

Yield of facility-based verbal screening amongst household contacts of patients with multi-drug resistant tuberculosis in Pakistan



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ABSTRACT

Background: Household contacts of multidrug-resistant tuberculosis (MDR-TB) patients are at a high risk of getting infected with TB/MDR-TB, therefore symptomatic or vulnerable individuals should be screened and treated early.

Methods: A cross-sectional study was conducted among household contacts of MDR-TB patients in three high-burden TB sites in Pakistan from July 2013 to June 2014. MDR-TB index patients were asked to provide a list of all members of their household and were asked whether any of them had TB symptoms such as productive cough, fever, weight loss and night sweat (“facility-based verbal screening”). Symptomatic contacts were defined as presumptive TB cases and were invited for investigations at the facility. Those who did not come were paid a home-visit. Confirmed TB/MDR-TB patients were registered in the nearest treatment facility.

Results: Of 209 MDR-TB index patients, 1467 household contacts were identified and screened, 95 of them children < 5 years. Of these 172 (12%) were symptomatic. Most common symptoms were cough 157 (91%) and fever 107 (62%). 58 (34%) presumptive TB contacts were not investigated. Of total contacts, 56 (3.8%) were diagnosed with TB, among them 54(96%) with MDR-TB and 2(4%) with drug-susceptible-TB. The number needed to screen (NNS) to identify a new MDR-TB case among adult household contacts was 27 and among presumptive adult and pediatric TB contacts was three. All 56 confirmed patients were registered for treatment.

Conclusion: Screening household contacts of MDR-TB index cases may be considered a feasible and high yield option, in high-burden, low-resource settings within Pakistan. The number of presumptive TB contacts required to screen to identify a new MDR-TB case was unusually low, indicating an effective strategy that could easily be scaled-up. The screening and management of vulnerable adults and children living with patients having TB of any form is a major priority in the combined efforts to end TB.

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Introduction

Tuberculosis (TB) remains a major global health problem, with an estimated 10.4 million new TB cases worldwide, most of whom live in low- and middle-income countries [1]. Globally, an estimated 3.9% of new TB cases and 21% of previously treated TB cases have multi-drug resistant tuberculosis (MDR-TB), a level that has changed little in recent years. In 2015, an estimated

250,000 people died of MDR/PR-TB. 30% of the 3.4 million new bacteriologically confirmed and previously treated TB cases notified globally were reported to have had drug susceptibility testing for rifampicin, with coverage of 24% for new TB patients and 53% for previously treated TB patients as compare to 58% and 12% respectively, in 2015 [1].

According to a Global TB Report published by the World Health Organization (WHO) in 2016, Pakistan ranks fifth in TB and fourth in MDR-TB among high burden countries (HBCs), contributing to approximately 60% of the tuberculosis burden in the Eastern Mediterranean Region (EMR) [1]. However, the TB burden may have silently risen, as the last nationwide population census was

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carried out in 1998. The first national anti-tuberculosis drug resistance survey conducted in Pakistan (2012–13) showed that the proportion of MDR-TB patients was 3.7% (95% CI, 2.5–5.0) among new and 18.1% (95% CI, 13.0–23.4) among previously treated cases [2]. Pakistan ranked 3rd among the countries with the highest number of estimated TB cases who were not notified (“missing”) [3]. In recent years, several studies have documented the overall trends of MDR-TB in Pakistan. A study has shown an almost consistent increase in the number of MDR-TB cases of tuberculosis from 1990 - 2007 with more than 15,000 isolates alone reported during that period [4]. This is not taking into account the cases in the unregulated private healthcare sector, although initiatives are being taken via technological innovations in TB control to further involve the private sector in surveillance [5].

Although estimates vary, systematic reviews conducted in 2008 and 2013 have shown that close contacts of TB and MDR-TB patients, especially children and people living in lower income countries are at increased risk of developing TB and MDR-TB [6–8]. No study from Pakistan was included in the systematic review on MDR-TB contacts. There is only one relatively small study conducted in Lahore, Pakistan in 2014, which showed that 0.5% of MDR-TB household contacts were diagnosed with rifampicin resistant TB.

