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

Chiori Kodama *[1 2], Berit Lange*[3 4], Ioana D. Olaru[5], Palwasha Khan[1], Marc Lipman[6], James A. Seddon[7], Derek Sloan[8], Louis Grandjean[1], Rashida Ferrand[9,10], Katharina Kranzer[11,1]

*equal contributions

1 Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, United Kingdom

2 World Health Organization, Geneva

3 Division of Infectious Diseases, Department of Medicine II, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Germany; Berit.Lange@uniklinik-freiburg.de , Hugstetterstr.55, 79106 Freiburg

4 Centre for Chronic Immunodeficiency, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Germany

5 Division of Clinical Infectious Diseases, Research Center Borstel, Germany

6 Royal Free London NHS Foundation Trust & UCL Respiratory, Division of Medicine, University College London, UK

7 Centre for International Child Health, Department of Paediatrics, Imperial College London, United Kingdom

8 School of Medicine, University of St Andrews, Scotland, UK

9 Department of Clinical Research, London School of Hygiene & Tropical Medicine, London, United Kingdom

10 Biomedical Research and Training Institute, Harare, Zimbabwe

11 National and Supranational Reference Laboratory, Leibnitz Research Centre, Borstel Germany

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.

## References


1. Mitchison DA. The Virulence of Tubercle Bacilli from Patients with Pulmonary Tuberculosis in India and Other Countries. Bulletin of the International Union against Tuberculosis. 1964;35:287-306.
2. Gagneux S. Fitness cost of drug resistance inMycobacterium tuberculosis. Clinical Microbiology and Infection. 2009;15:66-8.
3. Meftahi N, Namouchi A, Mhenni B, Brandis G, Hughes D, Mardassi H. 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(2):324-32.
4. Barroso EC, Mota RMS, Pinheiro VGF, Campelo CL, Rodrigues JLN. Ocorrência de tuberculose doença entre contatos de tuberculose sensível e multirresistente. Jornal Brasileiro de Pneumologia. 2004;30(4):311-8.
5. Teixeira L, Perkins MD, Johnson JL, Keller R, Palaci M, do Valle Dettoni V, et al. Infection and disease among household contacts of patients with multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2001;5(4):321-8.
6. Grandjean L, Gilman RH, Martin L, Soto E, Castro B, Lopez S, et al. Transmission of Multidrug-Resistant and Drug-Susceptible Tuberculosis within Households: A Prospective Cohort Study. PLoS Medicine. 2015;12(6).
7. Palmero D, Cusmano L, Bucci Z, Romano M, Ruano S, Waisman J. Infectiousness and virulence of multidrug-resistant and drug susceptible tuberculosis in adult contacts. Medicina. 2002;62(3):221-5.
8. Johnston J, Admon A, Ibrahim A, Elwood K, Tang P, Cook V, 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, del Portillo-Mustieles C, Villa-Rosas C, Oceguera-Palao L, et al. Latent tuberculous infection prevalence among paediatric contacts of drug-resistant and drug-susceptible cases. Int J Tuberc Lung Dis. 2014;18(5):515-9.
10. Snider DE, Jr., Kelly GD, Cauthen GM, Thompson NJ, Kilburn JO. Infection and disease among contacts of tuberculosis cases with drug-resistant and drug-susceptible bacilli. Am Rev Respir Dis. 1985;132(1):125-32.
11. Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: a systematic review and meta-analysis. Eur Respir J. 2013;41(1):140-56.
12. Shah NS, Yuen CM, Heo M, Tolman AW, Becerra MC. Yield of contact investigations in households of patients with drug-resistant tuberculosis: systematic review and meta-analysis. Clin Infect Dis. 2014;58(3):381-91.
13. Fox GJ, Anh NT, Nhung NV, Loi NT, Hoa NB, Ngoc Anh LT, et al. Latent tuberculous infection in household contacts of multidrug-resistant and newly diagnosed tuberculosis. Int J Tuberc Lung Dis. 2017;21(3):297-302.
14. Schaaf HS, Gie RP, Kennedy M, Beyers N, Hesseling PB, Donald PR. Evaluation of young children in contact with adult multidrug-resistant pulmonary tuberculosis: a 30-month follow-up. Pediatrics. 2002;109(5):765-71.
15. Knight GM, Colijn C, Shrestha S, Fofana M, Cobelens F, White RG, 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;61Suppl 3:S147-54.

