

Transmission of multidrug-resistant tuberculosis in the USA: a cross-sectional study



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Summary

Background Multidrug-resistant (MDR) tuberculosis is a potential threat to tuberculosis elimination, but the extent of MDR tuberculosis disease in the USA that is attributable to transmission within the country is unknown. We assessed transmission of MDR tuberculosis and potential contributing factors in the USA.

Methods In a cross-sectional study, clinical, demographic, epidemiological, and *Mycobacterium tuberculosis* genotype data were obtained during routine surveillance of all verified cases of MDR tuberculosis reported from eight states in the USA (California from Jan 1, 2007, to Dec 31, 2009; Texas from Jan 1, 2007, to March 31, 2009; and the states of Colorado, Maryland, Massachusetts, New York, Tennessee, and Washington from Jan 1, 2007 to Dec 31, 2008). In-depth interviews and health-record abstraction were done for all who consented to ascertain potential interpersonal connections.

Findings 168 cases of MDR tuberculosis were reported in the eight states during our study period. 92 individuals (55%) consented to in-depth interview. 20 (22%) of these individuals developed MDR tuberculosis as a result of transmission in the USA; a source case was identified for eight of them (9%). 20 individuals (22%) had imported active tuberculosis (ie, culture-confirmed disease within 3 months of entry into the USA). 38 (41%) were deemed to have reactivation of disease, of whom 14 (15%) had a known previous episode of tuberculosis outside the USA. Five individuals (5%) had documented treatment of a previous episode in the USA, and so were deemed to have relapsed. For nine cases (10%), insufficient evidence was available to definitively classify reason for presentation.

Interpretation About a fifth of cases of MDR tuberculosis in the USA can be linked to transmission within the country. Many individuals acquire MDR tuberculosis before entry into the USA. MDR tuberculosis needs to be diagnosed rapidly to reduce potential infectious periods, and clinicians should consider latent tuberculosis infection treatment—tailored to the results of drug susceptibility testing of the putative source case—for exposed individuals.

Funding Centers for Disease Control and Prevention.

Introduction

Drug-resistant tuberculosis is a major public health problem worldwide.^{1–5} WHO estimates that more than 650 000 cases of multidrug-resistant (MDR) tuberculosis—defined as *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampicin—emerge globally every year.⁶ The development of drug resistance can be attributed to several factors, such as poor adherence to treatment, inadequate clinical management, drug malabsorption, and unstable drug supply.⁷ Person-to-person transmission of MDR tuberculosis could be further fuelled by slow bacteriological conversion, delayed diagnosis and initiation of MDR-specific treatment, and treatment failure, as suggested by widespread outbreaks and secondary transmission of MDR tuberculosis within individual households and communities.^{8–10} Migration of foreign-born individuals from areas with a high burden of MDR tuberculosis to those with a low burden could be an important factor.^{11–13} A multiyear study of all cases of MDR tuberculosis reported in California, USA, showed that 92% were foreign-born individuals.¹⁴

MDR tuberculosis has a substantial economic effect on programmatic activities, which is a result of treatment

costs of long regimens, frequent admissions to hospital, and the necessary use of injectable drugs.¹⁵ Although some control programmes have successfully reduced transmission of MDR tuberculosis,^{16–18} the extent of MDR tuberculosis attributable to transmission in the USA is unknown. Previous studies^{14,17,18} have not had wide geographical scopes or in-depth examination of epidemiological and clinical information that is necessary to confirm transmission. In this study, we analysed *M tuberculosis* genotyping data and interpersonal connections between cases of MDR tuberculosis to assess potential factors contributing to transmission in eight US states.

Methods

Study population

This cross-sectional study was undertaken by the Tuberculosis Epidemiologic Studies Consortium (TBESC).¹⁹ It included all verified cases of MDR tuberculosis reported to the US National Tuberculosis Surveillance System (NTSS) and National Tuberculosis Genotyping Service (NTGS) from eight states: California from Jan 1, 2007, to Dec 31, 2009; Texas from Jan 1, 2007, to March 31, 2009; and Colorado, Maryland,

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Massachusetts, New York, Tennessee, and Washington from Jan 1, 2007 to Dec 31, 2008. Study periods were staggered because of delays in study approval in several sites and extended funding in California.

