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LETTER

High prevalence of multidrug-resistant TB among household contacts in a high burden setting

Dear Editor,

Contact investigation is an underutilised intervention to reduce TB morbidity and transmission.[1–3] An appreciable proportion of multidrug- and rifampicin-resistant TB (MDR/RR-TB) cases among new and relapsed TB case notifications can be attributed to the absence of active case-finding activities that include contact investigation. This results in delayed detection of disease and fosters transmission in the community through exposed contacts of MDR/RR-TB patients.[4,5] In high MDR/RR-TB burden settings such as Pakistan, TB programmes lack the resources for contact investigation and most of the donors' funding is focused on activities that attract TB financing, such as community- or facility-based active case-finding. This is often at the cost of deprioritising routine services such as contact tracing. Thus, an important proportion of people at high risk for MDR/RR-TB – household contacts – remain undiagnosed and transmit drug-resistant strains within the community. These challenges also prevent programmes from producing evidence on preventive therapy, which may require a treatment approach tailored to those exposed to drug-resistant TB (DR-TB) strains. There is therefore an urgent need for more evidence on transmission in household settings to motivate the implementation of existing policies.

We conducted a prospective observational study between May 2016 and December 2019 at three tertiary care hospitals providing DR-TB care in Pakistan (the Indus Hospital in Karachi, Institute of Chest Diseases in Kotri and Gulab Devi Chest Hospital in Lahore). As part of routine programmatic care, for every individual diagnosed with MDR/RR-TB using Xpert® MTB/Rif (Cepheid, Sunnyvale, CA, USA), phenotypic drug susceptibility testing (DST) on first- and second-line TB drugs was performed to inform the most suitable treatment regimen according to National TB Control Programme (NTP) and WHO guidelines. Patients included in this cohort received rigorous follow-up and monitoring as the majority were also enrolled in the endTB (Expand New Drug markets for TB) cohort (a multi-country observational study that aimed to increase access to newer TB drugs, bedaquiline and delamanid, as part of routine MDR/RR-TB care in 17 countries).[6] As a part of this contact tracing study, we designed and implemented operational procedures for screening household contacts of MDR/RR-TB patients, which included wide-scale community participation through the inclusion of treatment coordinators, treatment supporters and counselling of family members. All household contacts of the index patient were registered for verbal symptom screening based on common TB symptoms. This was followed by clinical investigations: chest X-ray (CXR) and bacteriological using Xpert testing. Clinical investigations were recommended for all contacts regardless of their symptom status, and tests were performed for those who visited a treatment facility that shared documented results. Contacts of index patients who showed clinical symptoms and/or changes on CXR but were unable to produce a sufficient sputum sample were clinically diagnosed and started on MDR/RR-TB treatment on a case-by-case basis. First- and second-line DST was performed for all contacts diagnosed with microbiologically positive RR-TB. The endTB observational study was reviewed and approved by the Institutional Review Board, Interactive Research & Development, Karachi, Pakistan (IRD_IRB_2021_05_012). Household contract tracing is part of programmatic care for all TB patients according to the Pakistan NTP.[7]

During the study period, 329 MDR/RR-TB patients were enrolled, and a contact registry was completed for 324 (98%) MDR/RR-TB patients, with 1,911 household contacts registered. Verbal symptom screening was completed for 1,734 (91%) contacts of 300 (93%) index patients, with Xpert tests completed for the 281 (16%) contacts who were able to produce sputum; 123 (7%) contacts received only CXR. Of the 1,330 (77%) contacts who did not attend the relevant health facility for further evaluation, 1,321 (99%) were asymptomatic and 9 (1%) were symptomatic contacts who did not return for further investigation. Overall, 20 contacts were diagnosed with MDR/RR-TB disease, resulting in a high prevalence of 1,153/100,000 population screened (95% confidence interval [CI] 706–1,776). Eighteen (6%) contacts tested positive for MDR/RR-TB on Xpert and two contacts were clinically diagnosed and started on treatment. Among the 18 contacts who tested positive on Xpert, seven (39%) were found to have fluoroquinolone-susceptible (FQ-S) MDR/RR-TB, or MDR/RR-TB only. The remaining 11 (61%) had pre-extensively drug-resistant TB (pre-XDR-TB). All 18 (100%) patients were started on MDR/RR-TB treatment.

