Transmission of multidrug-resistant tuberculosis in the UK: a cross-sectional molecular and epidemiological study of clustering and contact tracing

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Summary

Background Between 2000 and 2012 the number of multidrug-resistant (MDR) tuberculosis cases in the UK increased from 28 per year to 81 per year. We investigated the proportion of MDR tuberculosis cases arising from transmission in the UK and associated risk factors.

Method We identified patients with MDR tuberculosis notified in England, Wales, and Northern Ireland between Jan 1, 2004, and Dec 31, 2007, by linking national laboratory and surveillance data. Data for laboratory isolates, including drug sensitivities and 24-mycobacterial interspersed repetitive-unit-variable-number tandem repeat (MIRU-VNTR) typing were obtained routinely from the National Tuberculosis Reference laboratories as part of national tuberculosis surveillance. We investigated clusters of cases with indistinguishable MIRU-VNTR profiles to identify epidemiological links. We calculated transmission using the n–1 method and established associated risk factors by logistic regression. We also assessed the likelihood of transmission to additional secondary active tuberculosis cases, identified through conventional contact tracing.

Findings 204 patients were diagnosed with MDR tuberculosis in the study period; 189 (92·6%) had an MIRU-VNTR profile. We identified 12 clusters containing 40 individuals and 149 unique strains. The proportion of cases attributable to recent transmission, on the basis of molecular data, was 15% (40 cases clustered–12 clusters/189 with a strain type). The proportion of cases attributable to recent transmission (ie, transmission within the UK) after adjustment for epidemiological links was 8·5% (22 cases with epidemiological links–six clusters/189 cases with a strain type). Being UK born (odds ratio 4·81; 95% CI 2·03–11·36, p=0·0005) and illicit drug use (4·75; 1·19–18·96, p=0·026) were significantly associated with clustering. The most common transmission setting was the household but 21 of 22 of epidemiological links were missed by conventional contact tracing. 13 secondary active tuberculosis cases identified by conventional contact tracing were mostly contacts of patients with MDR tuberculosis from countries of high tuberculosis burden. 11 (85%) of 13 shared the same country of birth as the index case, of whom ten did not share a strain type or drug resistance pattern.

Interpretation Transmission of MDR tuberculosis in the UK is low and associated with being UK born or illicit drug use. MIRU-VNTR typing with cluster investigation was more successful at identifying transmission events than conventional contact tracing. Individuals with tuberculosis who have had contact with a known MDR tuberculosis source case from a country of high tuberculosis burden should have drug-sensitivity testing on isolates to ensure appropriate treatment is given.

Funding Public Health England.

Introduction

In 2012, WHO estimated that 450 000 new cases of multidrug resistant (MDR) tuberculosis—defined as *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampicin—occurred worldwide.[1] Although there is little evidence to suggest that patients with MDR tuberculosis are more infectious than those with fully sensitive tuberculosis,[2] the longer period during which these patients remain infectious provides greater opportunity for transmission. Additionally, people who acquire MDR tuberculosis strains develop disease with a poor prognosis, increasing the importance of tackling transmission of these strains. Understanding the transmission dynamics of MDR tuberculosis will help inform future tuberculosis control strategies.

In the UK, the number of MDR tuberculosis cases has increased substantially in the past decade from 28 cases in 2000 to 81 cases in 2012 (an increase from 0·9% to 1·6% of all cases).[3] Most individuals with MDR tuberculosis in the UK were born in sub-Saharan Africa or the Indian subcontinent but the proportion of cases of tuberculosis that are MDR is highest in the eastern European population,[3] which is indicative of the global situation.[1] Mycobacterial interspersed repetitive-unit–variable-number tandem repeat (MIRU-VNTR) strain typing is a useful method for rapid detection of patients infected with the same strain of *M tuberculosis*, which might result from recent transmission (ie, within the previous 2 years). A previous analysis[4] with 15 loci MIRU-VNTR strain typing estimated that 19% of MDR

tuberculosis in the UK was attributable to recent transmission. This estimate was based on a short observation period (2004–05), and data for epidemiological links were scarce. A study of extensively drug-resistant (XDR) tuberculosis did not identify evidence of transmission in the UK.[5]

In this study, we combined 24 loci MIRU-VNTR strain typing with epidemiological data collected routinely in the surveillance system and through a cluster investigation questionnaire, which was devised to identify potential epidemiological links between cases. We aimed to establish the proportion of MDR tuberculosis cases attributable to transmission in the UK between 2004 and 2007 and to identify associated risk factors. We used information obtained from contact investigations to identify additional secondary active tuberculosis cases and to subsequently assess the effectiveness of conventional contact tracing for identification of true transmission events, in the absence of routine strain typing.

Methods

Study population

We included all patients with culture-confirmed MDR tuberculosis notified between Jan 1, 2004, and Dec 31, 2007, in England, Wales, and Northern Ireland in this study.

Public Health England has the right under Section 60 of the National Health Service Act 2006 and approval from the National Information Governance Board to hold and analyse national surveillance data for the purposes of protection of public health and for infectious disease surveillance; as such, these analyses did not require separate ethics approval.

