 to 5.06)
Indian, Pakistani, Bangladeshi	9963	1.2	0.94 (0.59 to 1.50)
Chinese	448	1.3	0.83 (0.28 to 2.45)
Other	2327	1.7	0.97 (0.54 to 1.75)
Year (linear)	28485	1.2	1.03 (0.98 to 1.09)
Region of reporting:			
London	11851	1.5	0.81 (0.62 to 1.05)
Outside London	16634	1.0	Reference
Previous diagnosis:			
Yes	1889	3.5	4.72 (3.50 to 6.35)
No	20782	1.0	Reference
Site of disease:			
Pulmonary	18997	1.3	1.48 (1.10 to 1.98)
Extrapulmonary	9344	1.0	Reference

Risk factors for multidrug resistance in patients with tuberculosis

Risk factor	*n*	*% resistant*	*Adjusted OR (95% CI)*
Age (linear)	28481	0.9	0.98 (0.59 to 1.08)
Sex:			
Female	12283	0.9	0.80 (0.59 to 1.08)
Male	16164	0.9	Reference

Bibliographic reference	**Kruijshaar ME, Watson JM, Drobniewski F, Anderson C, Brown TJ, Magee JG, Smith EG, Story A and Abubakar I (2008) Increasing antituberculosis drug resistance in the United Kingdom: analysis of National Surveillance Data. BMJ 336(7655): 1231-4**

Born in UK:			
No	17522	1.1	1.62(0.99 to 2.66)
Yes	8035	0.5	Reference
Ethnic group:			
White	7541	0.4	Reference
Black Caribbean	770	0.5	1.01 (0.30 to 3.43)
Black African	5967	1.3	1.77 (0.92 to 3.41)
Black other	241	1.7	2.44 (0.68 to 8.81)
Indian, Pakistani, Bangladeshi	9963	1	1.63 (0.91 to 2.95)
Chinese	448	1.1	1.77 (0.56 to 5.54)
Other	2327	1.2	1.32 (0.62 to 2.84)
Year (linear)	28485	0.9	1.01 (0.95 to 1.08)
Region of reporting:			
London	11851	1.0	1.04 (0.76 to 1.42)
Outside London	16634	0.8	Reference
Previous diagnosis:			
Yes	1889	2.8	5.44 (3.88 to 7.63)
No	20782	0.7	Reference
Site of disease:			
Pulmonary	18997	1.0	1.40 (1.00 to 1.96)
Extrapulmonary	9344	0.8	Reference

Source of funding	None
Comments	

[1] Drug sensitivity results obtained from MycobNet, the UK Mycobacterial Surveillane Network; linked risk factor information obtained from Enhanced Tuberculosis Surveillance data

Bibliographic reference	Kruijshaar ME, Watson JM, Drobniewski F, Anderson C, Brown TJ, Magee JG, Smith EG, Story A and Abubakar I (2008) Increasing antituberculosis drug resistance in the United Kingdom: analysis of National Surveillance Data. BMJ 336(7655): 1231-4
Abbreviations: CI, confidence interval; IQR, interquartile range; OR, odds ratio	

Table 4: Maguire, 2011

Bibliographic reference	Maguire H, Brailsford S, Carless J, Yates M, Altass L, Yates S, Anaraki S, Charlett A, Lozewicz S, Lipman M and Bothamley G (2011) Large outbreak of isoniazid-monoresistant tuberculosis in London, 1995 to 2006: case-control study and recommendations. Euro Surveillance 16(13): pii: 19830
Study type	Unmatched case-control
Study quality	Sample sufficiently represents the population of interest with regard to key characteristics? *yes* Loss to follow-up sufficiently unrelated to key characteristics? *yes* Prognostic factor of interest adequately measured? *yes, although blinding not reported; some data collected by questionnaire (i.e. may be some reliance on recall)* Outcome of interest adequately measured? *yes, although blinding not reported; some data collected by questionnaire (i.e. may be some reliance on recall)* Important potential confounders appropriately accounted for? *multivariate analysis used, but unclear which confounders were controlled for; cases and controls unmatched* Statistical analysis appropriate? *yes*
Number of patients	n = 18040 • isoniazid-resistant tuberculosis = 293 • fully sensitive tuberculosis = 17747 For the following variables, only controls with a known place of residence were included (n=17,740): sex, age, site of disease, sputum smear status, type of employment, ethnicity and country of birth
Patient characteristics	*Study group(s)* All individuals with an isoniazid-monoresistant *M. tuberculosis* strain diagnosed from 1995 to the third quarter of 2006 with an indistinguishable RFLP or MIRU-VNTR pattern who was resident in or had an epidemiological link with London *Comparator* All other individuals with TB reported during 2000 to 2001 to the HPA London regional epidemiology unit as part of routine surveillance on a paper-based questionnaire and those reported during 2002 to 2005 electronically by clinicians to the HPA London TB Register.