The institutional review boards of the Centers for Disease Control and Prevention (CDC) and all participating institutions¹⁹ approved the study. All interviewed participants gave written informed consent.

Procedures

Clinical, demographic, epidemiological, and *M tuberculosis* genotype variables for each case were obtained during routine surveillance, as described elsewhere.²⁰ Additionally, for all individuals who gave consent, interviews (with a structured and standardised face-to-face questionnaire) and health-record abstraction were done by trained study staff to ascertain potential interpersonal connections (appendix). Health records were hospital-based medical records and public health records, which included contact investigation logs.

We defined drug resistance as any resistance on a drug susceptibility test (DST) reported to NTSS or identified during health-record abstraction. Results from conventional DST (ie, liquid-based or agar-based media) were used for NTSS reporting. Results of rapid drug-resistance tests (ie, molecular beacon, line probe assay, or other molecular test) were not included.

Isolates of the *M tuberculosis* complex were characterised with a standardised protocol for spacer oligonucleotide typing (spoligotyping), mycobacterial interspersed repetitive-unit-variable-number tandem-repeat (MIRU-VNTR) genotyping, and IS6110 restriction fragment length polymorphism (IS6110-RFLP) analysis as part of routine molecular surveillance at two contract laboratories with documented quality of performance and reproducibility.^{20,21} For the purposes of this study, a genotype

was defined as a discrete combination of spoligotype and 12-locus MIRU-VNTR results (ie, an exact match on all loci). When available, extended typing methods, 24-locus MIRU-VNTR, or IS6110-RFLP fingerprinting, or any combination of the three, were done to increase specificity.²¹

We defined genotype clusters as at least two cases of MDR tuberculosis, of which at least one was a study case, that had matching genotypes in a specific TBESC state between Jan 1, 2005, and June 30, 2011 (surveillance period). We created the surveillance period to allow sufficient time to estimate recent transmission within genotype clusters and to include potential transmission events with non-study cases. When extended typing methods were available, we defined genotype clusters as at least two cases of MDR tuberculosis with matching genotype and extended method data (ie, exact match on all 24-loci MIRU-VNTR or IS6110-RFLP patterns). Study cases with no matching genotype, or, when applicable, with matching genotype but different extended typing results, were deemed to be non-clustered. A conservative approach to definition of genotype clusters was taken, because nationally defined cluster proportions were shown to be greater than 75% in other studies.^{22,23}

We defined epidemiological links as named contacts or shared transmission venues identified during interview or documented as part of standardised tuberculosis contact investigation activities.²⁴ Briefly, contact investigations are multistep processes, in which contacts are systematically assessed on the basis of the amount of time spent with the infectious person, the environmental conditions of the transmission venue, and the host susceptibility to tuberculosis infection in individuals who are in close contact.^{24,25} Although genotype cluster definitions were based on state, the same strain could be in several states, and we applied no restriction for documentation of transmission occurring between states or set by arbitrary periods through epidemiological links.

We defined an index case as the first case of tuberculosis identified in a genotype cluster by case date (eg, earliest count date, treatment start date, or report date). Spoligotype and 12-locus MIRU-VNTR results were used to assign phylogenetic lineage, as described elsewhere.²⁶ To establish the likelihood of transmission in the USA, we classified cases on the basis of genotype, report date, and epidemiological link. Unlikely transmission was defined as cases of MDR tuberculosis with non-clustered genotypes reported in the same state (with or without extended typing data), and no epidemiological link. Possible transmission was defined as study cases for which at least one other case of MDR tuberculosis with matching genotype (with or without extended typing data) had been reported in the same state, but with no epidemiological link. Definite transmission was defined as study cases with at least one other case of MDR tuberculosis with matching genotype (with or without extended typing data) and an epidemiological link. To