Data collection

We identified patients with MDR tuberculosis by matching laboratory isolates to case reports in the enhanced tuberculosis surveillance system.[6] This system contains demographic (age, sex, country of birth, ethnicity, years since entry to the UK, and address) and clinical (site of disease, sputum smear status, and previous diagnosis of tuberculosis) characteristics of patients. We sent cluster investigation questionnaires to health-care workers in tuberculosis clinics to obtain information about social risk factors (history of alcohol or illicit drug use, homelessness, imprisonment), contact with a known drug-resistant case, and details of the contact investigation including personal identifiers of contacts diagnosed with active disease. After molecular cluster assignation we sent a second questionnaire (cluster questionnaire)[7] to health-care workers in all treating clinics to collect additional sociodemographic information (details of previous address, education, workplace, regular place of socialising, religious setting, prison, rehabilitation centre, homeless hostel, regular travel to or visitors from abroad or within the UK, all in the 2 years before diagnosis) for each clustered case. All questionnaires were completed by use of medical records and all were returned to the investigators. We obtained contact tracing notes from the tuberculosis clinics for each index case, when available. These notes contained information about the number of individuals screened (by Mantoux test or interferon γ release assay) and screening results for latent tuberculosis infection and active tuberculosis.

Laboratory methods

We did drug-susceptibility testing for all first-line (isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin) and second-line antibiotics (amikacin, capreomycin, kanamycin, moxifloxacin, ofloxacin, ethionamide, prothionamide, cycloserine, aminosalicylic acid, linezolid, and clofazimine) using the proportion or the resistance ratio method.[8] We identified one case of laboratory cross-contamination, confirmed as not tuberculosis with the treating clinic and excluded. Strains showing borderline resistance to a drug were deemed to be resistant to that agent. We did retrospective strain typing using 24 MIRU-VNTR, as previously described,[9] on all initial MDR tuberculosis isolates, when available.

Cluster analysis

We combined MIRU-VNTR strain typing data with epidemiological information to identify links between patients and transmission settings. We assembled clusters on the basis of their MIRU-VNTR profile. A cluster was defined as two or more patients with MDR tuberculosis with indistinguishable 24 loci MIRU-VNTR profiles, with at least 22 complete loci,[10] notified in the UK between 2004 and 2007. Patients were clustered irrespective of geographical area of residence. We established the *M tuberculosis* lineage as previously described.[11] We calculated the proportion of clustered cases using the n−1 method[12] (number of cases clustered–number of clusters / number of cases with a strain type). We used cluster questionnaires to identify common settings in which transmission could have occurred and to identify or confirm epidemiological links between patients.

Epidemiological links were confirmed if the patients named each other or lived at the same address; probable if patients were resident in London, had the same strain type and characteristics as patients with tuberculosis who were part of a known London outbreak,[13] and did not name each other or live at the same address; possible if patients were linked through a common setting, other than the household, but did not name each other; or not linked if patients did not name each other and no common setting was identified. These criteria were adapted from those defined in the national guidelines for cluster investigation.[7] Transmission was confirmed if clustered cases had a confirmed epidemiological link. We adjusted the proportion of cases resulting from recent transmission in the UK by including only cases and clusters with confirmed links in the calculation (number of cases with epidemiological links–number of clusters

Panel 1: **Definitions used in contact investigation**

Index case
A culture confirmed MDR tuberculosis case notified in the UK between 2004 and 2007. The first MDR tuberculosis case to be notified.

Contact
A person named as a contact by the index case.

Secondary case
(1) A contact who was named by the index case, screened, and was subsequently found to have active tuberculosis. Although this individual was notified later this individual could also be deemed the source of infection or source case for the index case. For example, in reverse contact tracing of a child or if the secondary case had an earlier onset of symptoms.
(2) A person who was not identified for screening initially but presented later with active tuberculosis and reported contact with an index case.

with epidemiological links/number of cases with a strain type). We generated cluster diagrams displaying epidemiological links using Cytoscape desktop, which is an open source software package for building links between cases to form networks that can be annotated. We used BioNumerics (version 5.10) to generate the cluster assembly and the dendrogram.

For more on **Cytoscape** see http://www.cytoscape.org

Contact investigation

For each patient with MDR tuberculosis, we used contact investigation notes to identify secondary active tuberculosis cases that were not included in the original study population because they were notified outside the study period or geographical area (Scotland), an isolate was unavailable for 24 loci MIRU-VNTR typing, or the isolate had a different MIRU-VNTR strain. Panel 1 shows definitions used in contact investigation. We obtained additional details about secondary cases from the enhanced tuberculosis surveillance system and, for one case, from the Scottish enhanced surveillance of mycobacterial infections system. 15 loci MIRU-VNTR typing was done in the UK before the introduction of 24 loci MIRU-VNTR and was available from the Mycobacterial Surveillance Network (MycobNet) for cases not in the original study population. We compared drug susceptibility patterns and, when available, strain typing information between index and secondary cases to assess the likelihood of transmission.