Bibliographic reference	**Maguire H, Brailsford S, Carless J, Yates M, Altass L, Yates S, Anaraki S, Charlett A, Lozewicz S, Lipman M and Bothamley G (2011) Large outbreak of isoniazid-monoresistant tuberculosis in London, 1995 to 2006: case-control study and recommendations. Euro Surveillance 16(13): pii: 19830**

Population characteristics

	Cases 2000 to third quarter 2006	*Controls 2000–2005*
Sex:		
Male	206	9753
Female	86	7959
Unknown	1	28
Age:		
0-14 years	5	1035
15-24 years	53	3109
25-34 years	91	5363
35-44 years	83	3184
45-64 years	47	3116
≥65 years	14	1092
Unknown	0	31
Ethnicity:		
Black African	43	5617
Black Caribbean	85	605
Black (other)	8	264
White	99	2434
Indian subcontinent	15	5691
Chinese	1	251
Other	18	2282
Unknown	24	596
Country of birth:		
Abroad	112	12953
UK	153	2930
Unknown	28	1857
Employment:		
Prisoner	13	26

Bibliographic reference	**Maguire H, Brailsford S, Carless J, Yates M, Altass L, Yates S, Anaraki S, Charlett A, Lozewicz S, Lipman M and Bothamley G (2011) Large outbreak of isoniazid-monoresistant tuberculosis in London, 1995 to 2006: case-control study and recommendations. Euro Surveillance 16(13): pii: 19830**

Healthcare	9	523
Unemployed	120	2095
Asylum seeker/refugee	2	52
Drug dealer/sex worker	7	3
Educational setting	18	2269
Retired	10	759
Other	114	11997
Unknown	0	16
Pulmonary disease:		
No	40	8531
Yes	253	9193
Unknown	0	16
Sputum smear status:		
Negative	79	4138
Positive	153	3266
Unknown	51	4365
Not tested	10	5971

Location	London
Approach to analysis	Logistic regression was used to obtain unadjusted odds ratios for each variable Those variables found to be statistically significant were included in a multivariable analysis using logistic regression to control for confounders
Outcomes measures and effect size	*Risk factors for isoniazid resistance in patients with tuberculosis*

Risk factor	*Adjusted OR (95% CI)*	*P-value*
Sex:		
Male	1.34 (0.98 to 1.83)	0.07
Female	Reference	-
Age:		
0-14 years	0.30 (0.09 to 1.01)	0.05
15-24 years	Reference	-

Bibliographic reference	Maguire H, Brailsford S, Carless J, Yates M, Altass L, Yates S, Anaraki S, Charlett A, Lozewicz S, Lipman M and Bothamley G (2011) Large outbreak of isoniazid-monoresistant tuberculosis in London, 1995 to 2006: case-control study and recommendations. Euro Surveillance 16(13): pii: 19830		
	25-34 years	0.79 (0.52 to 1.20)	0.27
	35-44 years	0.64 (0.41 to 1.00)	0.05
	45-64 years	0.45 (0.27 to 0.74)	0.002
	≥65 years	0.23 (0.10 to 0.51)	<0.001
	Ethnicity:		
	Black African	Reference	-
	Black Caribbean	12.52 (7.69 to 20.37)	<0.001
	Black (other)	3.29 (1.35 to 8.02)	0.009
	White	2.94 (1.79 to 4.83)	<0.001
	Indian subcontinent	0.57 (0.30 to 1.10)	0.092
	Chinese	0.68 (0.09 to 5.05)	0.703
	Other	1.210 (0.67 to 2.19)	0.528
	Country of birth:		
	Abroad	Reference	-
	UK	2.40 (1.68 to 3.43)	<0.001
	Employment:		
	Prisoner	20.21 (6.75 to 60.56)	<0.001
	Healthcare	1.53 (0.67 to 3.51)	0.316
	Unemployed	4.09 (2.97 to 5.63)	<0.001
	Asylum seeker/refugee	8.09 (1.02 to 64.41)	0.048
	Drug dealer/sex worker	187.07 (28.40 to 1232.35)	<0.001
	Educational setting	1.22 (0.67 to 2.23)	0.524
	Retired	1.69 (0.71 to 4.06)	0.239
	Other	Reference	-
	Pulmonary disease:		
	No	Reference	-
	Yes	1.52 (0.98 to 2.36)	0.61
	Sputum smear status:		
	Negative	Reference	-

Bibliographic reference	Maguire H, Brailsford S, Carless J, Yates M, Altass L, Yates S, Anaraki S, Charlett A, Lozewicz S, Lipman M and Bothamley G (2011) Large outbreak of isoniazid-monoresistant tuberculosis in London, 1995 to 2006: case-control study and recommendations. Euro Surveillance 16(13): pii: 19830		
	Positive	1.37 (0.98 to 1.93)	0.067
Source of funding	No details provided		
Comments			
Abbreviations: CI, confidence interval; HPA, Health Protection Agency; MIRU-VNTR, mycobacterial interspersed repetitive units variable number tandem repeat; OR, odds ratio; RFLP, restriction fragment length polymorphism			