See Online for appendix

Criteria	
Definite transmission	Documented transmission in the USA from a known source; no previous history of latent infection or active disease
Possible transmission	Putative transmission in the USA from an unknown source; no previous history of latent infection or active disease
Imported active tuberculosis	Foreign-born individual who was diagnosed with MDR tuberculosis within 3 months of entry into the USA, or who had symptom onset before entry and a subsequent MDR tuberculosis isolate obtained in the USA
Reactivation of remotely acquired tuberculosis infection*	Individuals with non-clustered genotypes (ie, unique) reported in the same state with no epidemiological link
Known tuberculosis episode outside the USA	Foreign-born individual who had no evidence of active disease at entry into the USA and no evidence of transmission of MDR disease within the USA; documented tuberculosis treatment outside of the USA; subsequent relapse after more than 3 months in the USA
Known relapse of MDR tuberculosis within the USA	Treatment of a previous episode within the USA; no evidence of exposure to another case
Unable to classify	Insufficient evidence to classify into one of the other categories

MDR=multidrug-resistant. *Infection acquired in the distant past.

Table 1: Categories of reason for disease occurrence

classify the reason for disease occurrence, we developed seven categories (table 1).

Statistical analyses

We compared the distribution of clinical, demographic, and epidemiological characteristics of clustered and non-clustered cases of MDR tuberculosis with differences of proportion, as assessed by Pearson's χ^2 or Fisher's exact test when the cell count was less than five. We used the Shapiro-Wilk test to test for normality. Unless otherwise specified, we used median values with IQRs as a measure of central tendency to avoid extreme values. We used relative risk and 95% CIs to assess the association of specific variables with the outcome of tuberculosis transmission. We used SAS (version 9.3) for all analyses.

Role of the funding source

The CDC Division of Tuberculosis Elimination and the TBESC led study design, training for data collection and monitoring, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

During the study periods, 29 050 verified cases of tuberculosis were reported in the USA. Of these, 22 725 (78%) were culture positive, including 22 222 (76%) with DST results for isoniazid and rifampicin. Of individuals with reported DST results, 268 (1%) had MDR tuberculosis. 168 (63%) of these individuals with MDR disease were reported from the eight study sites, of whom 92 (55%) consented to an in-depth interview. For the other 76 (45%), analysis was limited to routinely obtained surveillance variables.

Individuals who were members of genotype clusters were more likely to be male ($p<0.0001$), be Hispanic ($p<0.0001$), be in prison at time of diagnosis ($p=0.01$), and have an *M tuberculosis* isolate of Euro-American lineage ($p=0.004$) than were non-members (table 2). 144 individuals (86%) with MDR tuberculosis were born outside of the USA, but the proportion of individuals born outside the USA who were or were not members of clusters did not differ significantly ($p=0.53$; table 2). Additionally, we recorded no significant differences in clinical characteristics—the proportion with a positive sputum smear ($p=0.77$), pulmonary disease ($p=0.37$), or cavitation on chest radiography ($p=0.35$) did not significantly differ between cases that were and were not part of a genotype cluster (table 2).

Clinical, demographic, and genotypic characteristics did not differ between individuals with MDR tuberculosis from TBESC states and those in the rest of the USA during the study period, with the exception of ethnic origin. TBESC states had more Hispanic (54 [32%] of 168 vs 23 [23%] of 100; $p<0.0001$) and Asian individuals (89 [54%] vs 41 [41%]; $p=0.001$), and fewer black (15 [9%]

vs 23 [23%]; $p<0.0001$) and white individuals (10 [6%] vs 13 [13%]; $p=0.003$) than elsewhere in the country. Clinical, demographic, and genotypic characteristics did not differ between individuals who did and did not consent to interview (data not shown).