Transmission between patients was confirmed if isolates from the index and secondary cases had indistinguishable MIRU-VNTR profiles for the first 15 loci and the drug resistance pattern was consistent with transmission (patterns were the same or the isolate from the index case had resistance to fewer drugs than subsequent cases); possible if the strain type was not available for the secondary case but the drug resistance pattern was consistent with transmission; unknown if the strain type and drug resistance pattern of the secondary case were unavailable; or deemed not to have occurred if the MIRU-VNTR profile was different or the drug resistance patterns of isolates were different (the secondary case was not MDR).

Statistical analysis

We used univariable and multivariable logistic regression modelling to calculate odds ratios (ORs) for factors associated with being in a cluster compared with having a unique strain. We used a forward stepwise approach to select the multivariable model with a probability entry of less than 0·2. We used Stata (version 12.0) for statistical analyses.

Role of the funding source

There was no external funding source for this study. LFA, ST, DZ, and IA had full access to all the data in the study. LFA had final responsibility for the decision to submit for publication.

Results

Between 2004 and 2007, there were 32 578 notified tuberculosis cases in the UK, of which 58·5% (19 059) were culture confirmed; 99·1% (18 892) of culture-confirmed cases had drug sensitivity results available for at least isoniazid and rifampicin. 204 individuals were diagnosed with culture-confirmed MDR tuberculosis of whom 189 (92·6%) had MIRU-VNTR profiles. Most individuals with MDR tuberculosis were aged 15–44 years old (170 of 204; 83·3%), non-UK born (170 of 201; 84·6%), had pulmonary disease (143 of 204; 70·1%), and had no previous diagnosis of tuberculosis (128 of 184; 69·6%). The outcomes of treatment of these cases have been described previously.[14]

Of 189 cases with MIRU-VNTR profiles, lineages could be assigned to 184 (97·4%). The most common lineage was Euro-American (78; 42·4%) followed by east African-Indian (44; 23·9%), Beijing (42; 22·8%), Indo-Oceanic (16; 8·7%), and *Mycobacterium africanum* (4; 2·2%). We identified 12 clusters containing 40 individuals (table 1) and 149 unique strains. The proportion of cases attributable to recent transmission, on the basis of molecular data only, was 15% (40 cases clustered–12 clusters/189 cases with a strain type). Cluster size ranged from two to 12 cases: 35% (14 of 40) were in small clusters (of two cases), 35·0% (14) were in medium clusters (of three or four cases), and 30% (12 of 40) were in one large cluster (of 12 cases). The strains of most clustered cases were Euro-American (18 of 40; 45·0%) or Beijing (16 of 40; 40·0%).

We identified epidemiological links in half the clusters (six of 12; a total of 22 cases with known, probable, or possible links; table 1, figure), and in these clusters the household was the most common transmission setting (ten of 22; 45%). In all these clusters, the first case was

	Strain type	Lineage	Number of cases	Country of birth	Ethnicities	Index case non-UK born	Index case pulmonary smear positive	Risk factors	Epidemiological link	Transmission setting
1	424352332517333456443372	Beijing	12	5 UK, 2 Angola, 1 Iran, 2 Latvia, 1 Nigeria, 1 unknown	6 black African; 2 black Caribbean; 2 mixed/other; 1 white; 1 Indian; none of UK born cases were white	Yes	Yes	Drug use (4)	Yes	Household, work, and social
2	422342442517332442423374	East African/ Indian	2	India	Indian	Yes	Yes	No	Yes	Place of worship
3	424332431515321236423-52	Euro-American	4	UK	2 black Caribbean; 2 white	No	Yes	Drugs, prison, homeless, alcohol (3)	Yes	Unknown
4	3242325125113223324433-3	Euro-American	2	UK	2 white	No	Yes	No	Yes	Household
5	3243225125113223324433-3	Euro-American	3	2 Afghanistan; 1 UK	2 mixed/other; 1 Pakistani	Yes	Yes	No	Yes	Household
6	3233324125163244344434-3	Euro-American	3	2 UK; 1 India	3 Indian	Yes	Yes	No	Yes	Household and work
7	424332331515321234423-52	Euro-American	2	Nigeria	2 black African	Yes	No	No	No	Unknown
8	2223214326153243324132 62	Euro-American	2	India	2 Indian	Yes	No	No	No	Unknown
9	2243215326153273324132 92	Euro-American	2	Lithuania	2 white	Yes	No	No	No	Unknown
10	-2225254251633354-423384	East African Indian	2	1 India; 1 Pakistan	1 Indian; 1 Pakistani	Yes	No	No	No	Unknown
11	42234264251732344244 34-4	East African Indian	2	Pakistan	2 Pakistani	Yes	No	No	No	Contact with MDR tuberculosis identified abroad
12	424352332515333456443382	Beijing	4	2 UK; 1 Bangladesh; 1 China	2 white; 1 Bangladeshi; 1 Chinese	No	Yes	No	No	Contact with MDR tuberculosis identified abroad

MDR=multidrug-resistant.

