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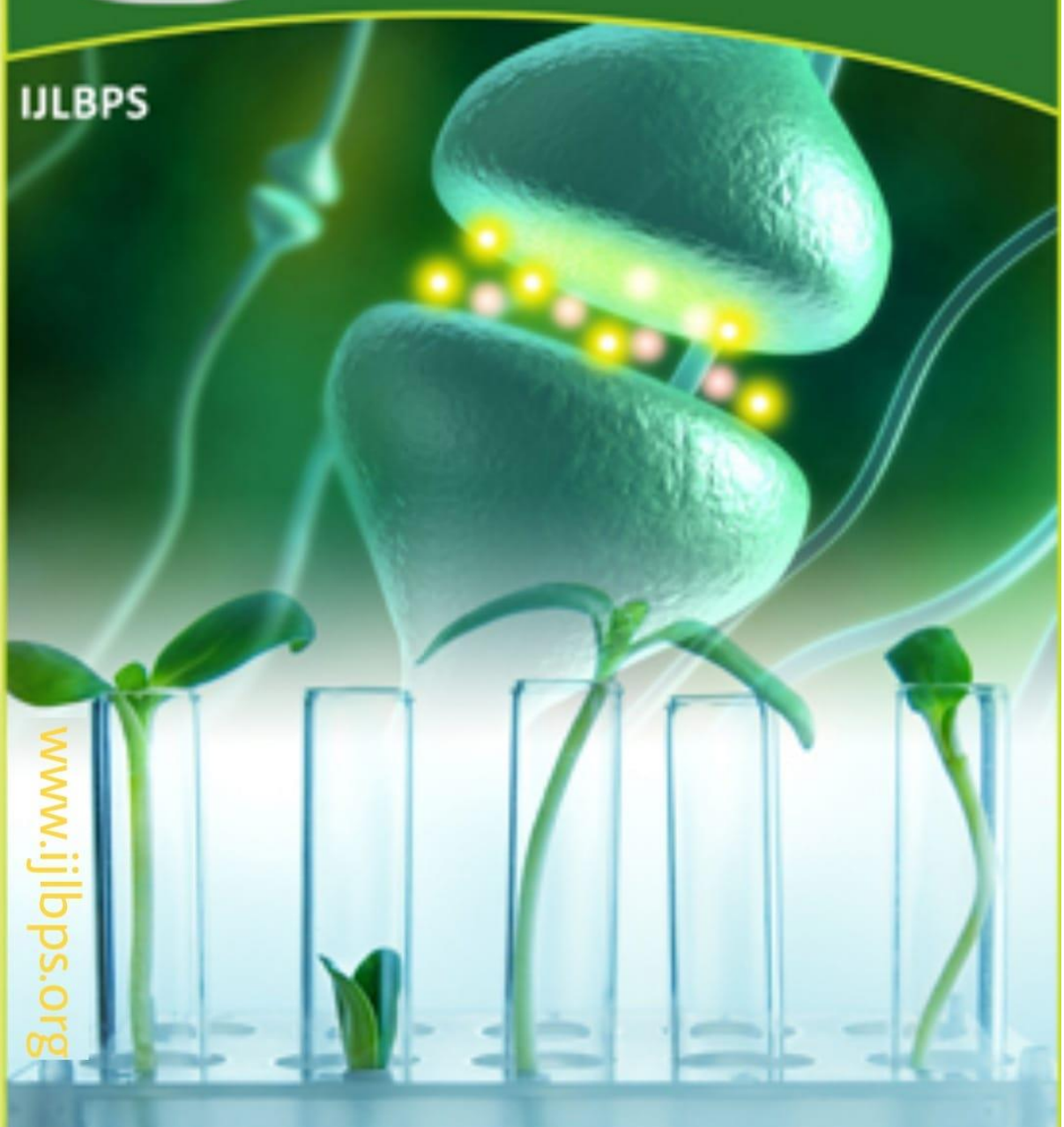

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Transmission of multidrug-resistant tuberculosis in the UK: a cross-sectional molecular and epidemiological study of clustering and contact tracing

