Mycobacterium tuberculosis transmission from patients with drug-resistant compared to drug-susceptible TB: a systematic review and meta-analysis

To the Editor:

The extent to which drug-resistant (DR) *Mycobacterium tuberculosis* strains cause infection and progression to tuberculosis (TB) disease in comparison to drug-susceptible (DS) strains is unknown. Studies in guinea pigs and *in vitro* experiments have suggested a reduced fitness of organisms that harbour mutations that confer drug resistance [1, 2]; it was therefore believed that transmitted drug resistance was a rare event. However, more recent work using molecular typing has shown transmission events occurring in the context of DR-TB [3]. Understanding the risk of transmission, infection and progression to disease in the context of DR-TB is important to guide control measures and help predict the evolution and magnitude of the multidrug-resistant (MDR)-TB epidemic. Hence, we performed a systematic review and meta-analysis to assess whether *M. tuberculosis* transmission and progression to TB disease (risk/rate of *M. tuberculosis* infection in all contacts, risk/rate of TB disease in all contacts and risk/rate of TB disease in infected contacts) differ between DR- and DS-TB.

Nine databases were searched. Eligible studies compared contacts of index cases with DS- and DR-TB and reported on risk of *M. tuberculosis* infection (determined either by the interferon gamma release assay (IGRA) or tuberculin skin test (TST)) or risk, or rate of TB disease and risk/rate of TB disease in infected (positive TST or IGRA) contacts. Fixed and random effects meta-analyses were used to obtain pooled estimates with 95% confidence intervals (95% CI) where possible. Results were stratified by resistance pattern of the isolate causing disease in the index patients, differentiating between DS, mono-resistant and MDR cases. Where data were not presented in the publication, first authors were contacted to obtain additional information. The quality of studies was assessed using an adapted Newcastle Ottawa Scale for cohort studies.

A total of 5316 citations were identified; 1962 duplicates were removed. Of those remaining, 3063 were considered not relevant and excluded. Of the 291 articles retained for full-text review, seven were included [4–10]. Characteristics of the index patients and their contacts are presented in table 1. The included studies enrolled participants during the years 1975 to 2013 and were conducted in six countries: Argentina (n=1) [7], Brazil (n=2) [4, 5], Peru (n=1) [6], Canada (n=1) [8], Mexico (n=1) [9] and the United States (n=1) [10]. No studies from Africa, Asia or Europe were identified. Two studies were conducted in a country classified as high TB-burden (Brazil) [4, 5] and one from a high MDR-TB-burden country (Peru) [6].

Two studies [5, 6] were marked as good quality; the other five were of moderate quality because of a high risk of selection bias due to loss to follow-up. All studies investigating TB disease as an outcome were considered at high risk for ascertainment bias. Furthermore, drug susceptibility testing (DST) was not performed on all secondary isolates. No study confirmed transmission through genotyping.

The *M. tuberculosis* infection was the outcome in five studies [5, 7–10]. The pooled relative risk of *M. tuberculosis* infection defined by positive TST using a fixed or random effects model was 1.24 (95% CI 1.08–1.42 fixed, 95% CI 0.98–1.44 random) comparing contacts of index cases with MDR-TB and DS-TB. Heterogeneity was high with an I^2 of 75%.

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TABLE 1 Characteristics of index patients, contacts and outcome measurements