In the 92 individuals who consented to an in-depth interview and health-record abstraction, eight (9%) developed MDR tuberculosis as a result of transmission in the USA from a known source case. 12 (13%) developed MDR disease as part of a transmission event in the USA, but no known source case was identified; four were identified as the source case for others in the USA. 20 (22%) had imported active tuberculosis. 38 individuals

	Part of genotype cluster		Total (n=168)	Relative risk (95% CI)
	Yes (n=26)	No (n=142)		
Sex*				
Male	19 (76%)	61 (45%)	80	3.2 (1.4-7.7)
Female	6 (24%)	76 (55%)	82	..
Hispanic ethnic origin				
Yes	18 (69%)	36 (25%)	54	4.8 (2.2-10.2)
No	8 (31%)	106 (75%)	114	..
Country of birth				
USA	4 (15%)	20 (14%)	24	1.1 (0.4-2.9)
Other	22 (85%)	122 (86%)	144	..
Homelessness within the past 12 months				
Yes	4 (15%)	8 (6%)	12	2.4 (1.0-5.7)
No	22 (85%)	134 (94%)	156	..
Substance abuse within the past 12 months				
Yes	6 (23%)	18 (13%)	24	1.8 (0.8-4.0)
No	20 (77%)	124 (87%)	144	..
In prison at time of diagnosis				
Yes	4 (15%)	3 (2%)	7	4.2 (2.0-8.9)
No	22 (85%)	139 (98%)	161	..
Pulmonary involvement				
Yes	23 (88%)	131 (92%)	154	0.7 (0.2-2.0)
No	3 (12%)	11 (8%)	14	..
Positive sputum smear				
Yes	15 (58%)	79 (56%)	94	1.1 (0.5-2.2)
No	11 (42%)	63 (44%)	74	..
Cavitary chest radiograph†				
Yes	10 (38%)	46 (33%)	56	1.2 (0.6-2.5)
No	16 (62%)	95 (67%)	111	..
Previous tuberculosis diagnosis				
Yes	2 (8%)	30 (21%)	32	0.3 (0.1-1.4)
No	24 (92%)	112 (79%)	136	..
Euro-American <i>Mycobacterium tuberculosis</i> lineage				
Yes	19 (73%)	57 (40%)	76	3.3 (1.5-7.4)
No	7 (27%)	85 (60%)	92	..

*Data not reported as part of routine surveillance for six individuals: one in genotype cluster and five not in genotype cluster. †Data not reported as part of routine surveillance for one individual who was not in genotype cluster.

Table 2: Characteristics of patients with multidrug-resistant tuberculosis for whom genotyped isolates were available

	Spoligotype	24-locus MIRU-VNTR	IS6110-RFLP band copies	Lineage	Ethnic origin of index or source case	Country of birth of index or source case	Potential transmission factors	Transmission source
1	7777777760771	223425153322	8	Euro-American	White	USA	Binational case management*	Source case identified
2	7777777720771	225325153323232%34423336†	7	Euro-American, Haarlem	Hispanic	Peru	None identified	Source case identified
3	00000000003771	223326173531	17	East Asian, Beijing	Black	USA	Excessive alcohol use; illicit drug use	Unknown
4	77777774020771	225325153323	11	Euro-American, Haarlem	Hispanic	Peru	None identified	Source case identified
5	77777607760771	224226153321443424115228	14	Euro-American, LAM	Hispanic	Guatemala	Excessive alcohol use; illicit drug use; homeless	Source case identified
6	7777677760601	224325143323243234423336	2	Euro-American, X	Hispanic	USA	Excessive alcohol use; illicit drug use; unemployment	Source case identified
7	77777607760771	224226153321543424115228	12	Euro-American, LAM	Hispanic	USA	Homeless; transmission to a child	Source case identified
8	77777607760771	224226153321	12/13	Euro-American, LAM	Hispanic	Mexico	Binational case management*; excessive alcohol use; illicit drug use	Source case identified
9	77777607760771	224327143221	10	Euro-American, LAM	Black	USA	Unemployment	Unknown
10	7777777760771	223321153224	11	Euro-American	Hispanic	Peru	Excessive alcohol use	Unknown
11‡	7677777760771	223425143322242324223324	NA	Euro-American	Hispanic	Guatemala	Occupational exposure; transmission to a child	Source case identified
12§	4777777720771	227325153323233534423335	10	Euro-American, Haarlem	Hispanic	Mexico	Migrant worker; occupational exposure; transmission between jurisdictions	Unknown
13	7777677760771	224325153314	4	Euro-American, X	Hispanic	USA	Binational case management*; excessive alcohol use; incarceration	Unknown
14	77777607760731	224226153321543324115224	13	Euro-American, LAM	Hispanic	Mexico	Diabetes; excessive alcohol use; illicit drug use	Unknown