WHO recommends contact investigation in ‘close contacts’ - defined as “living in the same household with TB index cases, either with drug-susceptible TB or with MDR-TB” [9]. Nevertheless, most national tuberculosis programs (NTPs) are often unable to conduct contact investigations due to inadequate investment in resources, staffing leading to unsustainable standardization of practices. Currently in Pakistan there is no standardized, routine implementation of household or community-based contact tracing. A pilot study in 2013 under the TB Reach Wave 3 project has detected more than 3000 TB cases including a significant number of MDR-TB cases during contact screening. These findings led the NTP to implement a new screening system, expanding the screening to household contacts of MDR-TB index patients. This strategy was piloted in three high burden Programmatic Management of Drug Resistant-TB (PMDT) sites.

This study aimed to assess the contact-tracing strategy and to determine the occurrence of new TB - drug susceptible and drug resistant - among adult and children (≤ 15 years) household contacts of MDR-TB patients in three PMDT sites in Pakistan from July 2013 to June 2014.

Materials and methods

Design

A facility based, cross-sectional study of household contacts screening of MDR-TB patients.

Setting

General setting

Pakistan is among one of the more diverse countries in the world in terms of ethnicity, culture, infrastructure, landscape, and climate. According to World Development Indicators (WDI, 2013) [10], 29.5% of Pakistan’s population are below national poverty lines. The population based on a recent projection was estimated to be over 178 million in 2011, making it the world’s sixth most-populous country [11,12].

Pakistan NTP

Pakistan’s mixed public-private healthcare system has vertical as well as horizontal components within the public sector and the largely unregulated private sector [13]. Despite the devolution

of the Ministry of Health (MoH), programs such as NTP comes under the Ministry of National Health Services Regulation and Coordination which is at the federal level, whereas the Provincial TB Control Program (PTP) covers TB managing sites at the provincial level. This has important implications for planning, sharing of resources, coordination and standardized implementation between the federal and provincial levels at a national scale in a sustainable manner. Although historically, the public sector has been the main source of TB directly observed therapy short course (TB-DOTS) care in the country, since 2010, efforts are being made to implement district-led public-private partnership models of care, with preliminary findings being reported in 2016 on how to involve the private pharmacies in early case detection as well [14].

The public sector TB care in a district is provided through a network of primary healthcare services; rural health centers (RHC), basic health units (BHU), and community-based Lady Health Workers (LHW). In most of the cases the first point of contact of presumptive TB cases is private providers who initially manage and those with partnerships refer these patients to public health care facilities (TB management units) for diagnosis. However, majority of the patients receiving care in private sector may not be notified to the national programme, with low microbiological diagnosis and low standards offered of drug-sensitivity tests (DST) leading to poor diagnosis of MDR-TB. TB-DOTS coverage was expanded at an accelerated pace to cover the public sector by May 2005, with the NTP being managed at 27 out of 30 PMDT sites.

On a national scale, TB case finding is primarily passive and standardized diagnosis is currently through sputum smear microscopy and chest radiography for pulmonary TB with specialized investigations for extra-pulmonary disease. All diagnosed patients are registered with a unique registration identification number; they are given standardized treatment and monitored for treatment outcomes according to national and international guidelines [15]. Public services including TB/MDR-TB diagnostic investigations and treatment are free of charge across the country.

MDR-TB contact tracing

In 2013, NTP Pakistan started active contact tracing of MDR-TB patients household in three high burden PMDT sites, namely; Ojha Hospital in Karachi, Gulab Devi Hospital in Lahore and Samli Sanatorium in Murree. The majority of cases chosen for this study were from the first two sites because these both are the highest burden, urban sites (most populated cities) in Pakistan and also patients prefer to seek treatment from these hospitals given they only deal with chest diseases. Furthermore Samli hospital had the lowest patients because of the cold weather, as it is located in Murree - which is a small, hill-station.

