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Screening outcomes of household contacts of multidrug-resistant tuberculosis patients in Peshawar, Pakistan

Arshad Javaid[1,2], Mazhar Ali Khan[2*], Mir Azam Khan[3], Sumaira Mehreen[2], Anila Basit[1,2], Raza Ali Khan[4], Muhammad Ihtesham[2], Irfan Ullah[2], Afsar Khan[2], Ubaid Ullah[2]

[1]*Post Graduate Medical Institute, Lady Reading Hospital, Peshawar, Pakistan*

[2]*Programmatic Management of Drug Resistant TB Unit, Lady Reading Hospital, Peshawar, Pakistan*

[3]*Peshawar Medical College, Peshawar, Pakistan*

[4]*Kohat University of Science and Technology, Kohat, Pakistan*

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ABSTRACT

Objective: To assess the profile of TB/multidrug-resistant TB (MDR-TB) among household contacts of MDR-TB patients.

Methods: Close contacts of MDR-TB patients were traced in the cross-sectional study. Different clinical, radiological and bacteriological were performed to rule out the evidence of TB/MDR-TB.

Results: Between January 2012 and December 2012, a total of 200 index MDR-TB patients were initiated on MDR-TB treatment, out of which home visit and contacts screening were conducted for 154 index cases. Of 610 contacts who could be studied, 41 (17.4%) were diagnosed with MDR-TB and 10 (4.2%) had TB. The most common symptoms observed were cough, chest pain and fever.

Conclusions: The high incidence of MDR-TB among close contacts emphasize the need for effective contact screening programme of index MDR-TB cases in order to cut the chain of transmission of this disease.

1. Introduction

Multidrug-resistant tuberculosis (MDR-TB) is caused by strain of *Mycobacterium tuberculosis* that is resistant to at least two of the most powerful 1st line anti TB drugs *i.e.* isoniazid (INH, H) and rifampicin (RMP, R). Because of emergence of resistant strains, tuberculosis adopted more dreadful nature in the form of MDR-TB, which poses a serious threat to ongoing national TB control programmes. According to the 2015 World Health Organization global report, approximately 300 000 people were infected by MDR-TB with 190 000 deaths [1]. In 2015 among all incident TB cases worldwide, 5% were estimated to have had MDR-TB (3.3% of new and 20% of previously treated TB cases) [2]. Based on 4.2% primary resistance and 19% resistance in re-treatment cases, WHO has estimated an annual incidence of about 15 000 MDR-TB cases in Pakistan [3].

MDR-TB is entirely man made and most commonly develops in the course of TB treatment, and is more commonly due to inappropriate treatment regimen, lack of patient's compliance and poor knowledge of patients towards therapy. Close and persistent contact between people in community promotes the transmission of infectious resistant strains from already infected person to normal healthy individuals. Also the MDR-TB treatment is less effective, patients with MDR-TB may remain infectious for longer periods than patients with drug susceptible TB [4]. Studies from the 1950s reported that INH-resistant human strains of *M. tuberculosis* lacked catalase activity and were less virulent in guinea pigs and mice [5–9] prompting the notion that drug-resistant strains of TB might be attenuated and less likely to be transmitted or produce secondary cases in contacts. Few studies have addressed this important issue in humans [8,10].

Close contacts of MDR-TB patients are more prone towards developing DR-TB. However, conflicting data have emerged from numerous studies conducted regarding the risk of TB in close contacts of drug-susceptible and MDR-TB patients. Pakistan is one of the top listed countries ranking 4th among top 22 MDR-TB countries but no data are available from Pakistan to

*Corresponding author: Mazhar Ali Khan, Programmatic Management of Drug Resistant TB Unit, Lady Reading Hospital, Pakistan.
E-mail: mali_smile2005@yahoo.com
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date on the occurrence of TB/MDR-TB among household contacts of MDR-TB patients.

The present study was carried out to study the occurrence of TB either in the form susceptible TB or MDR-TB in household contacts of patients, registered at PMDT unit, Lady Reading Hospital Peshawar from January 2012 to December 2012 who received a second line therapy for MDR-TB.