First author [ref.]	Country	Study period and type	DR/ DS	Method of patient selection	Index patients n	Age years mean ±SD	Sex F/M %	HIV status	DR pattern n (%)	Contacts n (mean)	Outcome measures for *M. tuberculosis* infection	TB infection events n/ N (%)	Latent TB therapy	TB disease events n/ N (%)	Timing of diagnosis	Risk of infection RR (95% CI)#	Risk of disease RR (95% CI)#	Overall risk of bias
Snider [10]	USA	1975–1977, cohort (prospective), NR (study period 32 months)	DR	Recruited from CDC laboratory	398	NR	NR	NR	INH⁻resistant: 178 (44.5); SM-resistant: 136 (34.0); INH/SM-resistant: 86 (21.5)	Paediatric contacts: 627 (1.6)	TST ⩾5mm (12 clinics), TST ⩾10mm (3 clinics),] unknown (2 clinics)	DR: 239/601 (39.8)	NR	DR: 4/601 (0.6 of total, 1.7 of infected)	NR	DR-non-MDR *versus* DS: 1.19 (1.03–1.36)	DR-non-MDR *versus* DS: 0.84 (0.24–2.94)	High-moderate (selection bias likely, comparability and outcome ascertainment likely)
			DS	Matched to study patients for age, race, sex and location	398	NR	NR	NR	Fully susceptible	778 (2.0)	TST ⩾5 mm (12 clinics), TST ⩾10 mm (3 clinics), unknown (2 clinics)	DS: 252/751 (33.6)	NR	DS: 6/753 (0.8 of total, 2.4 of infected)	NR			
Barroso [4]	Brazil	1990–1999, cohort (retrospective), 2 years	DR	Based on the results of DST at medical facilities	126	39±25	37.3/ 62.7	78 of 126 tested, all results negative	MDR	557 (4.4)	NR	NR	NR	MDR: 25/557 (4.5)	NR	NR	MDR *versus* DS: 0.84 (0.52–1.37)	Low-moderate (selection bias likely, comparability and outcome ascertainment likely)
			DS	Matched to study patients for sex, age, and year of first treatment	176	41±14	37.5/ 62.5	97 of 176 tested, all results negative	Fully susceptible	752 (4.3)	NR	NR	NR	DS: 41/752 (5.5)	NR			
Johnston [8]	Canada	1990–2008, cohort (retrospective), 123 (IQR 19–239) months	DR	Recruited from national TB registry	124	NR	NR	NR	INH-mono- resistant (HMR): 96	HMR: 249 (3.0)		Non-MDR (HMR)¶: 121/ 249 (49)		Non-MDR (HMR): 8/ 249 (3.0)		DR-non-MDR *versus* DS:] 1.53 (1.34 – 1.75)	DR-non-MDR *versus* DS: 1.43 (0.71–2.87)	Low-moderate (selection bias likely, comparability and outcome ascertainment likely)
									INH/RMP-resistant: 28 (MDR)	MDR: 89 (3.0)	TST ⩾5 mm (3 months to <1 year after source diagnosis)	MDR: 42/89 (47)	12/89 treated	MDR: 5/89 (6.0), all susceptible	All diagnosed within 3 months of index patients	MDR *versus* DS: 1.49 (1.19–1.86)	MDR *versus* DS: 2.5 (1.05–5.93)	
			DS	Recruited from national TB registry	2895	NR			Fully susceptible	7309 (3.0)	TST ⩾5 mm (3 months to <1 year after source diagnosis)	DS: 2321/7309 (32)	NR	DS: 168/7472 (2.0)	NR			
Teixeira [5]	Brazil	1994–1998, cohort (prospective), NR (study period 54 months)	DR	Recruited from TB referral centre	26	39.5 ±12	23/ 77	HIV+: 5 (20%) HIV-: 21 (80%)	INH/RMP⁻resistant: 6 (23); INH/RMP/ PZA-resistant: 11 (43); INH/RMP/PZA/ SM-resistant: 5 (19) INH/ RMP/PZA/SM-resistant: 1 INH/RMP/PZA/ EMB-resistant: 1 INH/ RMP/SM/ PZA-resistant: 1 INH/ RMP/PZA/ ethionamide: 1	157 (6.0)	TST ⩾10 mm	MDR: 59/133 (44), no therapy		MDR 6/157 (4.0)	3 a median 10 (range 2–34) months after initial evaluation,	MDR *versus* DS: 1.19 (0.92–1.54)	MDR *versus* DS: 0.7 (0.19–2.59)	Good (comparability and outcome ascertainment likely)
			DS	Two DS index patients were matched to each new MDR-TB patient	52	38.4 ±13	23/ 77	HIV+: 5 (10%) HIV-: 47 (90%)	Fully susceptible	251 (5.0)	TST ⩾10 mm	DS: 86/231 (37)	NR	DS: 11/251 (4.0)	Median 10 (range 2–34) months after initial evaluation			