MDR-TB index patients were asked to provide a list of all members of their respective households’ contacts and indirect verbal screening (“facility-based verbal screening”) was done through a structured questionnaire of all households by trained research assistants. Any person with productive cough, fever, weight loss and night sweat was defined as presumptive TB case. Those found symptomatic were invited for diagnostic test (smear microscopy, X-ray and GeneXpert) and diagnosis at the facility. Those who did not come for investigations were paid a home visit and encouraged to undergo diagnostic tests at the facility, to ensure they could be assessed for TB. Confirmed TB/MDR-TB cases were registered at the Basic Health Management Unit (BMU) - which is a primary healthcare service delivery unit - nearest to them, for ease of treatment and monitoring.

Study population

The study population was all household contacts of MDR-TB patients registered for treatment from July 2013 to June 2014 in three selected PMDT sites of Pakistan.

Data collection

The cross-sectional survey was conducted at three, selected PMDT sites of Pakistan between July 2013 and June 2014. Presumptive TB patients were identified by facility-based verbal screening and invited for TB diagnosis. Diagnostic tests were conducted at the facility after informed consent was obtained. Data were entered in the electronic index case register; the reference laboratory register and the household contact register by trained research assistants from the PMDT sites.

For this study, the data was double entered, cleaned and validated using Epi-Data entry software (version 3.1 for data entry). Variables included age, gender, date of screening/diagnosis/registration for treatment, Symptoms (cough, fever, night sweating, and weight loss), TB status, diagnostic test (smear microscopy, GeneXpert, X-ray), test result and type of TB.

Data analysis

Descriptive statistics and cross-tabulation was utilized to assess the number of people screened in the household, to determine the number (proportion) with TB symptoms and those diagnosed as MDR-TB/TB, among them. Analyses of household contacts numbers needed to screen (NNS) were done separately for adult and children (<15 years). Associations between selected demographic characteristics and occurrence of TB or MDR-TB were explored using binary logistic regression. A p-value <0.05 was considered significant. Data analysis was done using Epi-Data version 2.2.2.182 (Epi-Data Association, Odense, Denmark).

Ethics

The study protocol was approved by the National Bioethics Committee (NBC) of the Pakistan Medical and Research Council (PMRC) and the Ethics Advisory Group of International Union Against Tuberculosis and Lung Disease, Paris, France. Written informed consent was obtained from all study participants. In case of illiterate patients, their family member/attendant provided the consent on behalf of the patient, after explaining it to the patient and obtaining verbal consent.

Results

From July 2013 to June 2014, a total of 1467 household contacts of 209 MDR-TB index patients were identified and indirect verbally screened. The median age (interquartile range, IQR) was 24 years (14–38). 95 (6.5%) of them were children less than five years and 282 (19.3%) were between 5 and 15 years of age. Four household contacts were already on TB treatment. Among household contacts screened: 172 (12%) had TB symptoms. The most common symptoms were cough (91%) and fever (62%) (Table 1).

Fig. 1 shows the flow of the screening among MDR-TB patients' household contacts. More than one third of symptomatic patients had not undergone TB diagnostic tests because of refusal and transfer-out. Out of 114 patients tested, 62% were tested with GeneXpert. Of a total of 1463 contacts who were not on TB treatment, 56 (3.8%) were diagnosed with TB. Of the diagnosed patients 54 (96%) had MDR-TB with 2 (4%) having DS-TB. All 56 (100%) confirmed cases were registered for treatment.

Fig. 2 shows the proportion of children and adult household contacts, screened for TB symptoms, whose tests confirmed TB and were subsequently provided treatment.

Median (IQR) days from contact screening to diagnosis was 4.5 (2–7) days and from diagnosis to treatment initiation was 4.5 (2–7.7) days.

Table 1

Demographic and clinical characteristics of MDR-TB household contacts in three high burden PMDT sites in Pakistan, 2013–2014.

