Burden of drug-resistant pulmonary tuberculosis in Pakistani children: A cross-sectional study [version 2; peer review: 1 approved with reservations, 1 not approved]

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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 Mycobacterium tuberculosis 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 for acid-fast bacilli after two months of compliance to 1st line anti-tuberculous therapy were included after gaining informed consent. Specimens used for drug sensitivity testing 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: Fifty children, 32 male (64%) and 18 female (36%) were included 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, rifampicin resistance was highest at 33/50 (66%), and resistance to streptomycin and ethambutol were the lowest (6/50; 12%). There were 18 (36%) 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 general population regarding the importance of preventing TB household contact, especially amongst children. With the selected method used to identify mainly older children with drug resistance, the yield for drug-resistant TB was found to be high.
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. It is estimated that 5 million children are infected with isoniazid (INH) mono-resistant MTB strains and 2 million with multidrug-resistant (MDR) strains. 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 (XDR) in paediatric pulmonary tuberculosis, with almost 100,000 children found infected with XDR strains.

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 multidrug-resistant tuberculosis (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 (those not taking/not given their medications regularly as assessed 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 Indica-
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 sensitivity 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 resistant to INH and RIF were termed as MDR strains. MDR-TB strains were then tested for sensitivity 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. There were 32 (64%) children with combined sensitivity to INH and RIF and 18 (36%) children were multidrug-resistant i.e., combined resistance to INH and RIF. Other than MDR cases, and among the first line drugs used alone, RIF showed the
highest isolated resistance (n=33; 66%), while two of those MDR cases were also resistant to Ofloxacin (PreXDR-TB).

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.

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 child household contacts of MDR-TB cases not being screened and managed appropriately, has markedly contributed to the rising incidence of MDR-TB among both adults and children in Pakistan\(^7\). This study reported 66% of children to be resistant to Rifampicin, 36% to be MDR, and although no case of extensive drug resistance was seen, 24% of children tested positive for fluoroquinolone resistance. It can be extracted from the provided data that out of the total 33 cases of rifampin resistant strains, 15 were mono-resistant to rifampin. Including Pakistan, in other countries the incidence of rifampin resistance is rising and our results are parallel\(^7\)–\(^9\).

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\(^10\). 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%)\(^11\).

This study highlights the prevailing situation of anti-tuberculosis resistance in Pakistani children and their predisposing factors. It emphasizes 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 actual aim of this study was to identify drug resistance to ATT in children of all ages, however, most study participants are adolescents. Hence, this study doesn’t represent all TB population and the data cannot be compared to data of more general drug resistance surveys. 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 the importance of preventing TB household contact especially among the children. With the selected method used to identify mainly older children with drug resistance, the yield for drug-resistant TB was found to be high. 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

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).

Grant information
The author(s) declared that no grants were involved in supporting this work.

References

Open Peer Review

Current Peer Review Status: ✗ ?

Version 2

Reviewer Report 23 July 2019

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Nazia Jamil
Department of Microbiology and Molecular Genetics, University of the Punjab, Lahore, Pakistan

General Comments
1. Paediatric TB includes children between ages 0-14, not above them. You must clear this point.
2. In the previous version the reviewer asked about from how many children at that hospital who had TB. These 50 cases were selected and how many cases were excluded for the different exclusion reasons? This has not been addressed at all in the revised manuscript.

Specific comments
1. In introduction, first paragraph first line; figures and facts of 2014 are mentioned. Update them according to latest reports.
2. Introduction first paragraph, last line; add updated reference.
3. In Discussion, first paragraph, second last line it is written that “the incidence of rifampin resistance is rising”. Rifampicin resistance MTB, are not always MDR TB cases, make it clear whether you are talking about rifampicin mono-resistance or MDR-TB?
4. In Discussion section, second paragraph, line number 5; 1467 household contacts were screened not 1463. 1463 contacts were those who are not on TB treatment.
5. In the same line, 378 children were under the range of 0-14 years according to cited study, not ranging from 0-15.
6. In the very next line, it is written that “Of these, 11 children were symptomatic for TB, were tested”, but according to the cited study, only 9 out of 11 children were screened for MDR-TB.