Continued

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First author [ref.]	Country	Study period and type	DR/ DS	Method of patient selection	Index patients n	Age years mean ±SD	Sex F/M %	HIV status	DR pattern n (%)	Contacts n (mean)	Outcome measures for *M. tuberculosis* infection	TB infection events n/ N (%)	Latent TB therapy	TB disease events n/ N (%)	Timing of diagnosis	Risk of infection RR (95% CI)#	Risk of disease RR (95% CI)#	Overall risk of bias
Palmero [7]	Argentina	1998–2000, cohort (retrospective), 3 years	DR	Recruited from TB registry	37	31.3 ±9.3	33/ 68	HIV+: 21 (57%) HIV-: 16 (43%)	MDR	97 (2.6)	TST ⩾10 mm	MDR: 17/97 (17.5)	NR	MDR: 2/97 (2.1)	NR	MDR *versus* DS: 1.45 (0.87–2.43)	MDR *versus* DS: 0.92 (0.2–4.25)	Low-moderate (selection bias likely, comparability and outcome ascertainment likely)
			DS	Recruited from TB registry	100	29.6 ±8.6	24/ 76	HIV+: 38 (38%) HIV-: 62 (62%)	Fully susceptible	356 (3.5)	TST ⩾10 mm	DS: 43/356(12.1)	NR	DS: 8/356 (2.2%)	NR			
Grandjean [6]	Peru	2010–2013, cohort (prospective), DR 1425 person years (mean 494 days)	DR	Recruited at diagnosis from reference laboratories	213	32	61/ 39	HIV+: 18 (8%) HIV-: 195 (92%)	MDR	1055 (4.0)	NR	NR	12.5%	MDR: 35/1055 (3.3%), 28 DST performed of which 24 MDR and 4 DS	Day 1 of follow-up to day 600 of follow-up	NR	MDR *versus* DS: 0.71 (0.49–1.03)	Good (outcome ascertainment likely)
		2010–2013, cohort (prospective), DS 2620 person years (mean 406 days)	DS	Matched to study patients for age, race, sex and geographic location	487	33	61/ 39	HIV+: 20 (4%) HIV-: 467 (96%)	Fully susceptible	2362 (4.0)	NR	NR	17.2%	DS: 114/2441 (4.8%)	Day 1 of follow-up to day 600 of follow-up			
Laniado-Laborin [9]	Mexico	2011–2013, cross-sectional, no follow-up	DR	Recruited from TB clinic based on culture and DST performed at the clinic	33 (20 MDR)¶	NR			NR	MDR: 96/41 (4.0), paediatric contacts	TST ⩾5 mm, IGRA ⩾0.35 IU·m^{-1}	MDR TST-positive: 31/ 41 (75.6); MDR IGRA-positive: 24/41 (58)	Not treated	NR		MDR *versus* DS (TST): 0.91 (0.74–1.11)	NR	Low-moderate (selection bias likely, comparability and outcome ascertainment likely)
			DS	Recruited from TB clinic based on culture and DST performed at the clinic	37	NR			NR	77 (2.3)	TST ⩾5 mm, IGRA ⩾0.35 IU·m^{-1}	DS TST-positive: 64/77 (83); DS IGRA-positive: 32/77 (42)	Treated with INH or RMP, unclear proportion	NR				
Meta-analysis												**Events in DR-non-MDR contacts *versus* DS contacts: 360/850 *versus* 2573/8060; events in MDR contacts *versus* DS contacts: 149/360 *versus* 2514/7973**		**Events in DR-non-MDR contacts *versus* DS contacts: 12/850 *versus* 174/ 8225; events in MDR contacts *versus* DS contacts: 73/1931 *versus* 342/11279**		**DR-non-MDR *versus* DS: 1.33 (1.2–1.46); MDR *versus* DS: 1.24 (1.08–1.42)**	**DR-non-MDR *versus* DS: 1.23 (0.67–2.27); MDR *versus* DS: 0.81 (0.64–1.06)**	