Characteristics	MDR-TB household contacts (N = 1463)		
	n	%	
Age	<5 years	95	6.5
	5–14 years	282	19.3
	≥15 years	1086	74
Sex	Male	792	54
	Female	671	46
PMDT Sites	Gulab Devi Hospital, Lahore	782	53
	Ojha Hospital, Karachi	597	41
	Samli Hospital, Murree	84	6
History of TB	Yes	82	6
	No	1381	94
Symptoms	Yes	172	12
	No	1292	88
Sign & symptoms ^a	Cough	157	91
	Fever	107	62
	Weight loss	46	27
	Night sweating	18	12

^a A patient can have more than one symptom.

Demographic and clinical factors associated with new diagnosis of TB/MDR-TB are shown in Table 2. The odds of developing TB/MDR-TB was approximately five times higher both; among children less than 15 years of age (4.7 times) than adult contacts, and in contacts who had history of TB (4.6 times) compared to contacts who had no history of TB. Gender and screening site did not demonstrate significant association with the risk of TB/MDR-TB diagnosis. The NNS to identify a new TB/MDR-TB case among the total number of exposed household contacts and presumptive TB contacts are presented separately for adults and children in Table 3.

Discussion

This is the first study conducted by the Pakistan NTP that investigated a large number of household contacts of MDR-TB index cases using a resource-light strategy in high-burden settings. We found a relatively high overall yield for active TB cases (3.8%) and a low overall yield for children <15 years (1%). However, we found a very high yield for MDR-TB among symptomatic adults and children 31% (52 out of 161) and 36% (4 out of 11) respectively). In other words the vast majority of new TB cases among the household contacts investigated were suffering from MDR-TB. These findings support the growing need for epidemiologic evidence for household contact investigation of drug-resistant tuberculosis index cases, particularly early after diagnosis [8].

The relatively low proportion of presumptive TB cases and overall yield of TB among children in our study is worrying. Even though, little is known globally about the actual disease burden among children, they likely represent a large pool of exposed, undiagnosed, and untreated active and latent infections [16]. We therefore suspect that the yield in our setting is likely underestimated. Our screening strategy based on “verbal screening” among index cases and limited home visits may have missed an important number of symptomatic children. Moreover we did not have access to specific diagnostic procedures such as sputum induction and gastric aspiration which are indicated especially for younger children [17]. Still, we found that one third of the symptomatic children screened had MDR-TB.

Conventionally, household contacts of MDR-TB patients carry an increased risk of contracting active TB and MDR-TB. However, data on the rate of TB infection and subsequent risk of active disease among TB contacts has not been consistent. Limited data are