In discussion, second paragraph last sentence; you have compared your study with the paper entitled “Resistance patterns, prevalence, and predictors of fluoroquinolones resistance in multidrug resistant tuberculosis patients”. The authors in the above mentioned study didn’t specifically report the paediatric TB cases. In fact, more than 70% of cases in above mentioned study were adults, so, it is not a good idea to compare your study with the aforesaid study.
Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Microbial Genetics, MDR-TB

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 07 May 2019
https://doi.org/10.5256/f1000research.20854.r47707

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H. Simon Schaaf
Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

The revised manuscript shows improvement from the original version; however, the reviewer has some additional major comments which need correction.

Major comments:
Results:
- Page 3, 2nd column, last paragraph running over to page 4: The results are incorrectly reported in the text – there are not 32 children with combined sensitivity to INH and RIF – please delete this (see table 2). Eighteen (36%) children had MDR-TB, 2 (4%) had INH mono-resistant (or poly resistant?) TB and 15 (30%) had RIF mono- or poly drug-resistant TB. It is very important to
discuss possible reasons for the extremely high rate of RIF resistance without INH resistance. Please accurately report the numbers in the text.

- Page 4, Table 3 as well as text: The methods explicitly state that 2nd-line DST was done only in children with MDR-TB; however, in Table 3 the results are reported as ALL 50 children still being sputum culture positive after 2 months of 1st-line ATT had 2nd-line DST done – which is correct? If DST was only done in MDR-TB cases as stated in the methods, then the denominator should be 18 and 12/18 (67%) MDR-TB cases would then be resistant to ofloxacin, which is a huge number and should definitely be discussed (possible reasons).

Discussion:

- Page 4, 2nd column at top: The RIF “mono-resistant” numbers should be in the results. It is also important that the authors report whether the 15 RIF-resistant/INH-sensitive cases were ONLY resistant to RIF or whether there was resistance to another 1st-line drug, which would make the organism poly-resistant. This has not been presented either for RIF or INH resistant cases.

- Page 4, 2nd column, 2nd paragraph: Although the current study showed an association between household TB contact and MDR-TB, it does not show that this was the reason for MDR-TB, as the current study did not collect data to show which source cases had MDR or drug sensitive TB. For this reason, the discussion point is not correct. In the same paragraph, the ofloxacin resistance comparison is incorrect (see second bullet and major comments in results above). This needs to be corrected according to the true results.

- Page 4, 2nd column, last paragraph: The first sentence should be deleted, as this cannot be deducted from this current study. The study method does not allow for these conclusions at all.

Conclusions:

- The study method was constructed in such a way that only older children/adolescents were likely to be identified (more likely bacteriologically positive), BUT the study method also did not allow for determining the incidence of drug-resistant TB in this setting, as there was severe selection bias in the way the study was performed – this is not yet mentioned.

- In the previous review the reviewer asked about from how many children at this hospital who had TB this 50 cases were selected and how many cases were excluded for the different exclusion reasons – this has not been addressed at all in the revised manuscript.

Minor comments:

Introduction:

- Last line first paragraph: “found infected” should be “estimated being infected” (these were calculated estimates, not identified infected cases).

- Last paragraph, suggest change to read as follows (for grammatical and factual improvement: “Although there have been various studies highlighting the incidence of MDR-TB in Pakistani adults, with some studies including children, we could not find any study from Pakistan that determined the incidence of paediatric MDR-TB in particular. The aim of this study is to evaluate the pattern of drug sensitivity test results to 1st-line and 2nd-line ATT among Pakistani children (≤18 years) failing to convert to sputum smear- or culture-negative after 2 months of 1st-line ATT”.