DR: drug-resistant; DS: drug-susceptible; F: female; M: male; *M. tuberculosis*: *Mycobacterium tuberculosis*; TB: tuberculosis; NR: not recorded; CDC: Centers for Disease Control and Prevention; INH: isonicotinylhydrazide (isoniazid); SM: streptomycin; TST: tuberculin skin test; MDR: multidrug-resistant; DR-non-MDR: other resistance or not specified, not INH/ rifampicin (RMP); DST: drug-susceptibility testing; IQR: interquartile range; HMR: isoniazid mono-resistant; PZA: pyrazinamide; EMB: ethambutol; IGRA: interferon-γ release assay. #: fixed effects meta-analysis; ¶: additional information provided by authors, used in the meta-analysis.

Six studies [4–8, 10] reported the rate or risk of TB disease among contacts of DR-TB and DS-TB index patients after diagnosis of the index patient. The mean duration of follow-up ranged from 406 days [6] to 123 months [8]. Five studies provided data for a meta-analysis, showing no evidence of a reduced risk of active TB in contacts of MDR-TB index cases (Relative risk ratio 0.81, 95% CI 0.64–1.06, I^2=43%) or DR-TB including non-MDR-TB index cases only (Relative risk ratio 1.23, 95% CI 0.67–2.27). Calculation of pooled rate ratios was precluded as person-years of follow-up was not provided by all studies.

Incidence of TB disease among contacts already infected (positive TST) at time of first assessment was analysed by one study in young children with high exposure, without reporting information on chemoprophylaxis [10]. Over a total study period of 32 months, 1.7% of the infected contacts of DR-TB index patients and 2.4% of DS-TB index patients progressed to TB disease (p=0.41).

We believe this review offers important comparative information on the transmissibility of DR-TB. Overall, our meta-analysis demonstrates a greater likelihood of *M. tuberculosis* infection in contacts of DR-TB index patients. However, any estimate of transmissibility will be a compound effect of the strain and other factors influencing the risk of the contact becoming infected, such as infectiousness of the index case, and duration and intensity of the exposure. Contacts of DR-TB index cases are more likely to have been exposed for a longer duration on multiple occasions and possibly exposed to more infectious and poorly treated TB. This might explain the higher risk of *M. tuberculosis* infection among contacts of DR-TB index patients.

On the other hand, our meta-analysis did not find evidence of a reduced risk of TB disease among contacts of DR-TB compared to DS-TB index cases. However, data on the risk of active TB is more difficult to interpret, owing to a limited follow-up time in most studies.

This review has several limitations and highlights research gaps both geographically and with regards to risk groups. Few studies were identified comparing contacts of DR-TB and DS-TB index patients. Some studies, summarised in other systematic reviews, had to be excluded as they lacked contacts of both DR- and DS-TB index patients [11, 12], or susceptibility testing [13]. The generalisability of this review is geographically limited, as the studies included were all from the Americas. The lack of studies from high MDR-TB burden countries in Central Asia and high HIV-prevalence settings, such as sub-Saharan Africa, is both surprising and of concern. Only two studies involved paediatric contacts [9, 10] and none focused on people living with HIV. A previous prospective study without a drug-susceptible comparison group has shown a high risk of *M. tuberculosis* infection and progression to disease in paediatric contacts of adult index patients with MDR tuberculosis [14]. Studies using child contacts minimise misclassification, as children are less likely to have been infected by additional TB cases from outside the household than adults are.

The quality of studies was moderate, owing to the risk of selection and ascertainment bias. Measurement of loss to follow-up and follow-up periods varied between studies, and the pooled, as well as the individual study results could well be biased by differential loss to follow-up in contacts of DR- and DS-TB index patients. Outcome ascertainment for secondary TB and length of follow-up differed across studies, which might explain the heterogeneity of results. Comparison between studies was further challenged by differences in analysis. Some studies used incidence, whereas others used cumulative prevalence as the outcome measure. In addition, few studies adjusted for potential confounders, such as socio-economic differences, smoking or duration of contact.