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Introduction

Globally, 455,000 new cases of multidrug-resistant TB (MDR)—defined as Mycobacterium tuberculosis resistant to at least isoniazid and rifampicin—occurred in 2012, according to the World Health Organisation (WHO).1 There isn't much proof that multidrug-resistant TB patients are more contagious than completely sensitive tuberculosis patients, but the longer time these patients are infectious means more chances for transmission. It is much more important to combat the spread of MDR TB strains since infected individuals have a bad prognosis. Future TB control tactics may be better informed by gaining a better understanding of the transmission dynamics of multi-drug-resistant tuberculosis.From 28 instances in 2000 to 81 cases in 2012 (an increase from 0% to 1.6%) of all cases, the number of multi-drug-resistant TB cases in the UK has risen significantly over the last decade.3 In the UK, most multidrug-resistant TB patients were born in sub-Saharan Africa or the Indian subcontinent. quickly identify individuals infected with the same strain of Mycobacterium TB, which might be a consequence of a recent transmission (within the last two years), is mycobacterial interspersed repetitive-unit-variable-number tandem repeat (MIRU-VNTR) strain typing. Using 15 loci MIRU-VNTR strain type, an earlier study4 estimated that 1% of MDR
To find possible epidemiological ties between cases, we used a cluster research questionnaire and merged it with epidemiological data obtained regularly in the monitoring system. We also used 24 loci MIRU-VNTR strain typing. Our goals were to(1) determine the percentage of multi-drug-resistant TB cases in the United Kingdom that were transmitted and(2) identify risk variables linked with transmission. We evaluated the efficacy of traditional contact tracing in identifying actual transmission events when regular strain typing is not available by using data gained from contact investigations to find more secondary.

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Methods

Study population

Every patient in England, Wales, and Northern Ireland who was reported to have multi-drug-resistant TB (MDR) between January 1, 2004, and December 31, 2007, was included in this research. These analyses did not necessitate separate ethical approval because Public Health England has the authority to hold and analyse national surveillance data for the purposes of public health protection and infectious disease surveillance under Section 60 of the National Health Service Act 2006 and with approval from the National Information Governance Board.

Data collection

By cross-referencing laboratory isolates with case reports in the expanded TB surveillance system, we were able to identify individuals with multi-drug-resistant tuberculosis.6 Patients' demographic and clinical information, including their age, sex, nationality, ethnicity, number of years since entering the UK, and address, as well as their disease site, sputum smear status, and history of TB diagnosis, are stored in this system. To gather information about social risk factors (such as a history of alcohol or illicit drug use, homelessness, or imprisonment), contact with a known drug-resistant case, and details of the contact investigation, including personal identifiers of contacts diagnosed with active disease, we sent cluster investigation questionnaires to health-care workers in tuberculosis clinics. We sent a second questionnaire to health-care workers in all treating clinics after molecular cluster assignment to gather additional sociodemographic information for each clustered case. This information included details about each patient's previous address, education, workplace, religious setting, prison, rehabilitation centre, homeless hostel, and regular travel to or visitors from abroad or within the UK in the two years leading up to diagnosis. Through the use of medical data, all questionnaires were filled out and then returned to the researchers. When possible, we retrieved contact tracing notes for each index case from the TB clinics. The number of people examined (using either the Mantoux test or the interferon γ release assay) and the results of the screening for latent and active TB infection were detailed in these notes.

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 has isolated a single instance of laboratory cross-contamination; after consulting with the treating clinic, it was determined that the patient did not have TB. We considered a strain to be resistant to a medication if it showed signs of borderline resistance. When possible, we typed all original MDR tuberculosis isolates retrospectively using 24 MIRU-VNTR, following the methods previously reported. Using clustering In order to establish connections between patients and transmission settings, we integrated epidemiological data with MIRU-VNTR strain typing data. The MIRU-VNTR profile served as the foundation for the cluster assembly process. Clusters were identified in the UK between 2004 and 2007 as two or more patients with multidrug-resistant TB who had identical 24-locus MIRU-VNTR profiles, with a minimum of 22 full loci. No matter where the patients lived, they were all grouped together. Following the steps outlined earlier, we were able to trace the M tuberculosis lineage.11 Using the n-1 method12,

which is the following: (number of cases clustered - number of clusters / number of cases with a strain type), we determined the percentage of clustered cases. In order to find or confirm

epidemiological relationships between patients and have happened, we used cluster questionnaires. If patients named each other or lived at the same address, it was considered a confirmed epidemiological link. If patients were residents of London and shared the same strain type and characteristics as tuberculosis patients in a known London outbreak, but did not live at the same address or name each other, it was considered probable. If patients were linked through a common setting other than the household but did not name each other, it was considered possible. identified, it was considered not linked. We modified these standards from the ones laid forth in the official rules for cluster inquiry.7 If there was an established epidemiological relationship between clustered instances, then transmission was proven. To provide a more accurate picture of how many cases in the UK were caused by recent transmission, we subtracted the number of clusters from the total number of cases with epidemiological ties to get the percentage of cases caused by recent transmission.

