RESEARCH ARTICLE

Burden of drug-resistant pulmonary tuberculosis in Pakistani children: A cross-sectional study [version 1; peer review: awaiting peer review]

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Abstract

Introduction: The incidence of drug-resistant tuberculosis (TB) is rapidly increasing worldwide. Children in high TB burden countries are rapidly being reported to be affected by multidrug-resistant TB (resistant to isoniazid and rifampicin). The aim of this study is to evaluate the pattern of drug sensitivity among children suffering with TB.

Methods: Known cases of pulmonary TB, with sputum smear positive even after two months of compliance to 1st line anti-tuberculous therapy were included after gaining informed consent. Specimens used for drug sensitivity analysis were either sputum or bronchoalveolar lavage. Patient age, gender, history of TB contact, and duration of treatment were also recorded. Data was entered and analyzed using SPSS v.22.

Results: There were 32 male (64%) and 18 female (36%) children in the study. Their mean age was 12.84 ± 2.54 years. History of household TB contact was positive in 29 (58%) children. Among 1st line anti-tuberculous therapy, ethambutol and streptomycin were most sensitive (n=44; 88%). Rifampin was least sensitive (n=17; 34%). There were 32 (64%) children with multidrug-resistant tuberculosis (MDR-TB). A positive history of household TB contact (either resistant or non-resistant) was seen to have a statistically significant impact on incidence of MDR-TB (p value=0.03)

Conclusion: Pediatric drug-resistant TB is a rising concern. Awareness programs on national and international levels are needed to educate the general population regarding the importance of preventing TB household contact, especially amongst children.

Keywords
pediatric tuberculosis, multi-drug resistant tuberculosis, isoniazid, rifampicin, household T contact, Pakistan
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**Introduction**

Globally, there are approximately 67 million children suffering from *Mycobacterium tuberculosis* (MTB) infection. The incidence of isoniazid (INH) mono-resistance has been estimated to be 5 million, and 2 million for combined isoniazid and rifampicin (RIF) resistance. In 2014 alone, an estimated 850,000 children developed pulmonary tuberculosis with 25,000 multidrug-resistant cases. The statistics surged drastically, and in 2017 1 million new cases of paediatric TB were reported. Adding to the current poor trajectory there have also been reports of extensive drug resistance in paediatric pulmonary tuberculosis, with almost 100,000 such cases reported.

In TB patients, drug resistance results from spontaneous genetic mutations in the MTB genome. The risk of genetic mutation increases with increasing bacterial load, explaining why resistance is more commonly seen in adult cavitary TB, which has large bacilli load. In children the more common reasons of drug resistance are transmission of a resistant bacillus and previous treatment with anti-tuberculous therapy (ATT). Other factors that predispose to drug-resistant TB include inappropriate drug regimens, monotherapy, and drug non-adherence.

Pakistan is among the top 20 TB-endemic countries, which share 84% of global TB burden and 87% of MDR-TB burden, according to the World Health Organization (WHO). Though, there have been various studies highlighting the incidence of MDR-TB in Pakistani adults, and some studies also included children; we couldn’t find any study from Pakistan that discussed the incidence of paediatric MDR-TB in particular. The aim of this study is to assess the pattern of sensitivity to 1st line and 2nd line ATT among Pakistani children (≤18 years).

**Methods**

A prospective, cross-sectional study was conducted from 1st July 2018 to 31st Dec 2018 in the Department of Paediatrics, Civil Hospital, Jamshoro. Known cases of pulmonary tuberculosis being followed up at the outpatient TB clinic were recruited. The inclusion criteria included children <18 years with a working diagnosis of pulmonary TB who had been taking 1st line ATT for two months but still had sputum smears (or sputum culture) positive for MTB. For children less than five years old, informed consent was taken from their parents/guardians. For children of age five years or above, informed consent from the parents/guardians and assent from the children was taken. Children who had become negative for MTB on sputum smear or culture with 1st line ATT, indicating response to these drugs, were not included. Children who were sputum positive but also non-compliant to their medications (compliance checked from their TB dosage card) were also excluded. Follow up patients in the TB clinic whose parents/guardians did not consent or children older than 5 who did not assent to participate were also excluded.

For culture and sensitivity, either sputum sample was utilized or bronchoalveolar lavage specimen (in cases of no sputum production). The samples were not specifically taken for this research, but were a part of their standard management, hence, no additional burden was placed on the participants of the study. *Mycobacterium* was isolated from the specimens by using Lowenstein-Jensen medium and *Mycobacterium Growth Indicator Tube* (MGIT) medium (Becton Dickinson, Franklin Lakes, NJ, USA). BACTEC NAP test (Becton Dickinson) was then performed on the isolated mycobacterium to differentiate MTB from other mycobacteria. Drug susceptibility testing was then done using an agar proportion method on enriched Middlebrook 7H10 medium (BBL Microbiology Systems, Cockeysville, MD, USA) following the standard laboratory protocols of the Civil Hospital, Jamshoro. Concentrations used for every drug was: isoniazid (INH) 0.2μg/ml, rifampicin (RIF) 1μg/ml, ethambutol (EMB) 5μg/ml, and streptomycin (SM) 2μg/ml and 10μg/ml. For pyrazinamide (PZA) sensitivity, BACTEC 7H12 medium was used with pH 6.0, at 100μg/ml (BACTEC PZA test medium, Becton Dickinson). Strains which were not susceptible to INH and RIF were termed as MDR strains. MDR-TB strains were then tested for susceptibility to 2nd anti-tuberculosis agents: capreomycin 10μg/ml, ofloxacin 2μg/ml, ethionamide 5μg/ml, and kanamycin 6 μg/ml.