Table 5: Melzer, 2010

Bibliographic reference	Melzer M, Gupta N, Petersen I, Cook S and Hall B (2010) Previous treatment in predicting drug-resistant tuberculosis in an area bordering East London, UK. International Journal of Infectious Diseases 14(8): e717-22
Study type	Observational
Study quality	Sample sufficiently represents the population of interest with regard to key characteristics? *yes* Loss to follow-up sufficiently unrelated to key characteristics? *yes* Prognostic factor of interest adequately measured? *yes, although blinding not reported* Outcome of interest adequately measured? *yes, although blinding not reported* Important potential confounders appropriately accounted for? *multivariate analysis used, but unclear which confounders were controlled for* Statistical analysis appropriate? *yes, although analyses not reported for site of disease, which was recorded and reported in population characteristics*
Number of patients	n = 380 • drug-resistant tuberculosis = 30 • fully sensitive tuberculosis = 350
Patient characteristics	*Study group(s)* All cases of microbiologically confirmed drug resistant tuberculosis at King George, Harold Wood and Oldchurch hospitals in Essex, part of the Barking, Havering and Redbridge Trust between January 2003 to December 2006 Drug resistance was defined as MDR, isoniazid, or rifampin resistance. MDR was defined as resistance to at least rifampin and isoniazid *Comparator* All cases of microbiologically confirmed drug susceptible tuberculosis at King George, Harold Wood and Oldchurch

Bibliographic reference	Melzer M, Gupta N, Petersen I, Cook S and Hall B (2010) Previous treatment in predicting drug-resistant tuberculosis in an area bordering East London, UK. International Journal of Infectious Diseases 14(8): e717-22
	hospitals in Essex, part of the Barking, Havering and Redbridge Trust between January 2003 to December 2006 *Tuberculosis diagnosis* All samples were auramine stained and subcultured onto Lowenstein–Jensen and Middlebrook media All smear-positive and extrapulmonary samples were directly inoculated into Kirschner's broth and the automated liquid MB/BacT system to expedite the time to culture Speciation was determined by biochemical testing and DNA hybridization (Accuprobe) *Drug susceptibility testing* Antimicrobial susceptibility testing was performed using the resistance ratio method on Lowenstein-Jensen medium or the radiometric BACTEC 460 method *Exclusion* Patients on tuberculosis on treatment without microbiological confirmation or those with smear-positive specimens whose cultures failed to grow, grew mycobacteria other than *M. tuberculosis*, or were contaminated Patients without drug susceptibility results *Population characteristics*

Bibliographic reference	**Melzer M, Gupta N, Petersen I, Cook S and Hall B (2010) Previous treatment in predicting drug-resistant tuberculosis in an area bordering East London, UK. International Journal of Infectious Diseases 14(8): e717-22**
Location	Essex
Approach to analysis	Differences in demographic and risk factors for drug-resistant tuberculosis were examined by univariable analysis The association between drug resistance and the following variables was determined: age, gender, high incidence countries for drug resistance, date of arrival in the UK, HIV serostatus, previous treatment, exposure to drug- resistant tuberculosis, and site of infection A multivariable logistic regression model was developed to examine the association between past treatment and drug resistance, adjusted for those variables mentioned above
Outcomes measures and effect size	*Risk factors for drug resistance in patients with tuberculosis*

	Drug-resistant[a] $n = 30$ (7.9%)	Drug-susceptible $n = 350$ (92.1%)
Age, years		
0–19	4 (13.3%)	29 (8.3%)
20–39	18 (60%)	198 (56.6%)
40–59	4 (13.3%)	67 (19.1%)
60–79	4 (13.3%)	38 (10.9%)
≥80	0	18 (5.1%)
Sex		
Male	17 (56.7%)	182 (52%)
Female	13 (43.3%)	168 (48%)
Country of origin		
High-incidence (drug resistance)	14 (46.7%)	185 (52.9%)
Low-incidence (drug resistance)	16 (53.3%)	165 (47.1%)
Date of arrival in the UK		
<2000	9 (30%)	102 (29.1%)
≥2000	11 (36.7%)	127 (36.3%)
Missing or UK born	10 (33.3%)	121 (34.6%)
HIV status		
Positive	6 (20%)	37 (10.6%)
Negative or not known	24 (80%)	313 (89.4%)
Contact with drug-resistant TB		
Yes	1 (3.3%)	1 (0.3%)
No	29 (96.7%)	349 (99.7%)
Site of infection		
Pulmonary	20 (66.7%)	196 (56%)
Extrapulmonary	10 (33.3%)	138 (39.4%)
Both	0	16 (4.6%)
Previous treatment		
Yes	3 (10%)	21 (6%)
No	27 (90%)	329 (94%)

[a] Thirty-three drug-resistant isolates were cultured: 29 isoniazid-resistant, three multidrug-resistant, and one rifampin mono-resistant.