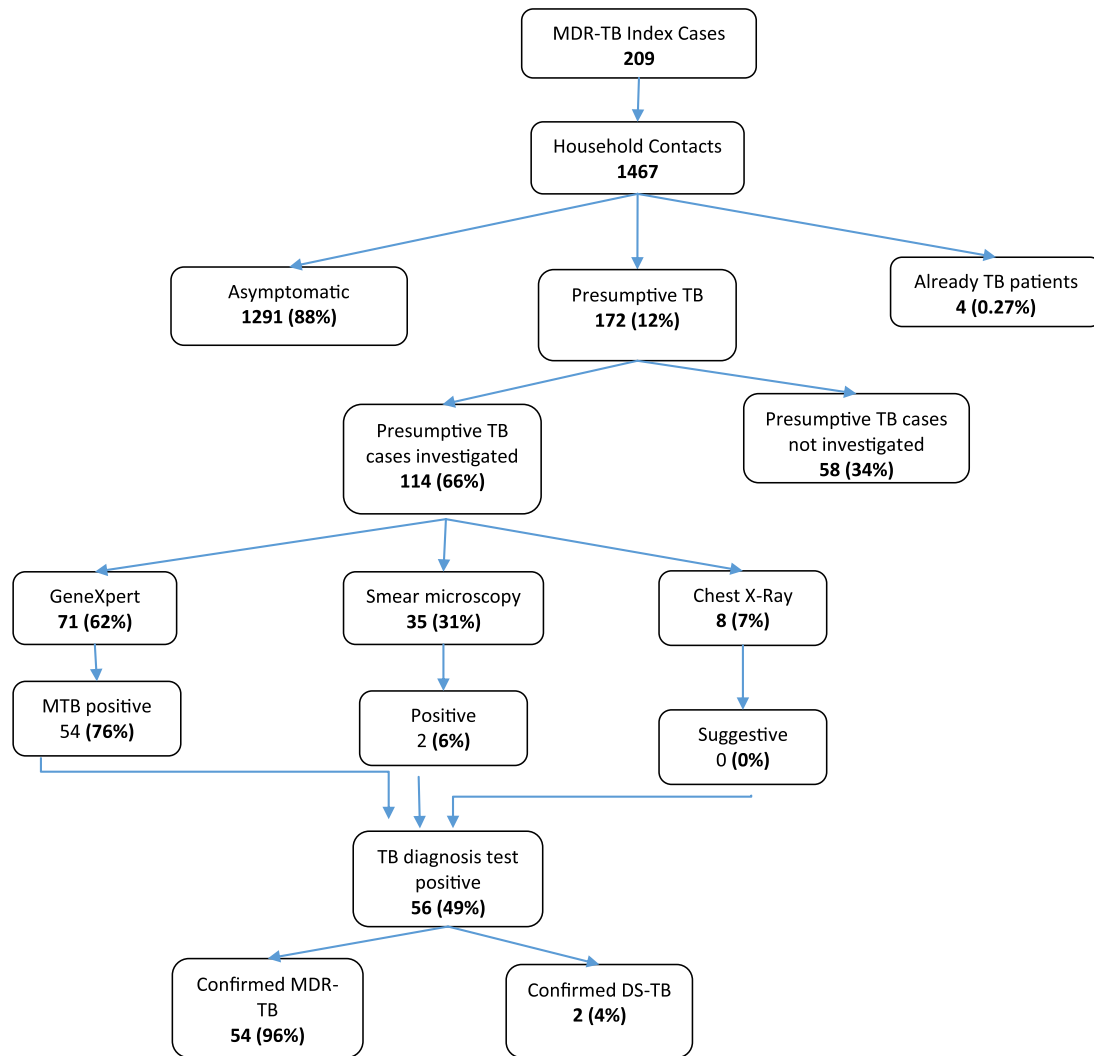


Fig. 1. Drug-resistant and drug-susceptible TB patients identified among household contacts of MDR-TB patients in Pakistan, 2013–2014.

Table 2

Association between demographic factors and occurrence of TB among MDR-TB household adult and children contacts in Pakistan, 2013–2014.

Characteristics	Diagnosed TB (DS-TB and MDR-TB)	Not diagnosed TB (DS-TB and MDR-TB)	OR	95% CI
Age	<15 years	4	4.69	1.68–13.06
	≥15 years	52	ref	
Sex	Male	27	1.28	0.75–2.18
	Female	29	ref	
Sites	Gulab Devi Hospital, Lahore	18	0.79	0.22–4.24
	Ojha Hospital, Karachi	36	2.63	0.62–11.13
	Samli Hospital, Murree	2	ref	
Past History of TB	Yes	11	4.6	2.28–9.27
	No	45	ref	

DS-TB= Drug sensitive tuberculosis; MDR-TB = multidrug-resistant tuberculosis; OR= odds ratio; CI= confidence interval.

Table 3

Number of household contacts of MDR-TB index cases needed to screen (NNS) to identify one new case of TB or MDR-TB, Pakistan, 2013–2014.

	Household contacts screened n	New DS-TB n	New MDR-TB n	NNS for new DS-TB N	NNS for new MDR-TB n
Total	1467	2	54	734	27
Children (≤ 15 years)					
Total	378	0	4	NE	95
Presumptive TB	11	0	4	NE	3
Adults (≥ 15 years)					
Total	1089	2	50	545	22
Presumptive TB	161	2	50	81	3

TB = tuberculosis; MDR-TB = multidrug-resistant tuberculosis; NNS=number needed to screen; NE = non-estimable.