Table 1: **Characteristics of clusters**

pulmonary sputum smear positive and drug-resistance patterns were consistent with transmission. In four clusters, the first case was non-UK born and in three of these clusters there was transmission to individuals from the same countries of birth (clusters 1, 2, and 5). We also identified confirmed transmission from non-UK-born individuals to non-white-UK-born individuals of the same ethnicity (clusters 1 and 6). The largest cluster of 12 patients (cluster 1) was a known outbreak that began in 2004[4] (figure). Although only three of 12 patients had epidemiological links confirmed, sociodemographic factors and links through the community, workplace, and drug use suggested that spread to the other seven patients was likely. A cluster of four patients with MDR tuberculosis (cluster 3) were part of the isoniazid mono-resistant outbreak in London[13] associated with UK-born individuals of white or black Caribbean ethnicities with social risk factors. At least one of these four patients acquired rifampicin resistance through non-compliance.

Of the 22 cases in clusters with epidemiological links, 95% (21) of links were not identified through conventional contract tracing. Household contacts were not disclosed by the index case because they had not been living at the same address at the time of diagnosis, they were an undisclosed frequent visitor, or were a temporary resident and had moved on. The proportion of cases attributable to recent transmission (ie, transmission within the UK) after adjustment for epidemiological links was 8·5% (22 cases with epidemiological links–six clusters/189 cases with a strain type).

Six clusters had no epidemiological links identified (table 1). Patients within each of these clusters were born in the same geographical region and were from countries with a high tuberculosis burden. The first case in each cluster was extrapulmonary or pulmonary sputum smear negative, suggesting that transmission in the UK was not likely. Although one cluster (cluster 12) contained both UK and non-UK-born individuals, patients had differing drug resistance patterns, UK-born patients had links to

countries of high tuberculosis burden through family or occupation, and non-UK-born patients were recent entrants (ie, within the year before diagnosis), reducing the likelihood of transmission in the UK.

Table 2 shows results of the univariable analysis. In the multivariable analysis, being UK born (adjusted OR 4·81; 95% CI 2·03–11·36; p=0·0005) and a history of illicit drug use (adjusted OR 4·75; 95% CI 1·19–18·96; p=0·026) were independently associated with clustering. After adjustment for place of birth and drug use, being a prisoner was no longer significantly associated with clustering (adjusted OR 1·05; 95% CI 0·85–12·73, p=0·975) and was not included in the final model.

Most of the 204 patients with MDR tuberculosis had contact tracing information available (187; 91·7%). For 187 MDR tuberculosis index cases, 1650 contacts were identified for screening, of whom 1472 (89·2%) were screened: 70 had latent infection (attack rate=4·8%) and