Bibliographic reference	**Melzer M, Gupta N, Petersen I, Cook S and Hall B (2010) Previous treatment in predicting drug-resistant tuberculosis in an area bordering East London, UK. International Journal of Infectious Diseases 14(8): e717-22**

Risk factor	*Adjusted OR (95% CI)*	*P-value*
Previous treatment	1.53 (0.41 to 5.62)	0.52
Age[1]	-	0.46
Sex Female	0.70 (0.33 to 1.49)	0.36
Country of origin High incidence of drug resistance	0.61 (0.25 to 1.47)	0.27
Date of arrival in the UK[2] ≥2000 i.e. <3-6 years in the UK	0.71 (0.27 to 1.87)	0.48
HIV-positive	1.93 (0.70 to 5.23)	0.19
Previous exposure to drug resistant tuberculosis	12.84 (0.68 to 240.2)	0.09

Source of funding	No details provided
Comments	

[1] Age was divided into quintiles and analysis for trend was performed
[2] Where date of arrival in the UK was not recorded, patients were assumed to be UK born

Abbreviations: CI, confidence interval; OR, odds ratio

Table 6: Neely, 2009

Bibliographic reference	**Neely F, Maguire H, Le Brun F, Davies A, Gelb D and Yates S (2010) High rate of transmission among contacts in large London outbreak of isoniazid mono-resistant tuberculosis. Journal of Public Health 32(1): 44-51**
Study type	Unmatched case-control
Study quality	Sample sufficiently represents the population of interest with regard to key characteristics? *yes* Loss to follow-up sufficiently unrelated to key characteristics? *unclear* Prognostic factor of interest adequately measured? *yes, although blinding not reported* Outcome of interest adequately measured? *yes, although blinding not reported* Important potential confounders appropriately accounted for? *multivariate analysis used, but unclear which confounders were controlled for* Statistical analysis appropriate? *yes, although analyses not reported for number of drug-using cases to whom contact*

<table>
<tr><th>Bibliographic reference</th><th>Neely F, Maguire H, Le Brun F, Davies A, Gelb D and Yates S (2010) High rate of transmission among contacts in large London outbreak of isoniazid mono-resistant tuberculosis. Journal of Public Health 32(1): 44-51</th></tr>
<tr><td></td><td>exposed, which was recorded and reported in population characteristics</td></tr>
<tr><td>Number of patients</td><td>n = 612 (87 of the 1st 100 cases[1] plus 525 people with tuberculosis among the contacts)
Outcome data available for 355[2]
• isoniazid-resistant tuberculosis = 127
• fully sensitive tuberculosis = 228</td></tr>
<tr><td>Patient characteristics</td><td>Recruitment
Screening of community (social and household) contacts of the first 100 confirmed cases reported during an outbreak of isoniazid monoresistant tuberculosis in London

Exclusions
Institutional contacts (i.e. school, hospital, work or prison inmates) could not be included in this analysis, as screening denominators and outcome records were dispersed through many different organizations and very incomplete

Study group(s)
Patients in whom an isolate of M. tuberculosis was cultured that was monoresistant to isoniazid and had the characteristic 15-band pattern of the outbreak strain on RFLP typing, or clinical cases that were epidemiologically linked to a case, had clinical signs or symptoms consistent with tuberculosis and were treated for isoniazid-resistant tuberculosis in the absence of a culture result

Comparator
Patients with drug susceptible tuberculosis

Population characteristics
<table>
<tr><th></th><th>Cases, n (%)</th><th colspan="2">Controls, n (%)</th></tr>
<tr><th></th><th></th><th>Receiving chemoprophylaxis</th><th>Discharge clear</th></tr>
<tr><td>Date of birth</td><td></td><td></td><td></td></tr>
<tr><td>1980–2003</td><td>14 (9.5)</td><td>32 (21.8)</td><td>101 (68.7)</td></tr>
<tr><td>1960–1980</td><td>14 (12.6)</td><td>8 (7.2)</td><td>89 (80.2)</td></tr>
<tr><td>1920–1960</td><td>4 (6.2)</td><td>1 (1.5)</td><td>60 (92.3)</td></tr>
<tr><td>Missing</td><td>8</td><td>4</td><td>20</td></tr>
<tr><td>Total</td><td>40</td><td>45</td><td>270</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Neely F, Maguire H, Le Brun F, Davies A, Gelb D and Yates S (2010) High rate of transmission among contacts in large London outbreak of isoniazid mono-resistant tuberculosis. Journal of Public Health 32(1): 44-51			
	Gender			
	Male	22 (15.1)	23 (15.7)	101 (69.2)
	Female	17 (9.1)	20 (10.8)	149 (80.1)
	Missing	1	2	20
	Total	40	45	270
	Cases to whom contact exposed			
	1	25 (8.2)	31 (10.2)	248 (81.6)
	≥2	15 (29.4)	14 (27.5)	22 (43.1)
	Total	40	45	270
	Nature of contact			
	Household	26 (20.2)	23 (17.8)	80 (62.0)
	Social	13 (6.1)	20 (9.3)	181 (84.6)
	Missing	1	2	9
	Total	40	45	270
	Degree of exposure			
	Close	31 (16.9)	27 (14.8)	125 (68.3)
	Casual	4 (2.9)	14 (10.2)	119 (86.9)
	Missing	5	4	26
	Total	40	45	270
	Sputum smear positive cases to whom contact exposed			
	≥1	30 (14.1)	29 (13.7)	153 (72.2)
	0	8 (7.3)	13 (11.8)	89 (80.9)
	Missing	2	3	28
	Total	40	45	270
	Number of prison cases to whom contact exposed			
	≥1	21 (18.4)	24 (21.1)	69 (60.5)
	0	16 (10.5)	10 (6.6)	126 (82.9)
	Missing	3	11	75
	Total	40	45	270