MIRU-VNTR=mycobacterial interspersed repetitive-unit-variable-number tandem-repeat. IS6110-RFLP=IS6110 restriction fragment length polymorphism. LAM=Latin American Mediterranean. NA=not available. *Patients who are residents of Mexico and clinically managed in the USA. †The % sign represents either 6 or 7 at MIRU-VNTR loci 2163b. ‡Investigated by the Centers for Disease Control and Prevention as part of an outbreak investigation. §Investigated by the Centers for Disease Control and Prevention as part of an outbreak investigation.¶

Table 3: Genotype and risk characteristics of identified clusters attributed to transmission in the USA

(41%) were deemed to have reactivation of tuberculosis, of whom 14 (15%) had a known previous episode of tuberculosis outside the USA. Five individuals (5%) had documented treatment of a previous episode within the USA, and so were deemed to have relapsed. For nine cases (10%), insufficient evidence was available to definitively classify reason for presentation.

Of the 92 individuals who underwent in-depth interview and health-record abstraction, 26 (28%) had the same genotype as another case of MDR tuberculosis in the same state during the surveillance period. Extended typing data were available for comparison for all but two pairs of cases. The lack of extended genotyping results in these cases did not affect classification of the likelihood of transmission. 14 *M tuberculosis* clusters were associated with US transmission (table 3). 13 (93%) *M tuberculosis* isolates were of Euro-American phylogenetic lineage. Eight clusters (57%) had an identifiable source case, seven (50%) were characterised by abuse of illicit drugs or alcohol, two (14%) included confirmed transmission to a child,²⁷ and one included transmission across state lines (table 3).⁸

Overall, people with MDR tuberculosis attributed to transmission in the USA were more likely to be male ($p < 0.0001$), have been born in the USA ($p < 0.0001$), be of Hispanic ethnic origin ($p < 0.0001$), abuse illicit drugs or alcohol ($p < 0.0001$), and to have an *M tuberculosis* isolate of Euro-American lineage ($p < 0.0001$) than were those who had disease not attributed to transmission in the USA (table 4).

75 (82%) of the 92 individuals who had an in-depth interview and health-record abstraction were born outside the USA. The 12 individuals whose disease was linked with transmission in the USA but of unknown source were all born outside the USA, and four were identified as the source case for others. Nine were diagnosed at least 12 months after US entry, and none had a US medical examination on arrival in the country.¹³ For the eight individuals for whom a known source case was identified, only three source cases were born in the USA. There were two US-born, paediatric MDR tuberculosis cases included in the study: both children were infected by people born outside the USA who had been diagnosed with MDR tuberculosis within 12