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.

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

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.

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

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 a forward stepwise approach to select

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

In the United Kingdom, 32,578 cases of TB were reported between 2004 and 2007. Out of these, 5,85 percent were confirmed by culture. Of those, 18,89 percent received drug sensitivity findings for at least two drugs, isoniazid and rifampicin. Out of 204 people who were found to have multi-drug-resistant TB (MDR), 18 (or 2.6%) tested positive for MIRU-VNTR. The majority of multidrug-resistant TB patients were between the ages of 15 and 44 (170 out of 204; 83.3%), were not born in the United Kingdom (170 out of 201; 84.6%), had pulmonary illness (143 out of 204; 70.1%), and had no history of tuberculosis (128 out of 184; 6.6%). Previous descriptions have detailed the results of treating these situations.14 Lineages could be attributed to 184 cases (D7·4%) out of 18D cases having MIRU-VNTR profiles. With 78 (or 42.4% of the total), the Euro-American lineage was the most prevalent, followed by the east African-Indian (or 23.2%), Beijing (or 42.8% of the total), Indo-Oceanic (16.7% of the total), and Mycobacterium africanum (4.2% of the total). There were 14D distinct strains and 12 clusters with 40 individuals each (table 1). Using solely molecular data, we found that 15% of cases (40 cases grouped, 12 clusters, and 18D cases with a strain type) were due to recent transmission. Two to twelve cases made up each cluster: There were two tiny clusters containing 35% of the cases, fourteen medium clusters containing 35% of the cases, and twelve big clusters containing 30% of the cases. Eighteen out of forty instances, or 45·0%, were of the Euro-American strain, whereas sixteen out of forty, or 40·0%, were of the Beijing strain.

We found epidemiological connections in half of the clusters (six out of twelve; 22 cases with known, probable, or plausible ties; table 1, figure), with the home being the most prevalent transmission setting (ten out of twenty-two; 45%) in these clusters. For each of these groups, the first instance was

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	4243523325153334564433 82	Beijing	4	2 UK; 1 Bangladesh; 1 China	2 white; 1 Bangladeshi; 1 Chinese	No	Yes	No		No	Contact with MDR tuberculosis identified abroad

The patient's drug-resistance characteristics and positive lung sputum smear were indicative of transmission. In four groups, the first patient was not born in the United Kingdom, and in three of those groups, the disease spread to people from the same country (clusters 1, 2, and 5). Clusters 1 and 6 also had proven cases of transmission from non-UK-born persons to non-white UK-born individuals of the same ethnicity. Outbreaks are known to have started in 20044 (figure), with the biggest cluster of 12 victims being cluster 1. Although only three out of twelve patients had verified epidemiological ties, the other seven were likely to have acquired the disease due to community, occupational, and drug use-related links, as well as other sociodemographic characteristics. Four patients with multi-drug-resistant TB (cluster 3) were involved in the isoniazid mono-resistant epidemic in London13, which was linked to people of white or black Caribbean descent who were born in the UK and had social risk factors. One of the four patients developed a resistance to rifampicin because they did not follow the prescribed treatment regimen.D5% (21 instances) of the 22 cases in clusters with epidemiological linkages could not be located using traditional contract tracking methods. The index case did not reveal household contacts since they were either not residing at the same home when the patient was diagnosed, were regular visitors who were not revealed, or were just a temporary resident who had already moved on. After accounting for epidemiological ties, the percentage of cases related to recent transmission (i.e., transmission inside the UK) amounted to 8.5% (22 cases with epidemiological links, six clusters, and 18D cases with a strain type).