<table>
<tr><th>Bibliographic reference</th><th>Neely F, Maguire H, Le Brun F, Davies A, Gelb D and Yates S (2010) High rate of transmission among contacts in large London outbreak of isoniazid mono-resistant tuberculosis. Journal of Public Health 32(1): 44-51</th></tr>
<tr><td></td><td>
<table>
<tr><td colspan="4">Number of drug-using cases to whom contact exposed</td></tr>
<tr><td>≥1</td><td>29 (16.7)</td><td>31 (17.8)</td><td>114 (65.5)</td></tr>
<tr><td>0</td><td>2 (2.9)</td><td>7 (10.1)</td><td>60 (87.0)</td></tr>
<tr><td>Missing</td><td>9</td><td>7</td><td>96</td></tr>
<tr><td>Total</td><td>40</td><td>45</td><td>270</td></tr>
</table>
</td></tr>
<tr><td>Location</td><td>London</td></tr>
<tr><td>Approach to analysis</td><td>Univariate analysis of risk factors for outcome of screening showed a high degree of correlation between the following variables: young contacts, household and close contacts as well as those in contact with prisoners or drug-using cases
Because of this, for the multivariable model, the authors used the variable whether contacts were exposed to more than one case, but did not use the variables indicating contact with sputum smear-positive cases, prison or drug-using case; further reasons for their exclusion from the multivariable analysis were that the univariate analysis revealed only a weak, non-statistically significant association between contact with a sputum smear-positive case and transmission of disease (contrary to other evidence and discussed later in the paper), and that for 30% of cases it was unknown whether they were prisoners or drug users
A strong statistical association was found between the degree of exposure (close or casual) and nature of contact (household or social) (P<0.001); this was inevitably the result of classifying all household contacts as close – therefore, the variable describing the degree of exposure was kept in the main multivariable model and nature of contact excluded</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Risk factors for isoniazid resistance in patients with tuberculosis
<table>
<tr><th>Risk factor</th><th>Adjusted OR (95% CI)</th><th>Reference</th></tr>
<tr><td>Age[3]:
25-44 years
≤24 years</td><td>
1.7 (0.5 to 6.3)
2.1 (0.6 to 7.7)</td><td>
≥45 years
≥45 years</td></tr>
<tr><td>Gender:
Male</td><td>
2.7 (1.1 to 6.6)</td><td>
Female</td></tr>
<tr><td>Degree of exposure:
Close[4]</td><td>
6.2 (1.7 to 21.8)</td><td>
Casual[4]</td></tr>
<tr><td>Cases to whom contact was exposed:
≥2</td><td>
3.1 (1.1 to 8.4)</td><td>
1</td></tr>
<tr><td>Sputum smear positive cases to whom contact was exposed:
≥1</td><td>
2.2 (0.8 to 6.2)</td><td>
0</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Neely F, Maguire H, Le Brun F, Davies A, Gelb D and Yates S (2010) High rate of transmission among contacts in large London outbreak of isoniazid mono-resistant tuberculosis. Journal of Public Health 32(1): 44-51**
Source of funding	No details provided
Comments	Study aim: for a continuing London outbreak of isoniazid monoresistant tuberculosis, the authors aimed to determine the rate of transmission of same strain TB to contacts, and to identify which contacts were most at risk of becoming cases with a view to informing future contact tracing strategies

[1] Exclusions: 6 institutional contacts; 3 for whom no information was given by the chest clinic to the research group; 4 cases who did nit report any contacts

[2] Exclusions amongst contacts: no outcome or demographic data available for 24; 79 did not attend; 67 moved districts

[3] Converted from 'date of birth' by reviewer:

Date of birth	*Approximate age groups*
1920-60	≥45 years
1960-80	25-44 years
1980-2003	≤24 years

[4] The degree of exposure the contact had with the case was defined and categorized as minimal (1-2 hours), moderate (several hours) or close (days); contacts with minimal or moderate contact were grouped together and their exposure classified as casual; household contacts were considered to have had close contact

Abbreviations: CI, confidence interval; OR, odds ratio; RFLP, restriction fragment length polymorphism

Table 7: Pritchard, 2003

Bibliographic reference	**Pritchard AJ, Hayward AC, Monk PN and Neal KR (2003) Risk factors for drug resistant tuberculosis in Leicestershire--poor adherence to treatment remains an important cause of resistance. Epidemiology and Infection 130(3): 481-3**
Study type	Case-control
Study quality	Sample sufficiently represents the population of interest with regard to key characteristics? *yes* Loss to follow-up sufficiently unrelated to key characteristics? *yes* Prognostic factor of interest adequately measured? *yes, although blinding unclear and authors had to rely on others' notes* Outcome of interest adequately measured? *yes, although blinding unclear* Important potential confounders appropriately accounted for? *cases and controls were matched on ethnic group, gender and age group; multivariate analysis used, but unclear which confounders were controlled for* Statistical analysis appropriate? *yes*