The characteristics of 300 index MDR/RR-TB patients for whom at least one household member

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Table Characteristics of index MDR/RR-TB cases who had at least one household contact screened ($n = 300$).

	Index cases with MDR/RR-TB diagnosed in contacts ($n = 15$) *n* (%)	All index cases ($n = 300$) *n* (%)
Sex		
Male	11 (63)	152 (51)
Female	4 (37)	148 (49)
Age group, years*		
≤15	0	4 (1)
15–25	3 (20)	80 (27)
25–35	5 (33)	93 (31)
35–45	3 (20)	50 (17)
45–55	2 (13)	47 (16)
55–65	2 (13)	21 (7)
≥65	0	5 (2)
Drug-resistance profile†		
MDR/RR-TB only	5 (33)	143 (48)
Pre-XDR-TB	10 (67)	157 (52)
Previous TB history[3]		
No TB history‡	2 (13)	27 (9)
History of drug-susceptible TB§	1 (7)	70 (23)
History of DR-TB¶	12 (80)	203 (68)

* Age at time of treatment enrolment.
† DR profile at the time of treatment enrolment.
‡ Has not received any TB treatment prior to starting a new treatment with regimen, including BDQ or DLM.
§ Only received treatment for drug-susceptible TB prior to starting a new treatment with regimen including BDQ or DLM.
¶ Received treatment for DR-TB prior to starting a new treatment with regimen including BDQ or DLM, regardless of whether drug-susceptible TB treatment was also received in the past.
MDR/RR-TB = multidrug-/rifampicin-resistant TB; XDR-TB = extensively drug-resistant TB; BDQ = bedaquiline; DLM = delamanid.

was screened are shown in the Table. The 20 household contacts diagnosed with MDR/RR-TB belonged to 15 index patient households. In this cohort, the majority of index patients with a household contact diagnosed with MDR/RR-TB were male (63%) and between 15–45 years of age (73%). They were also more likely to be diagnosed with pre-XDR-TB (67%) and have a prior history of DR-TB (80%). For the 18 household contacts who had bacteriologically confirmed MDR/RR-TB, all contacts diagnosed with pre-XDR-TB belonged to pre-XDR-TB index patient households, and all those with MDR/RR-TB only were contacts of MDR/RR-TB only index patient households. Together, these findings support the growing epidemiologic evidence for high yields of TB among household contacts of DR-TB index cases.[8,9]

Contact investigation is standard practice in high-income countries,[1] and an active case-finding strategy is internationally endorsed for high TB burden, low- and middle-income countries (LMICs).[10] However, its systematic and consistent implementation is often deficient due to resource limitations.[5,8] This is the case in Pakistan, where although the NTP recommends systematic household contact investigation at the treatment facility,[7] the implementation of this policy remains a challenge due to limited resources and social barriers.[1] Intra-household or transmission from a mutual close contact is likely, given the concordance in the DR profiles of the index patients and their contacts with microbiologically confirmed disease, although transmission chains cannot be established without pathogen genomic data. In the absence of a focused and prioritised approach to contact tracing, only a small proportion of presumptive household contacts were actually investigated clinically. Because further evaluations relied on screened contacts agreeing to visit designated facilities or share their results, we expect the yield of DR cases among household contacts would have been higher if a greater proportion had completed investigations.

In its recommendations for contact investigation, WHO acknowledges that contact investigation in LMICs is either not implemented at all, or implemented in a non-standardised manner owing to vague definitions, unclear procedures and the lack of clearly identified personnel to carry out this task.[11] Moreover, this also acts as a barrier to the collection of evidence on contact investigation, which is a crucial component of optimal TB prevention and management practices.[12] In an era of other health emergencies (such as COVID-19), the diversion of resources and workforce away from routine TB services, combined with a reduction in the number of health workers due to illness and self-isolation, is likely further deprioritising preventive interventions such as contact tracing. In addition, lockdown policies that keep families indoors likely increase household TB transmission.[13,14]

Despite the enormous health challenges faced during the COVID-19 pandemic, several examples of the successful use of mobile, digital and other automated technologies emerged, and have been applied to contact tracing in different settings.[13,14] Given that COVID-19 and TB share commonalities in transmission and public health response (i.e., case-finding, contact identification and evaluation), these new approaches provide opportunities to improve TB prevention and care.

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