Methods:

- Page 3 of 10, 2nd column, 2nd paragraph, 3rd last line: 2nd-line anti-tuberculosis agents (add “line”)

- Page 3, 2nd column, 1st line of last paragraph suggest change to: “The drug sensitivity test pattern of 1st-line anti-tuberculosis agents…”

Results:

- Page 4, 1st paragraph: Were all MDR-TB cases tested for ofloxacin resistance? If so, please present number/denominator and percentage of ofloxacin resistance amongst MDR-TB cases (2/18?)
Tables 2 and 3 – column headings should be “Sensitive” and “Resistant”.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Childhood tuberculosis with specific interest in drug-resistant tuberculosis.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Version 1

Reviewer Report 11 April 2019

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H. Simon Schaaf
Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

Data on the burden or incidence of drug-resistant tuberculosis (DR-TB) in children is sparse, as bacteriological confirmation of tuberculosis in children is challenging. This study did not set out to determine the incidence of DR-TB in Pakistani children in their setting, but rather to evaluate DR-TB in children (0-<18 years) who still had a positive smear microscopy for acid-fast bacilli or cultures for *Mycobacterium tuberculosis* positive after 2 months of adherent first-line antituberculosis treatment. The
authors found a very high rate of drug resistance in this highly selected patient group (previously treated, mainly adolescents), it is difficult to extrapolate this data to other settings even in the same country. The reviewer has the following comments:

Major comments:

1. Abstract: The way in which the drug susceptibility test (DST) results are presented is confusing and the abstract data regarding MDR-TB is different from the manuscript (32 cases in abstract vs 18 in manuscript text/table). I suggest change results to: rifampicin resistance was highest at 33/50 (66%), and resistance to streptomycin and ethambutol were the lowest (6/50; 12%). Please provide the correct data for MDR-TB.

2. Abstract conclusion: These conclusions cannot be made from this study. This is a biased study of highly selected, mainly older children for DST. What could be said is that with the selected method used to identify mainly older children with drug resistance, the yield for drug-resistant TB was high.

3. Introduction 1st paragraph: There is a clear difference between TB infection and TB disease. In this paragraph, these two entities are confused. It should clearly state that the numbers presented refer to infection and not disease, e.g. it is estimated that 5 million children are infected with INH mono-resistant M. tuberculosis strains, 2 million with MDR strains and (in the last line) 100,000 are infected with XDR strains. These are not TB cases! Also, there was not 1 million child TB cases “reported” – this was only estimated – only about a third of this number were reported cases.

4. Introduction 2nd paragraph: “Children” in this study covers a wide age range from 0-<18 years. Especially in young children <5-10 years of age (before they develop cavitary adult type disease) transmission of drug-resistant strains is the main reason for DR-TB. Once they become adolescents, with adult-type disease, incorrect prescribing and/or poor adherence to medication become much more common reasons for developing DR-TB. Previous treatment in children returning with DR-TB is often not because of developing resistance, but because DR-TB was not diagnosed at initial presentation. In young children, because of the low bacillary load, a two-month negative culture does not always mean a good response – they may fail later during treatment or relapse after completion of first-line treatment. This is likely one of the reasons why so few young children were identified in this study.

5. Methods: In resource limited settings, plans sometimes need to be made to identify the highest risk group(s) for DR-TB, which the authors likely did in this study. Unfortunately the highly selected group of children studied means that nothing can be said about the incidence of DR-TB in this community – other than maybe that DR-TB is unlikely to be higher than this study’s findings in this setting. It is unfortunate that children with poor compliance to treatment who were still positive (AFB smear or culture) after two months were excluded, as this group has a high risk of developing resistance in the first two months of treatment. The authors should define “non-compliant” to medication.

6. It would also be helpful for the readers to place the studied cases and DR-TB cases identified during this study into context if they knew how many children in total were on TB treatment at the time of the study in this setting, how many parents/children did not consent/assent to the study and how many were excluded due to non-compliance. Are these numbers available?