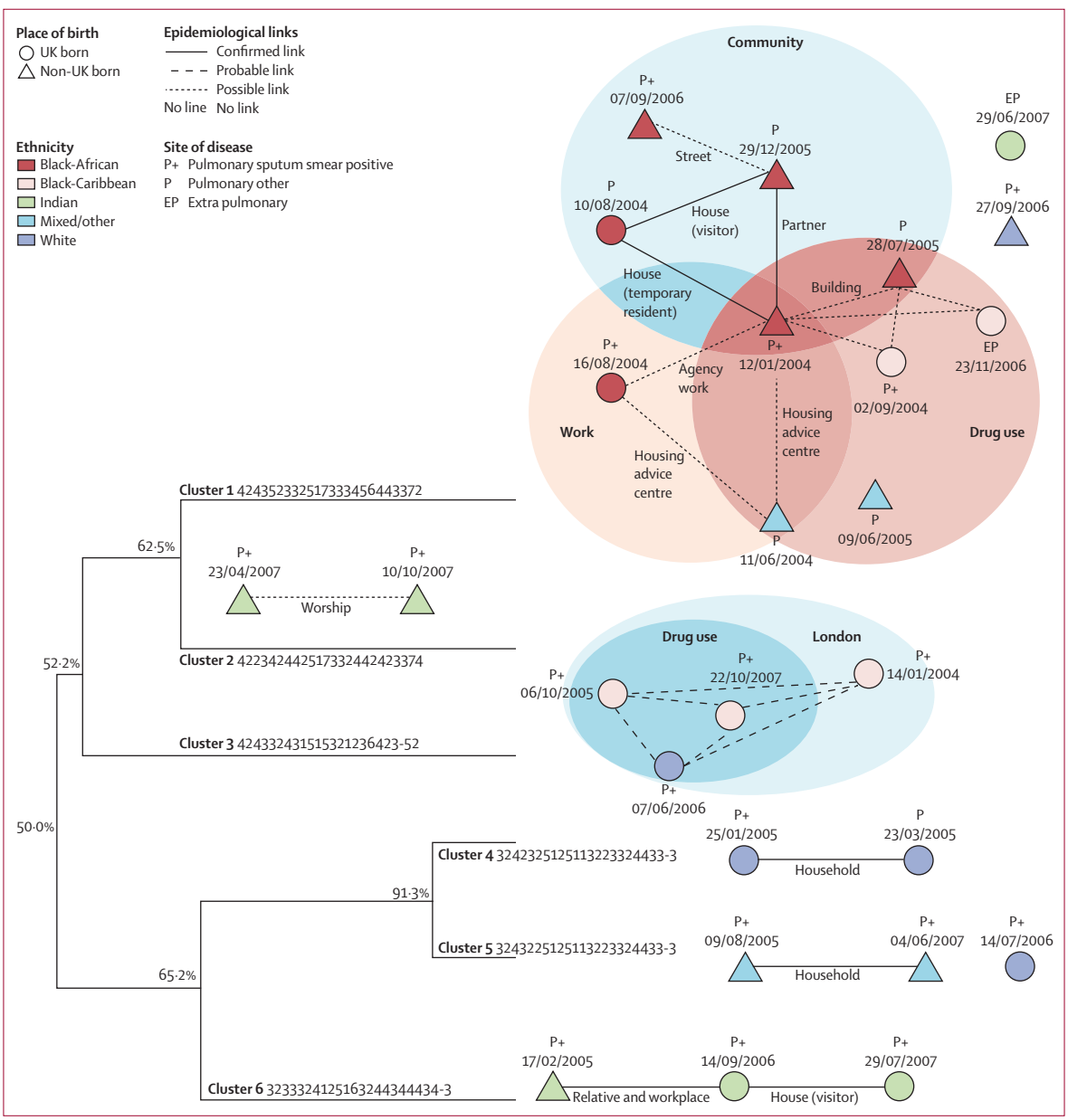

Figure: **Clusters with epidemiological links**

Each symbol (triangle or circle) represents a case in the cluster. Place of birth, ethnicity, epidemiological links identified between cases and the type of link (confirmed, possible, probable, or none) are indicated in the key. The likely transmission setting is stated next to the link. Site of disease and the date of notification are shown directly above or below the case. In clusters 1 and 3 broader transmission settings are indicated by shaded circles around the cases. The dendrogram provides a display of how closely related the strains are in terms of the percentage of similarity between mycobacterial interspersed repetitive-unit–variable-number tandem repeat profiles. This percentage is shown at each node between branches.

nine were diagnosed with active disease (attack rate=0·6%). These nine secondary cases were associated with eight index cases. A further five secondary cases occurred in individuals who were not identified for screening but self-referred when they became symptomatic and reported contact with an MDR tuberculosis index case. We excluded one index case and one secondary case from further analysis of laboratory results because they had already been identified in an MIRU-VNTR cluster. Therefore, there were a total of 13 secondary cases from 11 index cases.

All 11 index cases and 12 of 13 secondary cases were non-UK-born. 11 of 13 secondary cases shared the same world region of birth as the index case, which was most commonly the Indian subcontinent (table 3). All secondary cases were linked to the index case through the household but five were not identified through conventional contract tracing because they had previously lived at the same address as the index case but did not at the time of diagnosis.

We examined strain types and drug sensitivities to establish whether transmission between index and secondary cases was likely (table 3). Only two secondary cases had isolates with 15 loci MIRU-VNTR strain types indistinguishable from the index case (index 1 and 2). Both of the index cases had pulmonary sputum smear-positive disease. Isolates from secondary cases were resistant to an additional drug compared with isolates from the index cases (table 3), which is consistent with transmission. Five isolates from secondary cases had different drug-resistance patterns or strain types, or both, compared with the index cases (index 3–7). Only one secondary case had MDR tuberculosis and was thought to be the source of infection.

Drug susceptibility testing was unavailable for five secondary cases (index 6 and 8–11). Two were treated as fully sensitive and successfully completed treatment within 12 months. Neither had relapsed as of Oct 1, 2013. Three were treated for MDR tuberculosis; a non-UK-born child who was in contact with two cases of MDR tuberculosis in the household (index 6), a UK-born child with a sputum smear-positive mother from a country with high tuberculosis incidence (index 10), and a non-UK-born mother with extrapulmonary disease who was identified through contact tracing of her child (index 11).

Discussion

Between 2004 and 2007, we estimate that the proportion of MDR tuberculosis cases attributable to recent transmission, on the basis of molecular data, was 15%. Being UK born and illicit drug use were significantly associated with clustering. The proportion of cases attributable to recent transmission within the UK, after adjustment for epidemiological links, was 8·5%. The most common transmission setting was the household but for most clustered cases, epidemiological links were missed by conventional contact tracing. Secondary active tuberculosis cases identified by conventional contact tracing were contacts of patients with MDR tuberculosis from countries of high tuberculosis burden. Most shared the same country of birth as the index case but did not share a strain type or drug resistance pattern.