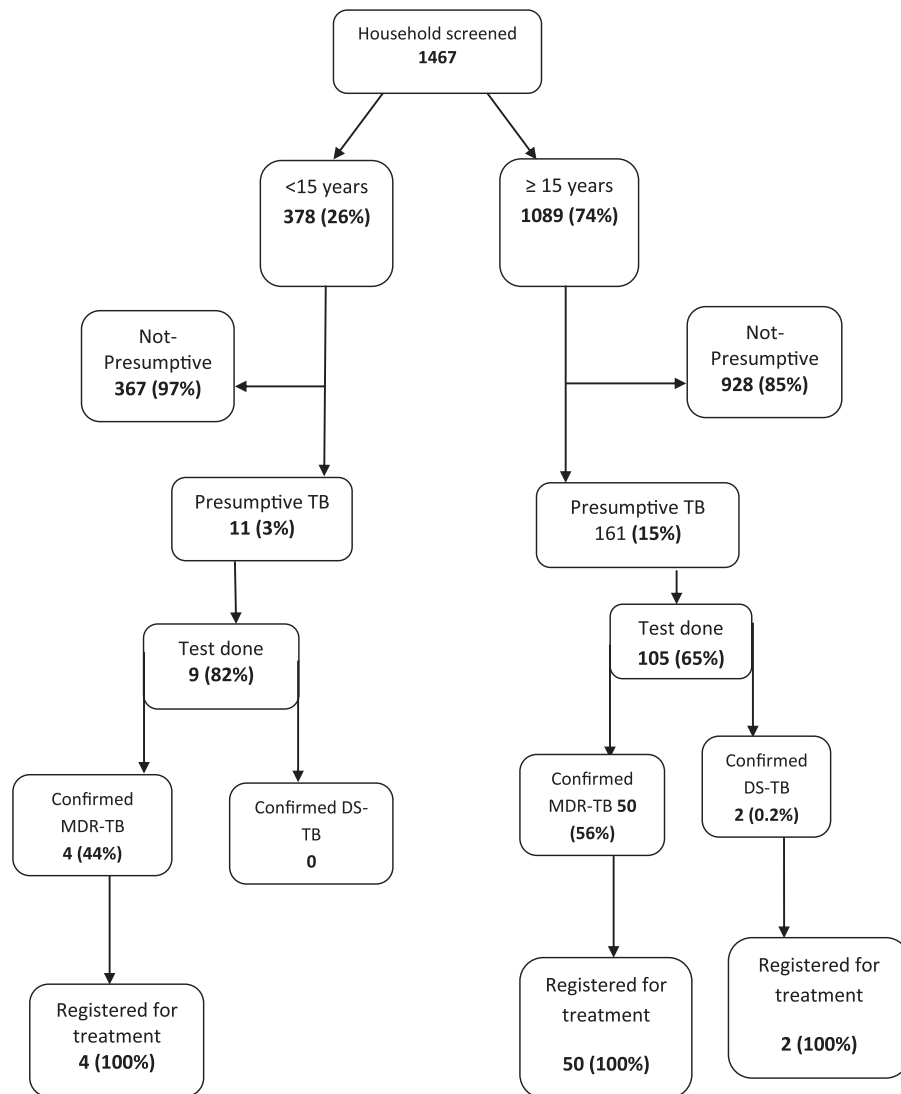


Fig. 2. Children and adult patients identified as drug-resistant and drug-susceptible TB and registered for treatment among household contacts of MDR-TB patients in Pakistan, 2013–2014.

available from the South Asian region regarding contact screening especially among MDR-TB patients. A small study conducted in a tertiary care center in Lahore, Pakistan investigated 692 contacts of 112 MDR-TB index patients and found only 4(0.8%) new MDR-TB cases [18]. A similar study in India had a relatively low yield; out of 302 contacts 16(5.3%) developed TB, with 2(0.7%) having MDR-TB [19].