A brief questionnaire (See Extended data) was generated which included patient demographics such as age, gender, history of TB contact, and duration of treatment. Data was entered and analyzed using SPSS Version 22.0, Armonk, NY: IBM Corp. Mean ± standard deviation (SD) was calculated for continuous variables such as age and duration of treatment. Frequency and percentages were calculated for all other variables including drug sensitivity.

**Results**

The study was completed by 50 children. There were 32 male (64%) and 18 female (36%) children in the study. Their mean age was 12.84 ± 2.54 years with the youngest child being 7 and the oldest 18. The demographic profile of these patients is shown in **Table 1** (data at patient level is available as Underlying data).

The sensitivity pattern of 1st line ATT is shown in **Table 2**. Ethambutol and streptomycin were most sensitive (n=44; 88%). RIF was least sensitive (n=17; 34%). There were 32 (64%) children with combined sensitivity to INH and RIF and 18 (36%) children were multidrug-resistant i.e., combined resistance to

<table>
<thead>
<tr>
<th>Table 1. Demographics profile of the patients.</th>
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<tr>
<td>Patient characteristics</td>
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<tr>
<td>Age in years (mean ± SD)</td>
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<td>Duration of treatment in months (mean ± SD)</td>
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<tr>
<td>Gender</td>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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<tr>
<td>History of TB contact</td>
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<td>Yes</td>
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TB – Tuberculosis
INH and RIF. Other than MDR cases, and among the first line drugs used alone, RIF showed the highest isolated resistance \(n=33; 66\%\).

Of the 18 MDR cases, 10 (55.6\%) were boys and 8 (44.4\%) were girls. Their mean age was 14.01 ± 1.50 years with the youngest of aged 12 and oldest aged 15.

The sensitivity pattern of second-line ATT is shown in Table 3. Kanamycin and capreomycin showed 100\% sensitivity. Ethionamide was sensitive in 47 (94\%) children and ofloxacin was sensitive in 38 (76\%) children.

A positive history of household TB contact (either resistant or non-resistant) was seen to have a statistically significant impact on incidence of MDR-TB as seen in Table 4.

### Discussion

The incidence of drug-resistant TB among children is a global health concern. Public health specialists must pay keen attention to this issue in order to prevent unnecessary mortalities. Pakistan is already a high TB burden country. Poor detection, diagnosis, and management of TB, along with unchecked household contact of children with tuberculosis patients, has markedly contributed to the rising incidence of MDR-TB among both adults and children in Pakistan\(^6\). This study reported 66\% of children to be mono-resistant to RIF, 36\% to be MDR, and although no case of extended drug resistance was seen, 24\% of children tested positive for fluoroquinolone resistance.

Comparatively, in a Pakistani study conducted in 2010–14, of all the MDR-TB cases in the study, only 1.6\% were aged 0–14\(^4\). In another survey from 2013–14, household contacts of 209 diagnosed cases of MDR-TB were screened. It was seen that 378 of 1463 contacts (26\%) were children aged 0–15. Of these, 11 children were symptomatic for TB, were tested, and 4 cases of TB were diagnosed from these children, all of which were MDR\(^7\). This study highly reinforces the impact of household TB contact on the development of MDR-TB in children, which has also been highlighted in our study. In another study, with 62\% individuals resistant to all first-line agents, ofloxacin resistance was among 52.7\%; which is relatively low in the current study (24\%)\(^8\).

This study highlights the prevailing situation of anti-tuberculosis resistance in Pakistani children and their predisposing factors. It emphasises the need to protect the children from TB infected persons. This study has its limitations too. It was based in one institute only which is in the rural part of Pakistan. The study cannot be generalised to the national status of Pakistan. Multi-center studies all across Pakistan must be conducted to completely understand the current status of anti-tuberculosis drugs resistance in Pakistan among both children as well as adults. Studies should also be conducted to evaluate disease outcome in these patients.

### Conclusion

Drug-resistant TB, especially in the pediatric population, is a public health concern. Awareness programs on national and international levels are needed to educate the masses regarding importance of preventing TB household contact especially among children. Long term studies should be conducted to study the prognosis of children with MDR-TB and deduce strategies to prevent drug resistance.

### Ethical approval and consent to participate

The study was assessed and approved by the Institutional Review Board of Civil Hospital, Jamshoro (IERB: 18-679) with informed consent taken from all participants.

### Data availability

#### Underlying data

Figshare: Burden of drug-resistant pulmonary tuberculosis in Pakistani children. [https://doi.org/10.6084/m9.figshare.7823741.v4](https://doi.org/10.6084/m9.figshare.7823741.v4)

This project contains the following underlying data:

- PTB.sav (Antibiotic sensitivity analysis data)
- Data Dictionary.spv (Data dictionary for underlying data)
Extended data

This project contains the following extended data:
• Questionnaire.docx (Study questionnaire)

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

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References
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