Bibliographic reference	**Pritchard AJ, Hayward AC, Monk PN and Neal KR (2003) Risk factors for drug resistant tuberculosis in Leicestershire--poor adherence to treatment remains an important cause of resistance. Epidemiology and Infection 130(3): 481-3**
Number of patients	n = 104 • tuberculosis resistant to any first line drug = 23 • fully sensitive tuberculosis = 81
Patient characteristics	*Study group(s)* All patients with culture confirmed tuberculosis which was resistant to any first line drug between 1993 and 1998, living in Leicestershire *Comparator* All patients with fully sensitive culture confirmed tuberculosis between 1993 and 1998, living in Leicestershire Cases and controls were matched on ethnic group, gender and age group *Drug susceptibility testing* Technique unclear *Population characteristics* Risk factor / Resistant n=23 (%) / Sensitive n=81 (%) Poor adherence* recorded in notes: 11 (47·8) / 12 (14·8) No evidence of poor adherence in notes: 12 (52·2) / 69 (85·2) Previous TB recorded in notes: 8 (34·8) / 10 (12·3) No evidence of previous TB in notes: 15 (65·2) / 71 (87·7) Non-pulmonary: 10 (45·5) / 47 (58·0) Pulmonary: 12 (54·5) / 34 (42·0) Foreign birth recorded in notes: 13 (56·5) / 53 (65·4) No evidence of foreign birth in notes: 10 (43·5) / 28 (34·6) Foreign travel† recorded in notes: 13 (56·5) / 35 (43·2) No evidence of foreign travel in notes: 10 (43·5) / 46 (56·8) Recent immigration‡ recorded in notes: 2 (8·7) / 6 (7·4) No evidence of recent immigration in notes: 21 (91·3) / 75 (92·6)
Location	Leicestershire

Bibliographic reference	**Pritchard AJ, Hayward AC, Monk PN and Neal KR (2003) Risk factors for drug resistant tuberculosis in Leicestershire--poor adherence to treatment remains an important cause of resistance. Epidemiology and Infection 130(3): 481-3**
Approach to analysis	Multivariate analysis
Outcomes measures and effect size	*Risk factors for first line drug resistance in patients with tuberculosis*

Risk factor	*Reference*	*Adjusted OR (95% CI)*	*P*
Poor adherence	No evidence of poor adherence	4.8 (1.6 to 14.4)	0.005
Previous history of tuberculosis	No previous history of tuberculosis	3.7 (1.2 to 11.8)	0.022
Pulmonary	Extrapulmonary	Not provided; authors state not significant	>0.05
Foreign birth	UK birth	Not provided; authors state not significant	>0.05
Foreign travel	No evidence of foreign travel	Not provided; authors state not significant	>0.05
Recent immigration	No evidence of recent immigration	Not provided; authors state not significant	>0.05

Source of funding	Leicestershire Health Authority
Comments	

Abbreviations: CI, confidence interval; OR, odds ratio

Table 8: Story, 2007

Bibliographic reference	**Story A, Murad S, Roberts W, Verheyen M, Hayward AC; London Tuberculosis Nurses Network (2007) Tuberculosis in London: the importance of homelessness, problem drug use and prison. Thorax 62(8): 667-71**
Study type	Observational
Study quality	Sample sufficiently represents the population of interest with regard to key characteristics? *yes* Loss to follow-up sufficiently unrelated to key characteristics? *unclear* Prognostic factor of interest adequately measured? *yes, although blinding not reported* Outcome of interest adequately measured? *yes, although blinding not reported*

Bibliographic reference	**Story A, Murad S, Roberts W, Verheyen M, Hayward AC; London Tuberculosis Nurses Network (2007) Tuberculosis in London: the importance of homelessness, problem drug use and prison. Thorax 62(8): 667-71**
	Important potential confounders appropriately accounted for? *multivariate analysis used, but unclear which confounders were controlled for* Statistical analysis appropriate? *yes, although analyses not reported for a number of variables recorded and reported in population characteristics*
Number of patients	1995 eligible patients Data available for 1941 • any drug resistance = 234 • multidrug resistance = 67 • isoniazid resistance = 167 • fully sensitive tuberculosis = 1473
Patient characteristics	*Study group(s)* All patients with drug resistant tuberculosis living in London who were or should have been on treatment on 1 July 2003 Drug resistance was divided into • multidrug resistance (resistant to at least isoniazid and rifampicin) • isonaizid resistant strains that were part of the London outbreak (defined as patients resident in London at the time of their diagnosis with isolates of Mycobacterium tuberculosis resistant to isoniazid that had the outbreak RFLP pattern) • isoniazid resistant strains that were not part of the outbreak *Comparator* All patients with fully sensitive tuberculosis living in London who were or should have been on treatment on 1 July 2003 *Exclusion* Cases subsequently found not to have tuberculosis *Population characteristics*

Bibliographic reference	**Story A, Murad S, Roberts W, Verheyen M, Hayward AC; London Tuberculosis Nurses Network (2007) Tuberculosis in London: the importance of homelessness, problem drug use and prison. Thorax 62(8): 667-71**