In a systematic review and meta-analysis by Shah et al in 2014 the rate of secondary cases of active tuberculosis among household contacts of drug-resistant tuberculosis index cases ranged between 0% - in countries such as United States of America, Taiwan and Spain - and 26%, in South Africa [8]. The pooled yield estimated was 7.8% (95% CI, 5.6%–10.0%) for active tuberculosis; our estimate was at the lower end of the range. However, in the meta-analysis approximately half of the secondary cases were concordant with those of the index case; we found that almost all newly diagnosed TB cases had rifampicin resistance TB, consistent with the index case.

Our strategy using “facility-based verbal screening” may be considered feasible and high yield. The number of symptomatic, presumptive TB contacts need to screen to find a new additional MDR-TB case was unusually low, indicating a very effective strategy.

Most, if not all, high TB burden settings and MDR-TB hotspots are in low or middle-income countries (LMIC). A contact tracing strategy based on home-visits of all index cases may result in a higher yield and more opportunities for raising awareness among exposed family members. However it is resource-intensive and therefore considered a low priority or unsustainable by most Lower Middle Income Countries (LMIC) NTPs. A formal evaluation of various screening strategies, their trade-offs and cost-effective analyses remain to be done. In the light of the End TB Strategy a more aggressive approach is warranted if we wish to end TB in our time [20].

A very encouraging finding was that diagnosis was done in a few days in symptomatic patients and all patients diagnosed with susceptible or resistant TB were registered for treatment mostly in a week, further stressing the importance of capitalizing on pre-existing opportunities in a timely manner to prevent missed opportunities even within the current setup. However, prophylaxis was not given to the exposed household members, as there is no recommendation for prophylaxis within the national guidelines. In 2015 evidence-based recommendations have been made for post-exposure management of all MDR-TB contacts; existing data suggest a fluoroquinolone-based regimen for at least 6 months [21].

This study had several strengths. First, the evidence of increasing the yield of TB through household contacts screening of MDR-TB patients generated in this study is robust. Second, the intervention was conducted in three large PMDT sites within the two most heterogeneously populous provinces of Pakistan hence they ought to be considered generalizable to similar urban and peri-urban settings in the rapidly changing settlement classifications within Pakistan and similar South Asian countries'. Third, despite being implemented by research staff, the intervention was conducted routinely under the stewardship of Pakistan NTP and is thus feasible for scale up in comparable scenarios or at the very least can be replicated at similar facilities. Finally, the study adhered to the STROBE guidelines for reporting of observational data [22].

The study has several limitations. First, the “verbal screening” strategy at the facility level may have led to a significant underestimation of exposed household members, especially young children. However the research assistants made efforts to visit all households that had at least one symptomatic contact who didn't report at the facility. Data on the number of home visits conducted are not available. Second, a very large number of presumptive TB cases refused to be tested for TB or were transferred out from the PMDT site; this may have led to a significant underestimation of the actual burden of TB and MDR-TB. Third, no data were collected on participants who did not consent to participate; it is likely that those participants were different from the consenting ones and reasons for not consenting should be collected if other such studies are conducted in the future. Fourth, the research assistants had no access to diagnostic cultures, first and second line DST and genotyping of index and secondary cases and therefore our ability to describe detailed resistance patterns and to determine whether transmission occurred in the household or community was also limited. Lastly, we were unable to systematically test for HIV in the index, presumptive and confirmed secondary TB and MDR-TB cases. Even if Pakistan is a low HIV prevalence country, such screening is rarely available, let alone performed; and for less than 1% of the TB patients in Pakistan the HIV status is known [3].

Despite these limitations, our study provides substantial evidence on the importance of conducting simple household contact investigation of drug-resistant tuberculosis index cases during routine visits in Pakistan. Adults and children who live with patients with any form of TB are at high risk for developing disease and therefore their screening and management is a major priority in the effort to end TB.

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Conflict of interest

None declared.

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