2. Materials and methods

A cross-sectional study was conducted over a period of 3 years from May 2012 and May 2015. The study population included household contacts of all MDR-TB patients registered under the Programmatic Management of Drug Resistant TB Unit, Lady Reading Hospital Peshawar (PMDT-LRH), Pakistan, who were initiated on MDR-TB treatment from January 2012 to December 2012. During this period all index cases received supervised ambulatory treatment with second-line drugs along with monthly food basket and travel incentives.

Household contacts were defined as individuals who had shared the same kitchen and sleeping area as the index case for at least 3 months before the diagnosis of the index case, and included spouses, children, parents, siblings and other relatives (uncles, grandfathers, cousins).

A Treatment Coordinator Hospital DOTS Linkages (Treatment Coordinator HDL), conducted home visits to create liaison between these patients with their district TB control officer, nearest DOTS centre and their treatment PMDT site, infection control measurement at patient house and to trace and motivate all household contacts to visit their nearest DOTS center to undergo the study investigations.

After obtaining informed consent, a standardized clinical form was filled out for all contacts of each index patient. Gender, age, occupation, and any history of TB (pulmonary/extra-pulmonary) were also recorded. All contacts were screened verbally and anyone of them presented with symptoms, such as cough, weight loss, fever, night sweets and anorexia, their sputum examination for acid-fast bacilli (AFB) was carried out and in case of any positive result for sputum microscopy, these cases were referred to PMDT-LRH for Xpert MTB/Rif testing. On confirmation of Rif resistance on Xpert MTB, these cases were registered at PMDT-LRH for treatment. Those cases whose sputum microcopies were positive but not Rif resistant on Xpert MTB/Rif testing, were referred to respective DOTS centers for registration and treatment initiation.

Contacts that were not present at the time of home visit, their history were obtained from the index cases or from other members of the family. In the case of death of any contacts due to TB, a history was taken from the index cases or from other members of the family.

3. Results

Between January 2012 and December 2012, 200 MDR-TB patients were initiated on anti-tuberculosis treatment. Home visits were carried out to trace the patients. Of the 200 index cases, contacts of 154 index cases were screened. The 154 index patients had a total of 610 household contacts screened. Their demographic profile is shown in Table 1.

Majority of contacts (58.4%) were female and most of them (62.0%) belongs to rural area. Four hundred and fifty nine (75.2%) of the contacts have age range from 15 to 44 years which are the most vulnerable age group of the community, whereas majority of the index case 119 (77.3%) were also belonged from the same age group *i.e.* 15–44 years (Table 2). In both groups of cases the main productive group of community (15–44 years) was affected.

Table 1
Demographic detail of investigated contacts during home visits (*n*; %).

	Characteristics	Index cases	Number of contacts
Gender	Male	74 (48.0)	254 (41.6)
	Female	80 (52.0)	356 (58.4)
Residence	Urban	50 (32.4)	238 (39.1)
	Rural	104 (67.6)	372 (61.9)
Marital	Married	103 (66.8)	201 (33.0)
	Unmarried	51 (33.2)	409 (67.0)

Sputum specimens were collected and examination was performed from 235 (38.5%) contacts, whereas the remaining 375 (61.5%) were unable to provide sputum. Chest X-ray was performed in 225 contacts. Sputum for AFB yielded negative result for 184 (78.3%) cases while it was positive in 51 (21.7%). All sputum positive and other suspected cases were referred to PMD-LRH unit for Xpert testing and Drug susceptibility testing (DST). Xpert and DST results of 41 (17.4%) contacts declared MDR-TB whereas 10 (4.2%) was declared drug susceptible TB. Among sputum smear positive cases 40% of the drug susceptible cases graded as +1 (10-99 AFB/100HPF) followed by+2 (1-9 AFB/HPF) (30%), scanty (1-9 AFB/100HPF) and +3 (>9 AFB/HPF) (10%). On another hand among contacts infected with Multi-drug resistant TB strain, most of the cases (36.5%) were graded as +3 (>9 AFB/HPF) by +2 (1-9 AFB/HPF) (26.8%), +1 (10-99 AFB/100HPF) (21.9%) and scanty (1-9 AFB/100HPF) (14.6%) (Table 3).