The findings of this study can be used to target interventions to reduce transmission and subsequently incidence of MDR tuberculosis in the UK and in Europe,

	Clustered (n=40)		Unique (n=149)		Unadjusted odds ratio (95% CI)	p value
	n	(%)	n	(%)		
UK born (n=186)						
Yes	16	51·6	15	48·4	5·82 (2·54–13·3)	<0·001
No	24	15·5	131	84·5	1·00	..
Illicit drug use						
Yes	7	58·3	5	41·7	6·11 (1·82–20·45)	0·004
No or unknown	33	18·6	144	81·4	1·00	..
Alcohol use						
Yes	4	33·3	8	66·7	1·96 (0·56–6·87)	0·311
No or unknown	36	20·3	141	79·7	1·00	..
Homeless						
Yes	3	33·3	6	66·7	1·93 (0·46–8·09)	0·385
No or unknown	37	20·6	143	79·4	1·00	..
Prison						
Yes	3	60·0	2	40·0	5·96 (0·96–36·97)	0·055
No or unknown	37	20·1	147	79·9	1·00	..
Age group						
0–14 years	5	38·5	8	61·5	2·48 (0·46–13·5)	0·505
15–44 years	31	20·1	123	79·9	1·00	..
45–64 years	3	20·0	12	80·0	1·00 (0·26–3·79)	..
≥65 years	1	14·3	6	85·7	0·66 (0·56–7·85)	..
Sex						
Male	20	20·8	76	79·2	1·00	0·910
Female	20	21·5	73	78·5	1·04 (0·52–2·09)	..
Ethnicity (n=185)						
White	8	36·4	14	63·6	2·95 (1·02–8·57)	0·183
Black African	10	18·9	43	81·1	1·20 (0·48–3·03)	..
Indian subcontinent	12	16·2	62	83·8	1·00	..
Other	10	27·8	26	72·2	1·98 (0·76–5·17)	..
Years since entry to the UK (n=116)						
0–2	5	17·2	24	82·8	1·00	0·328
3–4	0	0	0	0	Not estimable	..
5–10	8	32·0	17	68·0	2·25 (0·63–8·11)	..
>10 years	19	30·6	43	69·4	2·12 (0·70–6·40)	..
Site of disease						
Pulmonary sputum smear positive	21	25·6	61	74·4	1·00	0·330
Pulmonary sputum smear other	11	20·4	43	79·6	0·74 (0·32–1·69)	..
Extrapulmonary	8	15·1	45	84·9	0·52 (0·21–1·27)	..
Previous diagnosis (n=173)						
Yes	8	15·4	44	84·6	1·00	0·159
No	30	24·8	91	75·2	1·81 (0·77–4·28)	..

Table 2: **Univariable analysis of risk factors associated with multidrug-resistant tuberculosis clusters in the UK**

	Site of disease	Number of contacts screened	Number of contacts with active disease	Number identified through screening	World region of birth		Same MIRU-VNTR profile	Drug resistance pattern*		Transmission
					Index case	Secondary case(s)		Index case	Secondary case	
Index 1	Pulmonary smear positive	59	1	0	Eastern Europe	Eastern Europe	Yes	Isoniazid, rifampicin, streptomycin, pyrazinamide	Isoniazid, rifampicin, streptomycin, pyrazinamide, clofazimine	Confirmed
Index 2	Pulmonary smear positive	10	1	0	East Asia	Indian subcontinent	Yes	Isoniazid, rifampicin, streptomycin, ethambutol, pyrazinamide	Isoniazid, rifampicin, streptomycin, ethambutol, pyrazinamide, ethionamide	Confirmed
Index 3	Extrapulmonary	17	1	0	Indian subcontinent	Indian subcontinent	No	Isoniazid, rifampicin	Fully sensitive	No
Index 4	Extrapulmonary	3	1	1	Indian subcontinent	Indian subcontinent	No	Isoniazid, rifampicin, streptomycin, pyrazinamide, ethambutol, ethionamide	Isoniazid	No
Index 5	Pulmonary other	3	1	1	Indian subcontinent	Indian subcontinent	Unknown	Isoniazid, rifampicin, pyrazinamide, ethambutol	Fully sensitive	No
Index 6	Extrapulmonary	13	3	2	Sub-Saharan Africa	Sub-Saharan Africa	Unknown	Isoniazid, rifampicin, ethambutol, streptomycin	1 fully sensitive, 2 no culture, 3 isoniazid, rifampicin	Possible
Index 7	Pulmonary smear positive	8	1	1	Middle East	Middle East	Unknown	Isoniazid, rifampicin, pyrazinamide, ethambutol, ethionamide, streptomycin	Isoniazid, streptomycin	No
Index 8	Extrapulmonary	2	1	1	Sub-Saharan Africa	Sub-Saharan Africa	Unknown	Isoniazid, rifampicin	No culture	Unknown
Index 9	Pulmonary smear positive	4	1	1	Indian subcontinent	Indian subcontinent	Unknown	Isoniazid, rifampicin, ethambutol	No culture	Unknown
Index 10	Pulmonary smear positive	3	1	1	Indian subcontinent	UK	Unknown	Isoniazid, rifampicin, pyrazinamide	No culture	Unknown
Index 11	Pulmonary other	11	1	1	Indian subcontinent	Indian subcontinent	Unknown	Isoniazid, rifampicin, streptomycin	No culture	Unknown

MIRU-VNTR=mycobacterial interspersed repetitive-unit-variable-number tandem repeat.