7. Results: Presenting the results in the text as “most/least sensitive” and “combined sensitivity” is confusing – it even confused the authors themselves (see abstract vs text). It is actually not necessary to repeat results that are presented in the table in the text again.

8. An interesting observation to the reviewer is the very high rate of rifampicin mono/poly resistance – if the MDR-TB numbers are correct, 15 (30%) of these children had rifampicin mono/poly resistance. Do the authors have an explanation for this? This also has implications both for treatment and preventive therapy in contacts, as INH should still be effective. It would also be interesting to know how many of the MDR-TB cases had additional resistance to ofloxacin (PreXDR-TB)
9. Discussion: As mentioned above, this study cannot be used to determine DR-TB in the children of Pakistan or even in this setting, as the study method of highly selected children (or rather, adolescents) does not at all represent the TB population. This data cannot be compared to data of more general drug resistance surveys. This should be mentioned as study limitations. What it does show is that in a carefully selected high risk group of adolescents not responding well to TB treatment after two months, the rate of DR-TB is very high. However, it would be far more appropriate to do DST on all children with bacteriologically confirmed TB before starting any TB treatment.

Minor comments:

1. Abstract:
   - Line 2: suggest changing “rapidly” to “increasingly”.
   - Line 3: regarding definition - add: (*Mycobacterium tuberculosis* resistant to…).
   - Line 6: suggest: “…smear positive for acid-fast bacilli after…”.
   - Line 8: suggest: “drug susceptibility testing”.
   - Line 12 (Results): Start with total number of children in study: “Fifty children, 32 male (64%) … were included.

2. Methods:
   - Page 3, 2nd column, line 16: suggest change “not susceptible” to “resistant”.
   - Further, the authors use both “sensitive/sensitivity” and “susceptible/susceptibility” in the manuscript – for consistency suggest change all to “susceptible/susceptibility”.

3. Results:
   - Table 1: Do the authors know the concordance of child and adult source cases’ *M. tuberculosis* strains DST results in the source case/child contact pairs?

4. Discussion:
   - Page 4, 1st column, line 5: suggest: “…, along with child household contacts of MDR-TB cases not being screened and managed appropriately,…”
   - Page 4, 1st column, line 9: not RIF mono-resistant but resistant to RIF.
   - Page 4, 1st column, line 10: extensive drug resistance.

**Is the work clearly and accurately presented and does it cite the current literature?**
Partly

**Is the study design appropriate and is the work technically sound?**
Partly

**Are sufficient details of methods and analysis provided to allow replication by others?**
Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**
Not applicable

**Are all the source data underlying the results available to ensure full reproducibility?**
Partly

**Are the conclusions drawn adequately supported by the results?**
No

**Competing Interests:** No competing interests were disclosed.
Reviewer Expertise: Childhood tuberculosis with specific interest in drug-resistant tuberculosis

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 11 Apr 2019
Uzair Yaqoob, Jinnah Postgraduate Medical Centre, Karachi, Pakistan

Thank you so much for this great and comprehensive review, we will surely consider all comments and upload the updated versions with editing done as much as we can.

Competing Interests: No competing interests were disclosed.

Author Response 17 Apr 2019
Uzair Yaqoob, Jinnah Postgraduate Medical Centre, Karachi, Pakistan

Response to comments is following, a newer version has been uploaded. the reviewer will soon see the newer version.

Major comments:
1. Done
2. Done
3. Done
4. Rightly said, non-compliant has been defined
5. We were only allowed to access patients and data at the time of the study and currently we cannot access hospital data.
6. Done
7. Done
8. Done

Minor comments:
1. Done
2. Done, sensitive/sensitivity looked more appropriate esp in tables
3. Authors are not aware of this
4. Done

Competing Interests: No competing interests were disclosed.
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