No epidemiological linkages were found in six clusters (table 1). Each of these groups of patients has a commonality: they all hail from places where TB is prevalent. Since the first case in every cluster did not show signs of transmission in the United Kingdom, this indicates that transmission could not have occurred there. Cluster 12 included patients born in the United Kingdom as well as those born in other countries; nevertheless, patients' patterns of medication resistance varied; patients born in the United Kingdom had ties to

Being a prisoner was removed from the final model after adjusting for place of birth and drug usage, since it was no longer substantially linked with clustering (adjusted OR 1·05; D5% CI 0·85-12·73, p=0·D75). Contact tracing information was provided for the majority of the 204 patients with multi-drug-resistant TB (187; D1·7%). We identified 1650 contacts for screening out of 187 MDR TB index patients, and we screened 1472 (8.2%). Among the 70 individuals, 4·8% had latent infections and

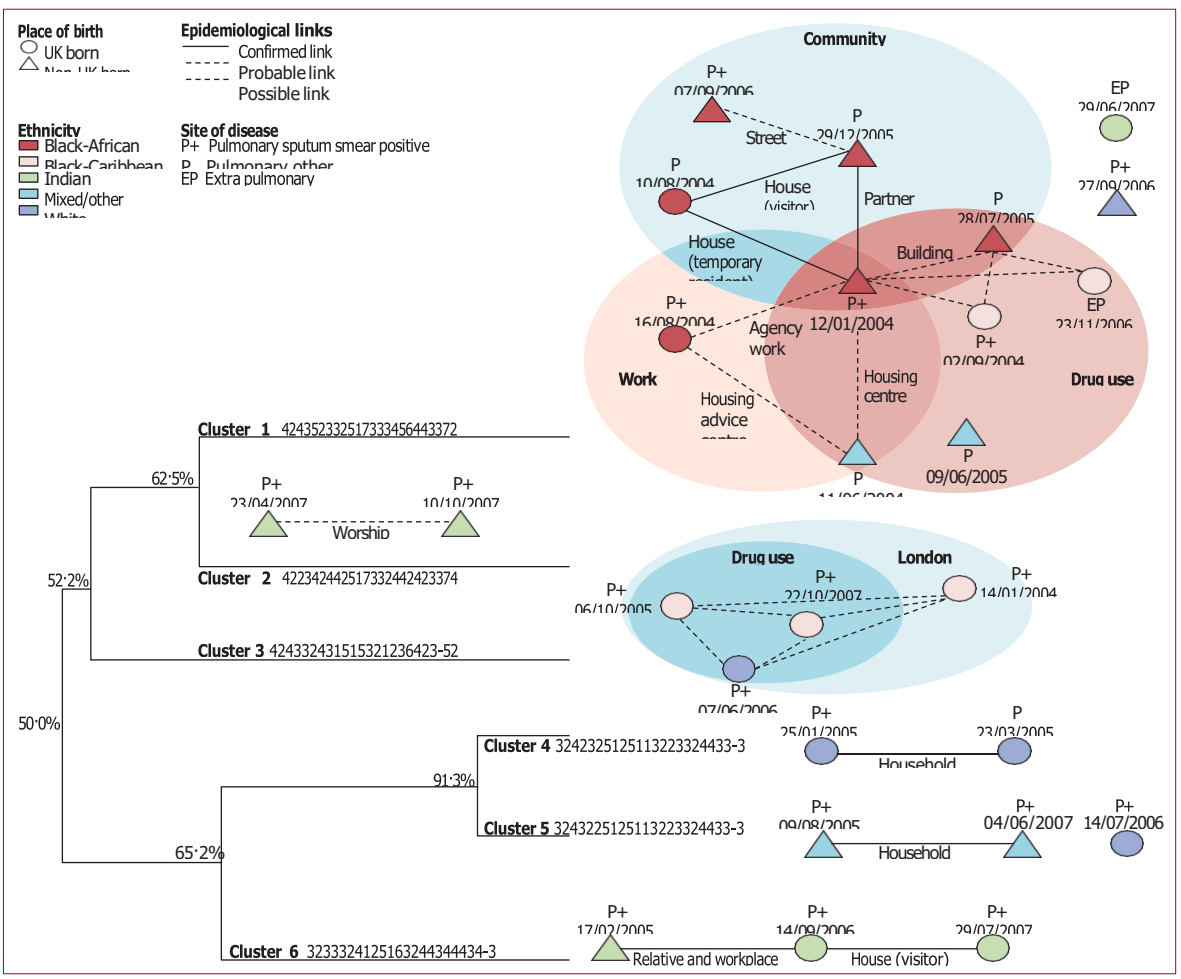

Figure: **Clusters with epidemiological links**

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.