Patient characteristics	n	Culture confirmed n (%)	Sputum smear positive n (%)	Any drug resistance n (%)	MDRTB n (%)	Isoniazid resistant (non-outbreak) n (%)	Isoniazid resistant (outbreak) n (%)
Overall	1941	1121 (57.8%)	381 (19.6%)	234 (20.9%)	67 (6.0%)	129 (11.5%)	38 (3.4%)
Age 0–14	92	29 (31.5%)	5 (5.4%)	6 (20.6%)	2 (6.9%)	3 (10.3%)	1 (3.4%)
Age 15–29	718	444 (61.8%)	158 (22.0%)	97 (21.8%)	27 (6.1%)	57 (12.8%)	13 (2.9%)
Age 30–59	919	536 (58.3%)	187 (20.3%)	116 (21.6%)	32 (6.0%)	61 (11.4%)	23 (4.3%)
Age 60+	203	108 (53.2%)	31 (15.3%)	13 (12.0%)	5 (4.6%)	7 (6.5%)	1 (0.9%)
Male	1064	637 (59.9%)	231 (21.7%)	139 (21.8%)	41 (6.4%)	74 (11.6%)	24 (3.8%)
Female	847	467 (55.1%)	147 (17.4%)	94 (20.1%)	26 (5.6%)	54 (11.6%)	14 (3.0%)
Foreign born	1548	902 (58.3%)	227 (14.7%)	179 (19.8%)	59 (6.5%)	106 (11.8%)	14 (1.6%)
UK born	376	206 (54.8%)	100 (26.6%)	52 (25.2%)	6 (2.9%)	23 (11.2%)	23 (11.2%)
Recent migrant (<1 year)	295	172 (58.3%)	54 (18.3%)	30 (17.4%)	10 (5.8%)	19 (11.0%)	1 (0.6%)
White	303	188 (62.0%)	85 (28.1%)	34 (18.1%)	6 (3.2%)	19 (10.0%)	9 (4.8%)
South Asian	650	339 (52.2%)	79 (12.2%)	52 (15.3%)	16 (4.7%)	33 (9.7%)	3 (0.9%)
Black African	748	449 (60.0%)	150 (20.1%)	100 (22.3%)	37 (8.2%)	59 (13.1%)	4 (0.9%)
Black Caribbean	92	64 (69.6%)	33 (35.9%)	25 (39.1%)	2 (3.2%)	6 (9.4%)	17 (26.6%)
Other	83	48 (57.8%)	19 (22.9%)	15 (31.3%)	5 (10.4%)	8 (16.7%)	2 (4.2%)
Previous TB	202	111 (55.0%)	42 (20.8%)	47 (42.3%)	26 (23.4%)	15 (13.5%)	6 (5.4%)
PDU	248	176 (71.0%)	97 (39.1%)	58 (33.0%)	11 (6.3%)	20 (11.4%)	27 (15.3%)
Alcohol	156	111 (71.2%)	64 (41.0%)	34 (30.6%)	5 (4.5%)	11 (9.9%)	18 (16.2%)
Prison during treatment	74	55 (74.3%)	29 (39.2%)	30 (54.5%)	8 (14.5%)	3 (5.5%)	19 (25.7%)
Homeless during treatment	110	77 (70.0%)	42 (38.2%)	30 (39.0%)	5 (6.5%)	13 (16.9%)	12 (15.6%)
Prison or homeless or PDU	321	221 (68.8%)	115 (35.8%)	67 (30.3%)	14 (6.3%)	26 (11.8%)	27 (12.2%)

Location	London
Approach to analysis	Logistic regression analysis was used to calculate univariate odds ratios, 95% confidence intervals and p values Multiple logistic regression models (backwards elimination) were used to control for confounding using robust standard errors to account for clustering at the clinic level
Outcomes measures and effect size	*Risk factors for any drug resistance in patients with tuberculosis*

Risk factor	*Adjusted OR (95% CI)*
Age:	
0-14 years	1.0 (0.3 to 3.4)
15-29 years	1.0 (0.8 to 1.6)
30-59 years	Reference
≥60 years	0.6 (0.4 to 1.0)
Male	1.0 (0.7 to 1.4)

Bibliographic reference	Story A, Murad S, Roberts W, Verheyen M, Hayward AC; London Tuberculosis Nurses Network (2007) Tuberculosis in London: the importance of homelessness, problem drug use and prison. Thorax 62(8): 667-71

Born in the UK	-
Ethnicity: White South Asian Black African Black Caribbean Other	 Reference 1.0 (0.6 to 1.6) 1.3 (0.8 to 2.0) 3.0 (1.2 to 7.7) 1.9 (1.0 to 3.4)
Previous tuberculosis	3.0 (1.9 to 4.9)
Problem drug use[1]	-
Imprisonment[2]	3.0 (1.7 to 5.5)
Hostel/street homeless[3]	-
Ever homeless[3]	1.6 (1.1 to 2.2)
Mental health problems	-