	Disease linked with transmission in the USA		Total (n=92)	Relative risk (95% CI)
	Yes (n=20)	No (n=72)		
Sex				
Male	15 (75%)	29 (40%)	44	3.1 (1.2–8.3)
Female	5 (25%)	43 (60%)	48	..
Age (years)*				
0–4	1 (5%)	0	1	..
5–14	1 (5%)	0	1	..
15–24	2 (10%)	15 (21%)	17	..
25–44	7 (35%)	34 (47%)	41	..
45–64	9 (45%)	21 (29%)	30	..
≥65	0	2 (3%)	2	..
Aged <25 years				
Yes	4 (20%)	15 (21%)	19	1.0 (0.4–2.5)
No	16 (80%)	57 (79%)	73	..
Ethnic origin†				
Asian	0	38 (53%)	38	..
Black	2 (10%)	7 (10%)	9	..
Hispanic	17 (85%)	20 (28%)	37	..
White	1 (5%)	7 (10%)	8	..
Hispanic ethnic origin				
Yes	17 (85%)	20 (28%)	37	8.4 (2.7–26.7)
No	3 (15%)	52 (72%)	55	..
Country of birth				
USA	8 (40%)	9 (13%)	17	2.9 (1.4–6.1)
Other	12 (60%)	63 (88%)	75	..
Homelessness within the past 12 months				
Yes	3 (15%)	4 (6%)	7	2.1 (0.8–5.6)
No	17 (85%)	68 (94%)	85	..
Abuse of alcohol or illicit drugs within the past 12 months				
Yes	9 (45%)	6 (8%)	15	4.2 (2.1–8.3)
No	11 (55%)	66 (92%)	77	..
In prison at time of diagnosis				
Yes	1 (5%)	1 (1%)	2	2.3 (0.6–10.0)
No	19 (95%)	71 (99%)	90	..
Resident of a long-term care facility at time of diagnosis				
Yes	1 (5%)	1 (1%)	2	2.3 (0.6–10.0)
No	19 (95%)	71 (99%)	90	..
Reported HIV status				
Positive	2 (10%)	2 (3%)	4	2.4 (0.8–7.1)
Not positive	18 (90%)	70 (97%)	88	..

(Continues in next column)

months of arrival in the USA. Median times between date of US entry and diagnosis was 9 years (IQR 6–25) for cases that could be attributed to transmission in the

	Disease linked with transmission in the USA		Total (n=92)	Relative risk (95% CI)
	Yes (n=20)	No (n=72)		
(Continued from previous column)				
Clinical presentation‡				
Pulmonary only	16 (80%)	66 (92%)	82	..
Extrapulmonary only	2 (10%)	2 (3%)	4	..
Both pulmonary and extrapulmonary	2 (10%)	4 (6%)	6	..
Pulmonary involvement				
Yes	18 (90%)	70 (97%)	88	0.4 (0.1–1.2)
No	2 (10%)	2 (3%)	4	..
Extent of disease§				
Extensive	11 (55%)	40 (56%)	51	..
Moderate	0	5 (7%)	5	..
Non-extensive	9 (45%)	26 (36%)	35	..
Unknown	0	1 (1%)	1	..
Positive sputum smear				
Yes	13 (65%)	45 (63%)	58	1.1 (0.5–2.5)
No	7 (35%)	27 (38%)	34	..
Cavitary chest radiograph				
Yes	7 (35%)	32 (44%)	39	0.7 (0.3–1.7)
No	13 (65%)	40 (56%)	53	..
Previous tuberculosis diagnosis				
Yes	0	16 (22%)	16	..
No	20 (100%)	56 (78%)	76	..
Mycobacterium tuberculosis spoligotype-based lineage¶				
East African Indian	0	2 (3%)	2	..
East Asian	1 (5%)	29 (40%)	30	..
Euro-American	19 (95%)	29 (40%)	48	..
Indo-Oceanic	0	11 (15%)	11	..
<i>Mycobacterium africanum</i>	0	1 (1%)	1	..
<i>Mycobacterium bovis</i>	0	0	0	..
Euro-American lineage				
Yes	19 (95%)	29 (40%)	48	17.4 (2.4–124.7)
No	1 (5%)	43 (60%)	44	..

On the basis of health-record review and interview data * χ^2 test: $p=0.06$. † χ^2 test: $p<0.0001$. ‡ χ^2 test: $p=0.10$. § χ^2 test: $p=0.57$; extensive disease when positive sputum smear and cavitary chest radiograph, positive sputum smear and bilateral infiltrates, or miliary tuberculosis; non-extensive when negative sputum smear and non-cavitary chest radiograph; moderate for all other clinical presentations. ¶ χ^2 test: $p<0.0001$.