Whereas heterogeneity and limitations indicate a need for caution in interpreting these findings, the suggestion of increased transmission risk from DR-TB patients does not support the previously held dogma that DR-TB is less transmissible than DS-TB. This is critical when predicting the evolution of the MDR-TB epidemic and the likely impact of measures, such as prompt diagnosis, treatment of active and latent TB and infection control. For clinicians and national tuberculosis programmes, these findings underscore the importance of infection control and contact tracing in the context of MDR-TB. The relative fitness of MDR-TB compared to DS-TB strains is the key modelling parameter for predicting the future MDR-TB epidemic [15]. Quantifying transmissibility and progression to TB disease in the context of dug resistance is paramount to ensure validity of predictions, as TB control policy becomes increasingly reliant on modelled estimates *of M. tuberculosis* infection and TB disease.

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References

1 Mitchison DA. The virulence of tubercle bacilli from patients with pulmonary tuberculosis in India and other countries. *Bull Int Union Tuberc* 1964; 35: 287–306.
2 Gagneux S. Fitness cost of drug resistance in *Mycobacterium tuberculosis*. *Clin Microbiol Infect* 2009; 15: 66–68.
3 Meftahi N, Namouchi A, Mhenni B, *et al.* Evidence for the critical role of a secondary site rpoB mutation in the compensatory evolution and successful transmission of an MDR tuberculosis outbreak strain. *J Antimicrob Chemother* 2016; 71: 324–332.
4 Barroso EC, Mota RMS, Pinheiro VGF, *et al.* Ocorrência de tuberculose doença entre contatos de tuberculose sensível e multirresistente. *Jornal Brasileiro de Pneumologia* 2004; 30: 311–318.
5 Teixeira L, Perkins MD, Johnson JL, *et al.* Infection and disease among household contacts of patients with multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2001; 5: 321–328.
6 Grandjean L, Gilman RH, Martin L, *et al.* Transmission of multidrug-resistant and drug-susceptible tuberculosis within households: a prospective cohort study. *PLoS Med* 2015; 12: e1001843.
7 Palmero D, Cusmano L, Bucci Z, *et al.* Infectiousness and virulence of multidrug-resistant and drug susceptible tuberculosis in adult contacts. *Medicina (B Aires)* 2002; 62: 221–225.
8 Johnston J, Admon A, Ibrahim A, *et al.* Long term follow-up of drug resistant and drug susceptible tuberculosis contacts in a low incidence setting. *BMC Infect Dis* 2012; 12: 266.
9 Laniado-Laborin R, Cazares-Adame R, Volker-Soberanes ML, *et al.* Latent tuberculous infection prevalence among paediatric contacts of drug-resistant and drug-susceptible cases. *Int J Tuberc Lung Dis* 2014; 18: 515–519.
10 Snider DE Jr, Kelly GD, Cauthen GM, *et al.* Infection and disease among contacts of tuberculosis cases with drug-resistant and drug-susceptible bacilli. *Am Rev Respir Dis* 1985; 132: 125–132.
11 Fox GJ, Barry SE, Britton WJ, *et al.* Contact investigation for tuberculosis: a systematic review and meta-analysis. *Eur Respir J* 2013; 41: 140–156.
12 Shah NS, Yuen CM, Heo M, *et al.* Yield of contact investigations in households of patients with drug-resistant tuberculosis: systematic review and meta-analysis. *Clin Infect Dis* 2014; 58: 381–391.
13 Fox GJ, Anh NT, Nhung NV, *et al.* Latent tuberculous infection in household contacts of multidrug-resistant and newly diagnosed tuberculosis. *Int J Tuberc Lung Dis* 2017; 21: 297–302.
14 Schaaf HS, Gie RP, Kennedy M, *et al.* Evaluation of young children in contact with adult multidrug-resistant pulmonary tuberculosis: a 30-month follow-up. *Pediatrics* 2002; 109: 765–771.
15 Knight GM, Colijn C, Shrestha S, *et al.* The distribution of fitness costs of resistance-conferring mutations is a key determinant for the future burden of drug-resistant tuberculosis: a model-based analysis. *Clin Infect Dis* 2015; 61: Suppl. 3, S147–S154.