| Study (Publication year), Country, Study period | DR/DS | Method of index patient selection | Number of index patients | Age (mean ± SD) *Gender (%female/male)* HIV status of index patients | Drug resistance pattern of index patients | N contacts (mean N of contacts/ index patient) *Outcome measurements for Mtb infection* | Events of TB infection in DR (non-MDR*) group/ MDR group and DS [%] (therapy of latent TB) | Events of TB disease in DR-non-MDR / MDR contacts and DS contacts [% of all contacts] {% of infected} (timing of diagnosis) | Relative risk ratio (calculated**) of risk of infection in DR-nonMDR or MDR compared to contacts of DS index patients | Relative risk ratio (calculated**) of risk of disease in DR or MDR compared to contacts of DS index patients | Overall risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Snider (1985)<br>USA<br>1975-1977 Cohort (prospective)<br>NR (study period 32 months) | DR | recruited from the CDC laboratory | 398 | NR | INH resistant: 178 (44.5%)<br>SM resistant: 136 (34.0%)<br>INH/SM resistant: 86 (21.5%) | 627 (1.6)<br>Pediatric contacts<br>*TST ≥5mm (12 clinics), TST≥10mm (3 clinics), unknown (2 clinics)* | DR 239/601 [39.8%] (NR) | DR: 4/601 [0.6%] {1.7%} (NR) | **DR-nonMDR vs DS**<br>RR 1.19, 95%CI 1.03-1.36 | **DR-nonMDR vs D:**<br>RR 0.84, 95%CI 0.24-2.94 | high - moderate (Selection bias likely, comparability and outcome ascertainment likely) |
| | DS | matched to study patients for age, race, gender and geographic location | 398 | NR | Fully susceptible | 778 (2.0)<br>*TST ≥5mm (12 clinics), TST ≥10mm (3 clinics), unknown (2 clinics)* | DS 252/751 [33.6%] (NR) | DS: 6/753 [0.8%] {2.4} (NR) | | | |
| Barroso (2004)<br>Brazil<br>1990-1999 Cohort (retrospective) 2 years | DR | based on the results of DST at medical facilities | 126 | 39 ± 25<br>*37.3/62.7*<br>78 of 126 were tested for HIV, all results were negative | MDR | 557 (4.4)<br>*NR* | NR (NR) | MDR: 25/557 [4.5%] (NR) | NR | **MDR vs DS**<br>RR 0.84, 95%CI 0.52- 1.37 | low moderate (Selection bias likely, comparability and outcome ascertainment likely) |
| | DS | matched to study patients for gender, age, and year of first treatment | 176 | 41 ± 14<br>*37.5/62.5*<br>97 of 176 were tested for HIV, all results were negative | Fully susceptible | 752 (4.3)<br>*NR* | NR (NR) | DS: 41/752 [5.5%] (NR) | | | |
| Johnston (2012)<br>Canada<br>1990-2008 Cohort (retrospective) 123 months (IQR 19-239) | DR | recruited from national TB registry | 124 | NR | INH mono- resistant: 96 (HMR) | HMR 249 (3.0) | Non-MDR (HMR): 121/249: [49%] | Non-MDR (HMR) 8/249 [3.0%] | **DR-nonMDR vs D:**<br>RR 1.53, 95%CI 1.34 – 1.75) | **DR-nonMDR vs DS**<br>RR 1.43 95%CI 0.71-2.87 | low moderate (Selection bias likely, comparability and outcome ascertainment likely) |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | INH/RMP resistant: 28 (MDR) | MDR 89 (3.0)<br><br>*TST ≥5mm (3months to <1year after source diagnosis)* | MDR: 42/89 [47%]<br><br>(12/89 treated for latent TB) | MDR: 5/89 (all susceptible) [6.0%] (all 5 diagnosed within 3 months of index patients) | **MDR vs DS**<br><br>RR 1.49 95%CI 1.19-1.86 | **MDR vs DS**<br><br>RR 2.5 95%CI 1.05-5.93 | |
| | DS | recruited from national TB registry | 2895 | NR | Fully susceptible | 7309 (3.0)<br><br>*TST ≥5mm (3months to <1year after source diagnosis)* | DS: 2321/7309 [32%] (NR) | DS: 168/7472 [2.0%] (NR) | | | |
| Teixeira (2001) Brazil 1994-1998 Cohort (prospective NR (study period 54 months) | DR | recruited from TB referral center | 26 | 39.5 ± 12<br>23/77<br>HIV+=5 (20%)<br>HIV-=21 (80%) | INH/RMP resistant: 6 (23%)<br>INH/RMP/PZA resistant: 11 (43%)<br>INH, RMP/PZA/SM resistant: 5 (19%)<br>INH/RMP/PZA/SM resistant: 1<br>INH/RMP/PZA/EMB resistant: 1<br>INH/RMP/SM/PZA resistant: 1<br>INH/RMP/PZA/ethionamide: 1 | 157 (6.0)<br><br>*TST ≥10mm* | MDR: 59/133 [44%] (no therapy) | MDR: 6/157 [4.0%] (3 a median 10 months after initial evaluation, range 2-34) | **MDR vs DS**<br><br>RR 1.19, 95%CI 0.92-1.54 | **MDR vs DS**<br><br>RR 0.7, 95%CI 0.19-2.59 | good (Comparability and outcome ascertainment likely) |