Table 4: Characteristics of patients with multidrug-resistant tuberculosis who consented to an in-depth interview

USA, and 4 years (1–9) for those that could not be attributed.

Notably, three individuals with extensively drug-resistant tuberculosis (from Kyrgyzstan, Nepal, and Russia) were categorised as imported disease, because

Panel: Research in context**Systematic review**

We searched PubMed with the term: "(tuberculosis OR TB) AND (multidrug resistance OR MDR) AND (transmission)" for reports published in any language between Jan 1, 1965, and April 31, 2013. We identified 630 reports, of which 134 were of peer-reviewed studies and contained original data for the epidemiology of drug-resistant tuberculosis, such as information about patients and tuberculosis genotype data. In 96 studies, information about interpersonal connections or transmission venues (as needed to accurately identify transmission events) was not obtained. 35 studies were done in outbreak conditions or were narrowly focused on specific groups, such as health-care workers, household contacts, people living with HIV infection, prisoners, or miners. Of the remaining three population-based studies that investigated transmission of multidrug-resistant (MDR) tuberculosis, only one was based in the USA: it was done in one state more than a decade ago.

Interpretation

As far as we are aware, ours is the largest multicentre, population-based study to include detailed information about the potential contributing factors of transmission of MDR tuberculosis. We showed that as many as one in every five individuals diagnosed with MDR tuberculosis in the USA could be linked to transmission. Evidence-based standardised regimens are urgently needed for people exposed to MDR tuberculosis to prevent progression to active disease.

diagnosis occurred within 3 months of immigration, their *M tuberculosis* isolates were non-clustering genotypes, and no epidemiological links were identified.

During our study period, we identified 1166 people by contact investigation who were exposed to MDR tuberculosis, of whom 353 (30%) were diagnosed with latent tuberculosis infection. Although which individuals will go on to develop active MDR tuberculosis is unclear, with the assumption that 10% will develop active disease,²⁸ 35 new cases of MDR tuberculosis could emerge in the USA from our cohort in the absence of efficacious preventive treatment.

Discussion

In this multicentre, multiyear, population-based study, transmission occurred in roughly a fifth of individuals with MDR tuberculosis. Although most people diagnosed with MDR tuberculosis were born outside of the USA, some were linked to transmission in the USA, including four individuals who were the source of transmission for other cases. A substantial proportion of MDR tuberculosis cases represented reactivation of tuberculosis or disease acquired outside the USA (20 imported active disease, 14 known previous episode outside the USA, five documented treatment of previous episode within the USA; 42%),

including 17 that were diagnosed within 3 months of entry into the USA.

The proportion of MDR tuberculosis cases attributed to transmission within the USA in our study (22%) was similar to that in another report of genotyped cases reported in the USA (23%),²² but higher than values reported for the state of California (14%¹⁴ and 8%¹⁸). However, in these previous studies,^{14,18,22} detailed information about interpersonal connections between cases was not available, and thus genotyping results alone were used as a proxy to determine tuberculosis transmission. In a study following the major outbreak of MDR tuberculosis and resurgence of tuberculosis in New York City (NY, USA),²⁹ about 13% of genotyped MDR tuberculosis cases were epidemiologically linked by medical-record review and interview of patients, most of whom were exposed to MDR tuberculosis long before the study.¹⁷

Notably, in our study, half the identified source cases were born outside the USA. This finding contrasts with those of other studies, which have suggested that transmission of *M tuberculosis* within a country generally occurs between individuals born there,^{17,18,22,23} and rarely occurs between these people and those born elsewhere.³⁰ Therefore, our findings could have important implications for algorithms that assign the likelihood of tuberculosis transmission in the USA in the absence of routinely identified epidemiological linkages and because important transmission events might be missed in people born elsewhere.³¹

The large proportion of cases of reactivated disease acquired outside the USA might have been prevented had appropriate diagnostic screening and treatment been implemented at or before immigration (reducing the potential for transmission in the USA). Our results were similar to those of a cross-sectional study of all patients born outside the USA with an *M tuberculosis* isolate genotyped in the USA between 2005 and 2009:²³ 50% of cases were attributable to reactivation of disease acquired elsewhere. Importantly, the primary purpose of the present US immigration screening programme is to identify active disease, and not latent tuberculosis infection.³² There is no policy to test for latent tuberculosis infection in adults born outside the USA before or during the US entry process.³² Moreover, for individuals who already live in the USA but were born elsewhere, present guidelines³³ recommend testing for latent tuberculosis infection only for those who have been in the USA for less than 5 years.