Ten contacts that were diagnosed with TB were referred back to their respective district for registration at DOTS center whereas the remaining 41 contacts which were diagnosed as MDR-TB patients were registered for drug resistant TB treatment at PMDT-LRH.

Table 2
Age distribution of index cases *vs* contacts investigated during home visits (*n*; %).

Age (years)	Index cases	Contacts investigated	Drug susceptible TB	MDR-TB
<15	7 (4.5)	62 (10.16)	–	–
15–44	119 (77.3)	459 (75.24)	7 (70.0)	35 (85.3)
45–64	26 (16.8)	75 (12.3)	2 (20.0)	04 (9.8)
>65	2 (1.3%)	14 (2.3)	1 (10.0)	02 (4.9)

Table 3
Grading of sputum AFB of smear positive contacts (*n* = 51).

Bacterial load	Contacts with drug susceptible TB	Contacts with MDR-TB
Scanty (1-9 AFB/100HPF)	2 (20.0)	6 (14.6)
+1 (10-99 AFB/100HPF)	4 (40.0)	9 (21.9)
+2 (1-9 AFB/HPF)	3 (30.0)	11 (26.8)
+3 (>9 AFB/HPF)	1 (10.0)	15 (36.5)

Among 610 screened contacts, 218 (35.73%) were symptomatic. The most common symptoms were cough (220, 91.7%) followed by fever (80, 36.7%), loss of appetite (78, 35.7%) and haemoptysis (28, 12.8%). History of loss of weight was present in fifty three (n = 53) contacts. MDR-TB patients included in the study were resided in houses with an average of 2 rooms and with monthly income of less than 10000 Pakistani rupees. Cough was reported by all of the MDR-TB index cases, while cavitary disease was present on the initial chest X-ray in 92% of the MDR-TB index cases.

4. Discussion

In Pakistan, National TB control Programme covers the entire protocol of MDR-TB including prevention, diagnosis, treatment, and overall monitoring with the planning to cover the entire nation in a phased manner. Household contacts constitute a high-risk group for TB and MDR-TB, and the importance of selective case finding in such groups cannot be overemphasized. Although not all cases found through contact investigations are the result of transmission from the index case, early identification and treatment of the infectious cases will greatly decrease the transmission rate in the community [11].

Household contacts of MDR-TB offer more frequent risk of contracting active TB and MDR-TB. However, data on the rate of TB/MDR-TB infection among MDR-TB contacts have not been consistent. Studies on disease and infection among contacts of MDR-TB patients from the country Pakistan are scarce. The objective of our study was to estimate the occurrence of TB or MDR-TB in household contacts of MDR-TB patents registered at PMDT unit. Of the 610 contacts studied, 41 (17.4%) contacts developed MDR-TB whereas 10 (4.2%) cases developed drug susceptible TB after the index case. Overall rate of disease in the present study was 21.6% which is very low as compared to study conducted by Dhingra *et al*. who reported a 53.5% prevalence of TB infection in household contacts [12].

Another study conducted in India showed that, 58 index cases with 302 contacts were traced with detection of 16 TB and 2 DMR-TB cases. This study concluded that screening and evaluation of MDR-TB contacts may lead to early diagnosis and prevention of the disease [13].

Very few studies have examined the burden of active disease in close contacts of MDR-TB patients [8,13,14]. In a study from Brazil, Teixeira *et al*. reported that despite of the frequent exposure of close contacts towards the index cases, occurrence of MDR-TB as well as drug susceptible TB was comparable [8].

Major programmatic objective of PMDT in management of MDR-TB is the early diagnostic of MDR-TB and precaution of transmission to close contacts. Our study highlights significant proportion of MDR-TB in household contacts of MDR-TB cases.