Table 3: **Characteristics of index and secondary cases**

as part of the European tuberculosis control and elimination strategy in low-incidence countries (panel 2).[16,17]

Our estimate that about one in 12 cases of MDR tuberculosis resulted from transmission in the UK is lower than previously reported.[4] This finding is much the same as that for MDR tuberculosis transmission in California for the same time period[18] but lower than estimates from another study[19] that showed that one in five cases of MDR tuberculosis were the result of recent transmission across eight states in the USA. Our estimate is also substantially lower than that for MDR tuberculosis clustering for Europe,[20] which was 43% and mainly attributable to Baltic states or former Soviet Union countries. By contrast, in a study from Ireland none of the MDR tuberculosis cases were clustered, although numbers were small.[21] In our study, most cases with unique MDR tuberculosis strains were in individuals who were born outside of the UK and had recently arrived in the UK from countries with high tuberculosis burden, and therefore probably arose as a result of reactivation.

The two independent risk factors associated with transmission were being born in the UK and a history of illicit drug use. This finding is much the same as those from the USA[19] where transmission of MDR tuberculosis was associated with being US born and drug or alcohol abuse. We identified transmission among non-UK-born and non-white UK-born individuals of the same ethnicity, but there was no evidence of MDR tuberculosis transmission from non-UK-born individuals to white UK-born individuals. This finding is indicative of transmission within specific communities in the UK. Among clusters, transmission was less likely if individuals with MDR tuberculosis were non-UK-born from the same country of

birth, which is probably indicative of importations of common strains from abroad.

National guidance[7] issued in 2011 for cluster investigation in the UK recommends that all clusters of two or more MDR tuberculosis cases should be investigated for recent transmission irrespective of other risk factors. Our findings suggest that clusters involving individuals with MDR tuberculosis who are UK born or have social risk factors, such as illicit drug use, should be investigated with greater urgency than clusters of cases from the same foreign country of birth. Non-UK born patients, who are part of a cluster and have no epidemiological links identified, probably acquired a common strain of tuberculosis from abroad and subsequently reactivated after entering the UK.

Beijing strains accounted for only 22% of all strains, but this lineage was associated with a high proportion of clustered strains (40%); however, this finding is mostly attributable to one large cluster of 12 cases. Some evidence suggests that Beijing MDR tuberculosis strains are more transmissible than MDR tuberculosis strains of other lineages.[22,23] However, this association could also be attributed to immigration from countries with a high prevalence of both Beijing strains and MDR tuberculosis or alternatively, Beijing strains might be less likely to differ by MIRU-VNTR profile because they evolved more recently than other strains.[24]

Contact investigation among household contacts is a routine part of tuberculosis control in the UK.[25] Nevertheless, in our study a substantial proportion of household contacts who were diagnosed as secondary cases were missed by conventional contact tracing. Results of a large meta-analysis[26] of contact screening showed that in high-income countries active tuberculosis among contacts of individuals with MDR or XDR tuberculosis was 0% but the proportion of contacts with latent infection was 52·6% (95% CI 49·5–55·7%).[26] We identified a much lower proportion of latent infections in the UK, which suggests that additional contacts might have been missed. Possible reasons for failing to identify these contacts include reluctance to disclose household contacts, the non-disclosure of visiting household contacts, and the failure to identify temporary residents who had moved on. The use of peer support and workplace and home visits can improve contact identification.[27] In the largest cluster, links were often suspected but never confirmed because of the involvement of illicit drug use and because infected individuals were reluctant to name contacts. Traditional name-based contact identification has limitations in some high-risk groups, in which contacts identified by methods other than naming are more likely to be infected than named contacts.[28–31] Use of a dedicated outreach service targeting high-risk populations in specific settings is effective in active case finding to tackle tuberculosis in these groups.[32]

This study provides evidence that the epidemiological investigation of MDR tuberculosis MIRU-VNTR clusters was more successful at identifying cases in the same chain of transmission than conventional contract tracing. Sintchenko and colleagues[15] showed that second interviews for clustered cases could optimise detection of epidemiological links and secondary cases if the occurrence of clustering was at least 4%. The UK recommends this strategy as part of the National Strain Typing Service in which a combination of prospective strain typing and social networking questionnaires are used to identify transmission chains and inform public health action.[7] In regions with a high tuberculosis case-load clinical case managers might find it difficult to provide epidemiological information to health protection teams in a timely manner. The introduction of local public health oriented teams employing staff dedicated to cluster investigation would ensure rapid identification of transmission settings and subsequent contact screening.