More importantly, prevention of transmission and progression to active disease is more challenging after exposure to MDR *M tuberculosis* than after exposure to drug-susceptible *M tuberculosis*. The principal strategy to interrupt tuberculosis transmission and reduce the likelihood of remote reactivation of disease is to use treatment for latent infection. Several treatment regimens are available for people who have latent

tuberculosis and are exposed to drug-susceptible *M tuberculosis*, including a once weekly, 12-dose regimen.³⁴ However, because all isolates of MDR *M tuberculosis* have resistance to isoniazid and rifampicin, most evidence-based regimens are not appropriate for individuals exposed to MDR tuberculosis. The American Thoracic Society and CDC recommend that immunocompetent people exposed to MDR tuberculosis be followed up for 24 months, irrespective of treatment.³³ When treatment is given, a two-drug regimen taken for 6–12 months is recommended if bacteria from the index case are known to be susceptible to pyrazinamide and ethambutol, or pyrazinamide and a fluoroquinolone.³³ Unfortunately both pyrazinamide regimens have high toxicity;^{35,36} thus, careful follow-up without any treatment is a justifiable option for immunocompetent individuals. Therefore, the decision to treat latent tuberculosis infection as a result of exposure to MDR disease—and how to go about it—remains highly controversial.

As yet, no randomised controlled trials of the efficacy of recommended treatment combinations for latent MDR tuberculosis infection have been reported.³⁷ Several approvals for new antituberculosis drugs are imminent, including some with early bactericidal activity,^{38,39} but these drugs might not be available for routine clinical care for several years. Because these drugs are being developed primarily to shorten treatment and improve clinical outcomes, whether they will be effective in prophylaxis or whether they should be used at all for latent infection to protect against potential acquired drug resistance is unknown.^{40,41}

During our study, contact investigation identified 1166 individuals who were exposed to MDR tuberculosis, including 353 (30%) diagnosed with latent tuberculosis infection. Although which individuals will go on to develop active disease is unclear, 35 new cases will potentially emerge in the future in the USA from this cohort without efficacious preventive treatment.

Our study was one of the largest population-based studies of MDR tuberculosis transmission (panel), and we included all genotyped cases reported in eight states during the surveillance period, but only about 60% of eligible cases were available for in-depth interview. Genotypic and epidemiological linkages based on both interview and public health records provided a strong assessment of transmission between enrolled individuals, but because not all isolates received all three genotyping methods (ie, spoligotyping, 24-locus MIRU-VNTR and IS6110-RFLP), some clusters could possibly be divided into small subsets. Therefore, we might have underestimated transmission. Moreover, not all individuals with MDR tuberculosis, including those in adjacent states, were interviewed, so we might have underestimated the proportion of cases with epidemiological linkages and therefore transmission between states. Additionally, because MDR tuberculosis

was a rare event, our sample size was small and cell size could affect some statistical inferences.

In conclusion, although roughly four-fifths of individuals with MDR tuberculosis included in our study were born outside the USA, a fifth could be linked to transmission after immigration. These findings, in addition to the substantial proportion of cases that were reactivation of MDR disease or disease acquired outside the USA, further emphasise the immediate need for evidence-based, standardised regimens to prevent transmission of MDR tuberculosis and progression of active disease.

Contributors

PKM, JF, and EAG designed the study on behalf of the Tuberculosis Epidemiologic Study Consortium. LDT, KS, SG, and SDA collected data. PKM, LDT, SG, JF, and EAG analysed and interpreted data. All authors wrote the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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