More efforts are required for TB infection control as suggested by high rate of MDR-TB among household contacts. This was suggested by others as well.

In low and middle endemic countries for TB, case detection can be improved by systemic contact investigation [15]. In both high and low incident areas, potential diseased population among disease contacts has been studied previously [16,17]. In countries with high prevalence, 22% of the household contacts were infected by either TB or MDR-TB [17]. Moreover in those areas where there is high incidence of HIV-positive TB cases, screening of household contacts showed high occurrence of active infection up to nine folds compared with passive case finding [18]. Recently, different programs are starting to utilize resources for targeted screening of contacts of MDR-TB patients, HIV positive contacts and children in different parts of the world [19].

As this is not a genetic study, therefore we could not ascertain whether the infection was caused by the index case or no. However, there is considerable evidence to support human-to-human MDR-TB strain transmission. It is estimated that globally half of MDR-TB cases result from primary transmission [20]. Furthermore, as most of the index cases were retreatment cases, the transmission may have taken place previously, when they were drug-susceptible.

This study identified a number of operational problems with the simple contact tracing and testing strategies used. Nearly a third of close contacts with cough for more than two weeks could not to provide sputum samples for testing. Although some contacts were unable to produce sputum on demand, many others were simply not present when the Treatment Coordinator HDL visited their homes. This needs to be addressed seriously for in time screening scheduled and disease detection. As reported by other studies, children aged <10 years were significantly less likely to provide sputum samples than older individuals [21–25]. Diagnosing TB in children is a challenging task for health professionals, and as noted in one of the editorial on case finding in children, 'We only find what we look for' [26]. In our study we did not diagnose any case of active TB among children less than 10 years old, which was not at all a surprising; It is despite the fact that children are more prone to be infected with TB/MDR-TB, yet better methods of case detection among children are required to assess the burden of undiagnosed TB/MDR-TB in this vulnerable group.

Although household contacts with MDR-TB may have acquired infection independently in high-incidence areas, there are no well-established estimates regarding the probability that two household members with multidrug-resistant TB share the same genotype and are members of the same transmission chain. Molecular epidemiologic data from households with more than one MDR-TB case can explain the transmissibility of highly drug-resistant disease and also help guide public health policy. For instance, international guidelines for the management of known contacts of MDR-TB patients recommend conventional second line drug therapy based either on drug resistance pattern of an isolate from the suspected index MDR-TB case-patient or in accordance with the most commonly observed resistance strains in the community [27,28]. Since the study is conducted for the 1st time in Pakistan and among few from the developing world regarding MDR-TB contact from Pakistan and among few from the developing world, it provides useful information that can serve us input for planning contact investigation at larger scale.

The limitations of the study were the small sample size due to the inability to trace all index patients and their contacts. In a significant number of contacts, the history could not be obtained directly. This may have led to observational errors. We considered only household contacts and not other casual or close contacts. Fourth, the investigation considered only recorded household contacts, were not able to find each household contact. Furthermore, as genotype studies could not be carried out among contacts who developed TB, it could not be ascertained whether or not the source of infection was the index case.

Finally, the diagnostic approach used relied on sputum culture, and because it is difficult to obtain sputum specimens from

children, this approach may have missed cases in children who are at high risk of contracting TB from household contacts.

Our study focuses the importance of early in time detection of TB in household contacts of MDR-TB, who represent a high-risk group. It is hoped that early identification and treatment of potential cases will eventually translate into reduced morbidity, mortality and transmission of infection in the community. We conclude that targeted modifications in routine case finding approaches may improve TB and MDR-TB case detection in high burden areas.

The study suggests that active tracing of household contacts of index MDR-TB cases could contribute to prompt identification and treatment of MDR-TB cases. Indeed this would be a more effective approach in saving more lives as well as in cutting the chain of the transmission in the community. This measure should be implemented broader for wider adoption and dissemination. Larger scale studies should be performed to know about the effectiveness and sustainability in similar settings.

Conflict of interest statement

We declare that we have no conflict of interest.

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