Risk factors for multidrug resistance in patients with tuberculosis

Risk factor	*Adjusted OR (95% CI)*
Age: 0-14 years 15-29 years 30-59 years ≥60 years	 - - - -
Male	-
Born in the UK	-
Ethnicity: White South Asian Black African Black Caribbean Other	 Reference 1.6 (0.8 to 3.0) 2.5 (1.2 to 5.7) 1.6 (0.3 to 10.2) 2.5 (0.9 to 7.1)
Previous tuberculosis	7.8 (4.8 to 12.5)

Bibliographic reference	Story A, Murad S, Roberts W, Verheyen M, Hayward AC; London Tuberculosis Nurses Network (2007) Tuberculosis in London: the importance of homelessness, problem drug use and prison. Thorax 62(8): 667-71	
	Problem drug use[1]	-
	Imprisonment[2]	-
	Hostel/street homeless[3]	-
	Ever homeless[3]	2.1 (1.1 to 4.1)
	Mental health problems	-
	Risk factors for isoniazid resistance in patients with tuberculosis in a non-outbreak situation	
	Risk factor	*Adjusted OR (95% CI)*
	Age:	
	0-14 years	0.8 (0.2 to 4.6)
	15-29 years	1.1 (0.7 to 1.7)
	30-59 years	Reference
	≥60 years	0.5 (0.3 to 1.2)
	Male	1.0 (0.7 to 1.6)
	Born in the UK	-
	Ethnicity:	
	White	Reference
	South Asian	1.0 (0.5 to 2.1)
	Black African	1.4 (0.7 to 2.6)
	Black Caribbean	1.6 (0.3 to 10.2)
	Other	2.5 (0.9 to 7.1)
	Previous tuberculosis	-
	Problem drug use[1]	-
	Imprisonment[2]	-
	Hostel/street homeless[3]	2.0 (0.9 to 4.5)
	Ever homeless[3]	-
	Mental health problems	-
	Risk factors for isoniazid resistance in patients with tuberculosis in an outbreak	
	Risk factor	*Adjusted OR (95% CI)*
	Age:	

Bibliographic reference	Story A, Murad S, Roberts W, Verheyen M, Hayward AC; London Tuberculosis Nurses Network (2007) Tuberculosis in London: the importance of homelessness, problem drug use and prison. Thorax 62(8): 667-71		
		0-14 years	-
		15-29 years	-
		30-59 years	-
		≥60 years	-
		Male	-
		Born in the UK	2.8 (1.1 to 7.0)
		Ethnicity: White South Asian Black African Black Caribbean Other	 Reference 1.1 (0.2 to 6.7) 0.8 (0.1 to 7.2) 9.7 (2.6 to (35.4) 6.1 (1.6 to 23.3)
		Previous tuberculosis	-
		Problem drug use[1]	3.5 (1.6 to 7.7)
		Imprisonment[2]	10.3 (4.0 to 26.5)
		Hostel/street homeless[3]	-
		Ever homeless[3]	-
		Mental health problems	-
Source of funding	No details provided		
Comments			

[1] Problem drug use was defined as injecting drug use or long duration/regular use of opiates, cocaine and/or amphetamines
[2] Imprisonment was defined as any period of incarceration during the current treatment episode
[3] Homelessness was defined as living in direct access hostels or rough sleeping ever or during the current treatment episode

Abbreviations: CI, confidence interval; OR, odds ratio; RFLP, restriction fragment length polymorphism

International surveillance data

High MDR-TB burden countries according to WHO ‘s Global TB Report 2014

	ESTIMATED % OF NEW TB CASES WITH MDR-TB[a]	CONFIDENCE INTERVAL	ESTIMATED % OF RETREATMENT TB CASES WITH MDR-TB[a]	CONFIDENCE INTERVAL
Armenia	9.4	7.0–12	43	38–49
Azerbaijan	13	10–16	28	22–34
Bangladesh	1.4	0.7–2.5	29	24–34
Belarus	35	33–37	55	51–57
Bulgaria	2.3	1.3–3.8	23	17–31
China	5.7	4.5–7.0	26	22–30
DR Congo	*2.6*	*0.01–5.5*	*13*	*0.2–28*
Estonia	17	12–24	48	32–63
Ethiopia	1.6	0.9–2.8	12	5.6–21
Georgia	11.0	9.7–13	38	34–42
India	2.2	1.9–2.6	15	11–19
Indonesia	1.9	1.4–2.5	12	8.1–17
Kazakhstan	25	24–26	55	54–56
Kyrgyzstan	26	23–31	55	52–58
Latvia	8.8	6.6–12	26	18–35
Lithuania	11	9.5–14	44	39–49
Myanmar	5.0	3.1–6.8	27	15–39
Nigeria	2.9	2.1–4.0	14	10–19
Pakistan	4.3	2.8–5.7	19	14–25
Philippines	2.0	1.4–2.7	21	16–29
Republic of Moldova	24	21–26	62	59–65
Russian Federation	19	14–25	49	40–59
South Africa	1.8	1.4–2.3	6.7	5.4–8.2
Tajikistan	13	9.8–16	56	52–60
Ukraine	14	14–15	32	31–33