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

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Word count: 1163

The extent to which drug-resistant (DR) *Mycobacterium tuberculosis (Mtb)* strains cause infection and progression to tuberculosis (TB) disease compared to drug-susceptible (DS) strains is unknown. Studies in guinea-pigs and *in vitro* experiments had suggested a reduced fitness of organisms harbouring 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 have 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 to 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 *Mtb* transmission and progression to TB disease (risk/rate of *Mtb* 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 *Mtb* infection (determined either by IGRA or 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 5,316 citations were identified; 1962 duplicates were removed. Of the remaining, 3,063 were considered not relevant and excluded. Of 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 from 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 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, DST

was not performed on all secondary isolates. No study confirmed transmission through genotyping.

Mtb infection was the outcome in five studies.(5, 7-10) The pooled relative risk of *Mtb* 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%.

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 (RR 0.81, 95%CI 0.64-1.06, I^2=43%) or DR-TB including non-MDR-TB index cases only (RR 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, not 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 *Mtb* 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, duration and intensity of the exposure. Contacts of DR-TB index cases are more likely to have been exposed for longer duration, on multiple occasions and possibly to more infectious and poorly treated TB. This might explain the higher risk of *Mtb* 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 due to 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, summarized 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 generalizability 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 *Mtb* infection and progression to disease in pediatric contacts of adult index patients with MDR tuberculosis (14). Studies using child contacts minimise misclassification, as children are less likely than adults to have been infected by additional TB cases from outside the household.

The quality of studies was moderate due 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, while others cumulative prevalence as outcome measure. Additionally, few studies adjusted for potential confounders such as socio-economic differences, smoking or duration of contact.

Whilst 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 prior 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 programs 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 Mtb* infection and TB disease.

Contributions of authors: KK conceived the idea for the systematic review. KK, CK and BL designed the study. KK, CK and BL performed screening and data extraction. CK and BL

assessed risk of bias. BL and KK performed the meta-analysis. IO, PK, ML, JS, DS, LG, RF contributed to the analysis and manuscript writing. All authors read and approved the final version of the manuscript.

Acknowledgment and Funding Institutional funding for Berit Lange was supported by the German Federal Ministry of Education and Research (BMBF 01EO1303 grant to the Center for Chronic Immunodeficiency). Palwasha Khan is funded by a Wellcome Trust clinical research training fellowship [grant number 100137/Z/12/Z]. We would like to acknowledge the valuable administrative support during the conduct of this study by Johannes Camp and Lucy Wong of University Hospital Freiburg.

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