At the attack rate of 0.6%, nine individuals were found to have active disease. Eight index cases were linked to these nine secondary cases. Five more cases were documented in people who were not initially screened for TB but who voluntarily sought treatment after experiencing symptoms and reporting contact with an MDR index case. Due to their prior identification in a MIRU-VNTR cluster, we did not include one index case and one secondary case in our subsequent study of laboratory data. As a result, eleven index cases led to thirteen secondary cases. To determine the likelihood of transmission between index and secondary cases, we looked at medication sensitivities and strain types (table 3). Index 1 and 2 were the only two secondary instances where the isolates had 15 loci MIRU-VNTR strain types that were indistinguishable from the index case. Illness was confirmed by a positive lung sputum smear in both index cases. According to table 3, it is consistent with transmission that secondary case isolates were resistant to an extra medication when compared to index case isolates. In comparison to the index cases (index 3-7), five secondary case isolates exhibited distinct drug-resistance patterns, strain types, or both. The only secondary case with multi-drug-resistant TB was believed to have originated from that patient. Subject under consideration From 2004 to 2007, we used molecular data to estimate that 15% of multi-drug-resistant TB infections were due to recent transmission. Having a birthplace in the UK and using illegal drugs were both strongly linked to

	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

in nations with low TB incidence rates, as part of the European effort to manage and eliminate the disease (panel 2).the number of Contrary to earlier reports, we now believe that transmission was the cause of less than one in twelve instances of multi-drug-resistant TB in the United Kingdom.4 This figure is comparable to that for multidrug-resistant TB transmission in California over the same time period (18), but it is lower than the estimates from another research (1D), which demonstrated that one out of every five cases of multidrug-resistant tuberculosis in the United States were caused by recent transmission in eight states. Our estimate is also far lower than the 43% clustering of multi-drug-resistant TB across Europe, which was mostly due to the Baltic republics and countries that were formerly part of the Soviet Union. While there were a tiny number of multi-drug-resistant TB patients in an Irish investigation, none of them were grouped.21 Our research shows that most instances of multi-drug-resistant TB were

people whose parents were born in a country with a high TB burden, likely reactivated, and who had only recently moved to the UK from that country. Having a history of drug abuse and being born in the United Kingdom were the two separate risk variables linked to transmission. Consistent with previous research, this conclusion links being born in the United States and abusing drugs or alcohol to an increased risk of contracting multi-drug-resistant TB. We found transmission between people of different ethnicities who were born in the UK, but no evidence of multi-drug-resistant TB transmission between people of different ethnicities who were born in the UK and white people. This discovery suggests that there may be transmission among some populations in the UK. Clusters with multiple drug-resistant TB were less likely to transmit the disease when members of the same country of birth had the disease, suggesting that common strains of tuberculosis are being imported from outside the UK.

In 2011, the UK established national guidelines7 for cluster inquiry, which said that regardless of other risk indicators, each cluster of two or more MDR TB patients should be examined for recent transmission. Based on our research, it is more important to explore clusters of multi-drug-resistant TB cases involving people born in the United Kingdom or who have societal risk factors such drug abuse than clusters of cases from the same country of birth. Patients who were born outside of the United Kingdom and who are now part of a cluster with no known epidemiological ties likely brought a common strain of TB with them when they came to the country and then had it reactivate.

Although only 22% of all strains were Beijing strains, this lineage was linked to 40% of clustered strains; nevertheless, this discovery is mostly due to one major cluster of 12 instances. Compared to MDR TB strains from other lineages, there is some indication that the Beijing strains are more contagious.22,23 dollars This correlation may be due to the fact that immigrants come from regions where both Beijing strains and multidrug-resistant TB are common, or it might be that Beijing strains are less likely to vary by MIRU-VNTR profile due to their recent evolution.24

In the United Kingdom, TB control measures sometimes include investigating connections within households.25 However, traditional methods of contact tracing failed to identify a large number of household contacts in our sample who were later identified as secondary cases. Active TB among contacts of patients with MDR or XDR tuberculosis was 0% in high-income countries, according to a major meta-analysis26 of contact screening. However, 52·6% of contacts had latent infection, with a 95% confidence interval of 4D·5-55·7%.26 We may have missed more connections in the UK since we found a much lower prevalence of latent infections there. Reluctance to report home contacts, non-disclosure of visiting household connections, and inability to identify temporary inhabitants who had moved on are all possible reasons why these contacts were not identified. Contact identification may be enhanced via the utilisation of workplace and home visits, as well as peer assistance.27 Due to the participation of illegal drug use and the reluctance of afflicted persons to disclose connections, ties were often inferred but never proven in the biggest cluster. In some high-risk populations, when contacts detected using non-naming approaches are more likely to be infected than named contacts, traditional name-based contact identification has its limits.pages 28–31 One successful strategy for actively tackling TB in high-risk communities is to use a specialised outreach programme that targets these individuals in particular contexts.32

This research demonstrates that MIRU-VNTR clusters are associated with multi-drug resistant TB, according to epidemiological investigations.