| | DS | two DS index patients were matched to each new patient of MDR-TB patient | 52 | 38.4 ± 13<br>23/77<br>HIV+=5 (10%)<br>HIV-=47 (90%) | Fully susceptible | 251 (5.0)<br>*TST ≥10mm* | DS: 86/231 [37%] (NR) | DS: 11/251 [4.0%] median 10 months after initial evaluation, 2-34) | | | |
| Palmero (2002) Argentina 1998-2000 Cohort (retrospective) 3 years | DR | recruited from TB registry | 37 | 31.3 ± 9.3<br>33/68<br>HIV$^+$=21 (57%)<br>HIV$^-$=16 (43%) | MDR | 97 (2.6)<br>*TST ≥10mm* | MDR: 17/97 [17.5%] (NR) | MDR 2/97 [2.1%] (NR) | **MDR vs DS**<br><br>RR 1.45, 95%CI 0.87-2.43 | **MDR vs DS**<br><br>RR 0.92, 95%CI 0.2-4.25 | low-moderate (Selection bias likely, comparability and outcome ascertainment likely) |
| | DS | recruited from TB registry | 100 | 29.6 ± 8.6<br>24/76<br>HIV+=38 (38%)<br>HIV-=62 (62%) | Fully susceptible | 356 (3.5)<br>*TST ≥10mm* | DS 43/356 [12.1%] (NR) | DS: 8/356 [2.2%] (NR) | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Grandjean (2015)<br>Peru<br>2010-2013 Cohort (prospective)<br>DR: 1425 py (mean 494 days)<br>DS: 2620 py (mean 406 days) | DR | recruited at diagnosis from the reference laboratories | 213 | 32<br>61/39<br>HIV+=18 (8%)<br>HIV-=195 (92%) | MDR | 1055 (4.0)<br>*NR* | NR<br>(12.5%) | MDR 35/1055 [3.3%] (28 DST performed: 24 MDR, 4 DS)<br>(Day 1 of follow-up to day 600 of follow-up) | NR | **MDR vs DS**<br><br>RR 0.71, 95%CI 0.49-1.03 | good<br>(Outcome ascertainment likely) |
| | DS | matched to study patients for age, race, gender and geographic location | 487 | 33<br>61/39<br>HIV+=20 (4%)<br>HIV-=467 (96%) | Fully susceptible | 2362 (4.0)<br>*NR* | NR<br>(17.2%) | DS: 114/2441 [4,8%]<br>(Day 1 of follow-up to day 600 of follow-up) | | | |
| Laniado-Laborin (2014)<br>Mexico<br>2011-2013<br>Cross-sectional no follow-up, | DR | recruited from TB clinic based on culture and DST performed at the clinic | 33 (20 MDR)* | NR | NR | 96 /41 (MDR) (4.0) pediatric contacts<br>*TST ≥5mm, IGRA ≥0.35IU/m* | MDR:<br>31/41 [75.6% TST pos ]<br>24/41 [58% IGRA pos]<br>(not treated) | NR | **MDR vs DS (TST)**<br>RR 0.91, 95%CI 0.74-1.11 | NR | low - moderate<br>(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)<br>*TST ≥5mm, IGRA ≥0.35IU/m* | DS :<br>64/77 [83% TST pos]<br>32/77 [42% IGRA pos]<br>(treated with INH or RMP, unclear proportion) | NR | | | |
| **Meta-analysis** | ***fixed effects meta-analysis ** Additional information provided by authors, used in the meta-analysis** | | | | | | **Events in DR-nonMDR contacts vs DS contacts**<br>360/850 vs 2573/8060<br><br>**Events in MDR contacts vs DS contacts**<br>149/360 vs 2514/7973 | **Events in DR-nonMDR contacts vs DS contacts**<br>12/850 vs 174/8225<br><br>**Events in MDR contacts vs DS contacts**<br>73/1931 vs 342/11279 | **DR-nonMDR vs DS**<br><br>**RR 1.33**<br>(95%CI 1.2-1.46)<br><br>**MDR vs DS**<br><br>**RR 1.24**<br>(95%CI 1.08 -1.42 | **DR-nonMDR vs DS**<br><br>**RR 1.23**<br>(95%CI 0.67-2.27)<br><br>**MDR vs DS**<br><br>**RR 0.81**<br>(95%CI 0.64-1.06) | |

*Table 1 Characteristics of index patients, contacts and outcome measurements DS=Drug-susceptible DR=Drug-resistant, DR-nonMDR=other resistances or not specified, not INH/RMP MDR= multidrug-resistant, Mtb=Mycobacterium tuberculosis, HRS=Hours, HMR=isoniazid mono-resistant, IGRA=interferon gamma release assay, NR=not recorded, PY=Person years, TB=tuberculosis, TST=tuberculin skin test RR=relative risk ratio*