In this study, household contacts of non-UK born patients with MDR tuberculosis, who developed active disease, were more likely to have a different strain of tuberculosis than a strain indistinguishable from that of the index case. These individuals were from countries with high tuberculosis burden where the risk of exposure to different circulating strains is substantial, resulting in several strains within one household.[33–35]

***Panel 2:* Research in context**

Systematic review

We searched PubMed using the terms "multi-drug resistant tuberculosis/MDR-TB", "transmission", "genotyping", "clustering", "outbreak", "MIRU-VNTR", "mycobacterial interspersed repetitive-unit-variable-number tandem repeat", "risk factors", "contact tracing", and "active case finding", alone and in combination. About a fifth of multidrug resistant tuberculosis cases arising in the UK were previously estimated to result from recent transmission.[4] This study was based on 15 loci MIRU-VNTR typing, which has a lower discriminatory power than 24 loci MIRU-VNTR typing, which is now routinely used in the UK to inform cluster investigation. Additionally, in the previous study[4] epidemiological links between cases were not taken into account and it therefore probably overestimated the amount of multidrug-resistant (MDR) tuberculosis transmission. There was no transmission of extensively drug-resistant tuberculosis in the UK between 1995 and 2007.[5] Whether conventional contact tracing effectively identifies MDR tuberculosis cases in a true transmission chain is unclear and risk factors for transmission of MDR tuberculosis in the UK are unknown. Identification of risk factors for transmission is crucial to establish specific resources that are needed for timely targeted public health interventions to control tuberculosis and to prevent further transmission of drug-resistant tuberculosis in the UK.

Interpretation

As far as we are aware, this study is the first to combine molecular, contact tracing, and epidemiological information for a detailed investigation of MDR tuberculosis transmission in the UK. We have shown that transmission of MDR tuberculosis in the UK is lower than previously estimated[4] at 15%, which decreased to 8·5% after taking epidemiological links into account. This study has shown the benefits of using strain typing data and cluster investigation to detect transmission chains, which increases the likelihood of additional active cases being detected and diagnosed early.[15] It has also shown the need for improved contact tracing, which can be addressed through training and resourcing frontline staff.

Some secondary cases were treated with the same MDR regimen as the index case, as recommended,[36] whereas others were treated empirically as fully sensitive cases. Attempts to obtain samples for culture confirmation and drug-susceptibility testing are essential for household contacts of non-UK-born individuals with MDR tuberculosis from countries of high tuberculosis burden to minimise inappropriate use of drug regimens and exposure of patients to serious side-effects. A comprehensive risk assessment for drug resistance should be done in all cases and provision of additional advice from dedicated MDR tuberculosis networks[37,38] should be encouraged. The management of contacts of individuals with MDR tuberculosis who are latently infected remains challenging because evidence for best practice is scarce, therefore further work in this area is welcomed.

A strength of this study is the methodological design in which a combination of epidemiological and strain typing data, including data obtained from cluster investigation, was used for an in-depth investigation and analysis of factors associated with transmission of MDR tuberculosis in the UK. Robust methods for data validation and completeness, the high proportion of contact tracing notes available at clinics, and the high coverage of strain typing provides confidence that the findings are accurate and can be generalised to similar MDR tuberculosis populations, such as those of other countries with low tuberculosis incidence.

Some factors in this study might have led to the overestimation of MDR tuberculosis transmission in the UK. A genotyping method with higher discriminatory power, such as whole genome sequencing, might have detected molecular differences between clustered strains.[39] This limitation might explain why links were only detected in half the clusters—ie, the clusters without links might not have been true clusters.

Transmission might have been underestimated if secondary cases did not admit to having contact with one of the index cases. Additional secondary cases might have left the UK either before reactivation or diagnosis. Undiagnosed cases of MDR tuberculosis or those without culture will also have been excluded from clusters. However, the existence of many undiagnosed cases of MDR tuberculosis is unlikely because of the widespread availability of drug-susceptibility testing of culture-confirmed cases in the UK. Only about 60% of tuberculosis cases in the UK are culture confirmed;[3] low culture confirmation is partly driven by the high proportion of cases with extrapulmonary tuberculosis, and means additional cases with epidemiological links might have been missed. Furthermore, in the UK strains with single locus variants are deemed to be different but there is now evidence, from next generation sequencing, to show that genetically linked strains can differ by one or two MIRU-VNTR loci,[39] which might have also underestimated transmission in this study.

We note that although ORs and risk ratios will be similar when the outcome is rare, the outcome (clustering) is not uncommon in our study at 15%. Therefore ORs will tend to be slightly more extreme than their corresponding risk ratio, although calculating risk ratios (data not shown) did not affect the significance or interpretation of results.

Although clustering of MDR tuberculosis was most strongly associated with being UK-born and injection drug use, we also detected transmission in non-UK-born populations and ethnic communities, with little transmission between communities. Targeted approaches are needed to prevent further transmission in these communities, through awareness strategies, active case finding among the UK-born population with social risk factors in specific settings, and screening of migrant populations from countries with a high incidence of MDR tuberculosis. The process that case managers use for interviews for contact identification needs to be reviewed to establish the type of training and resources needed to enhance contact identification. Cluster data should also be made available to clinical teams in a timely manner to direct contact tracing.

Contributors

LFA designed the study, collected and collated the epidemiological and laboratory data, did all statistical and cluster analysis on the data and wrote the report. ST designed the study, collected the contact tracing data, and wrote the report. TB did all laboratory procedures and provided all associated data. JPW collected a substantial amount of patient data and contributed to writing the report. CM did out cluster investigation, collected the associated data, and provided useful comments on the report. DZ provided intellectual input and contributed to writing the report. IA designed the study, provided supervision and support, contributed to writing the report, and provided intellectual input.

Declaration of interests

We declare that we have no competing interests.

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