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.

was superior to traditional contract tracing in locating instances that occurred along the same gearbox chain. With a clustering frequency of at least 4%, Sintchenko and colleagues15 shown that secondary cases and epidemiological linkages might be better detected with the use of a second interview. In order to discover transmission chains and guide public health actions, the United Kingdom suggests this method as

part of their National Strain Typing Service, which uses a mix of social networking surveys and prospective strain typing.7 It may be challenging for

quick detection of transmission settings and subsequent

contact screening, local public health focused teams with professionals specialised to cluster inquiry should be established. Active TB among household contacts of non-UK born patients with multidrug-resistant tuberculosis was associated with a distinct strain of the illness than an indistinguishable one from the index case, according to this research. These people came from nations where TB is quite common, so there's a good chance that they may have contracted many strains of the disease in their home.numbers 33–35

While it is suggested to treat certain secondary patients with the same MDR regimen as the index case,36 some instances were handled empirically as completely sensitive. Household contacts of non-UK-born individuals with MDR tuberculosis from countries with a high tuberculosis burden must have samples obtained for drug-susceptibility testing and culture confirmation in order to reduce patients' exposure to harmful drug regimens and side effects. All patients should undergo a thorough risk assessment for drug resistance, and individuals should be encouraged to seek extra guidance from specific MDR tuberculosis networks37,38. Since there is a lack of evidence for best practices in the care of contacts of latently infected patients with multidrug-resistant TB, more research in this area is highlyencouraged.

The methodological approach of this research is one of its strengths; it thoroughly investigated and analysed aspects related with the transmission of multi-drug-resistant TB in the UK using a mix of epidemiological and strain typing data, including data derived from cluster investigation. You can trust that the results are accurate and can be applied to similar MDR tuberculosis populations, like those in countries with low tuberculosis incidence, because of the robust methods for data validation and completeness, the high coverage of strain typing, and the high proportion of contact tracing notes available It is clinical case managers to promptly supply health protection teams with epidemiological data in areas with a high TB case load. To guarantee

possible that the research overestimated the spread of multi-drug-resistant TB in the UK due to certain variables. Molecular differences between clustered strains may have been found using a genotyping technology like whole genome sequencing, which has stronger discriminatory power.3D Because of this restriction, it is possible that the clusters that did not have connections were not really clusters, and that is why only half of the clusters had linkages discovered. If subsequent instances denied ever having come into touch with the index cases, the true extent of transmission could have been underreported. It is possible that more secondary patients departed the UK prior to reactivation or diagnosis. Patients without a culture or those with an undiagnosed multidrug-resistant TB diagnosis will also not have been included in the clusters. Since drug-susceptibility testing is widely available for culture-confirmed cases in the UK, it is very improbable that there are many undetected instances of MDR TB. There may have been more cases with epidemiological ties that went unnoticed due to the poor rate of culture confirmation, which is in part caused by the large number of individuals with extrapulmonary TB. In the UK, only around 60% of tuberculosis cases are confirmed. Moreover, strains with a single locus mutation are considered distinct in the UK. However, new data from next generation sequencing suggests that even genetically connected strains may vary by one or two MIRU-VNTR loci,3D which might explain why this research downplayed transmission. Clustering is a frequent result in our sample at 15%, but even when the event is rare, the odds ratios and risk ratios will be comparable. Thus, odds ratios (ORs) will be somewhat higher than the risk ratios that correspond to them; nonetheless, the significance and interpretation of the findings were unaffected by the calculation of risk ratios (data not shown). We found transmission among non-UK-born populations and ethnic groups, with minimal trans-

mission across communities, however being born in the UK and injecting drugs were the strongest associations with clustering of multi-drug-resistant TB. Efforts should be made to raise awareness, screen migrant populations from countries with a high incidence of multidrug-resistant tuberculosis, and actively seek out cases among the UK-born population with social risk factors in specific settings in order to prevent further transmission in these communities. In order to determine what kind of training and resources are necessary to improve contact identification, it is necessary to analyse the method that case managers utilise for interviews. Additionally, clinical teams should have prompt access to cluster data in order to facilitate contact tracing.

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