RESEARCH ARTICLE

REVISED Characteristics and contributing factors of adverse drug reactions: an analytical study of patients with tuberculosis receiving treatment under the National TB Program of India

[version 2; peer review: 1 approved, 2 approved with reservations, 1 not approved]

Harsh Shah[1], Sandul Yasobant[1,2], Jay Patel[1], Priya Bhavsar[1], Somen Saha[1,2], Yogesh Patel[3], Deepak Saxena[1,2], Anish Sinha[1]

[1]Department of Public Health Science, Indian Institute of Public Health, Gandhinagar, Gandhinagar, Gujarat, 382042, India
[2]School of Epidemiology and Public Health, Datta Meghe Institute of Medical Sciences, Wardha, Sawangi (Meghe), Wardha, Maharashtra, 442004, India
[3]Department of CGC Project, World Health Partners, Noida, Uttar Pradesh, 201301, India

v2 **First published:** 25 Nov 2022, **11**:1388
https://doi.org/10.12688/f1000research.125815.1
Latest published: 23 Jul 2024, **11**:1388
https://doi.org/10.12688/f1000research.125815.2

Abstract

Background

Tuberculosis (TB) continues to pose a serious threat to the public health system in India. Although the National Tuberculosis Elimination Program (NTEP) is providing a wide range of interventions from early diagnosis to complete treatment to reduce morbidity and mortality from TB, adverse drug reactions (ADR) remain a challenge in treatment adherence and completion.

Methods

An observational cross-sectional study was conducted in selected districts of Gujarat state. A total of 593 reported TB patients were recruited with an adjusted unified distribution based on the type of cases, site of diseases, and service facility through a simple random sampling method. A semi-structured questionnaire tool was used to collect socio-demographic, clinical, and ADR-related data from the TB patients. Data was analyzed for the frequency, percentage, chi-squared, and adjusted odds ratio to find the association between the variables.

Results

Open Peer Review

Approval Status ✓ ✗ ? ?

	1	2	3	4
version 2 (revision) 23 Jul 2024	✓ view	✗ view	? view	
version 1 25 Nov 2022	? view	✗ view		? view

1. **Gyanshankar Mishra**, Indira Gandhi Government Medical College, Nagpur, India
2. **Aditi Gupta**, Pulmonary Medicine, BRAIMS, Mohali, India
3. **Anurag Agarwal**, Maulana Azad Medical College & Associated Hospitals, New Delhi, India
4. **Yogendra Shah**, Province Public Health Laboratory, Kailali, Nepal
National One Health Alliance for Nepal,

The majority of the study participants were male (87.2%), aged 15 to 60 (57.8%), daily laborers (22.4%), and married (64.2%). Over 75% of individuals had pulmonary TB, with 87% having experienced their first episode, 83% being new cases, and 44.7% having a history of addiction. ADR with mild symptoms was reported by more than a quarter (29%) of TB patients during the intensive phase (77%). The association between ADR experience and drug susceptibility was significant ($p<0.005$) and drug-resistant TB patients experience two times more ADRs than drug-sensitive TB patients (OR 2.04). Binomial logistic regression was carried out to describe the association between various variables and occurrence of ADRs.

Conclusion

The study highlighted a need to enhance health care providers' capacity and program structure for managing ADRs among TB patients. In order to completely eliminate TB across the country, it also emphasized the attention for a holistic and all-encompassing strategy for managing TB patients at the field level.

Keywords
Tuberculosis, Adverse Drug Reactions, National TB Program, India

Corresponding author: Harsh Shah (harsh.423@gmail.com)

Author roles: Shah H: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Yasobant S**: Conceptualization, Data Curation, Formal Analysis, Methodology, Resources, Supervision, Validation, Writing – Review & Editing; **Patel J**: Formal Analysis, Validation, Writing – Review & Editing; **Bhavsar P**: Formal Analysis, Investigation, Methodology, Resources, Writing – Review & Editing; **Saha S**: Formal Analysis, Funding Acquisition, Methodology, Supervision, Writing – Review & Editing; **Patel Y**: Conceptualization, Funding Acquisition, Methodology, Resources, Validation, Writing – Review & Editing; **Saxena D**: Conceptualization, Funding Acquisition, Methodology, Resources, Supervision, Writing – Review & Editing; **Sinha A**: Methodology, Resources, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This study is made possible by the generous support of the American people through the United States Agency for International Development (USAID) (Co-operative Agreement no. 72038620CA00012).
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

How to cite this article: Shah H, Yasobant S, Patel J *et al.* **Characteristics and contributing factors of adverse drug reactions: an analytical study of patients with tuberculosis receiving treatment under the National TB Program of India [version 2; peer review: 1 approved, 2 approved with reservations, 1 not approved]** F1000Research 2024, **11**:1388
https://doi.org/10.12688/f1000research.125815.2

First published: 25 Nov 2022, **11**:1388 https://doi.org/10.12688/f1000research.125815.1

Kathandu, Nepal

Any reports and responses or comments on the article can be found at the end of the article.

REVISED **Amendments from Version 1**

The updated manuscript has incorporated feedback received during peer review, including suggestions from specific studies integrated into the discussion sections. The discussion now reflects updated insights on the variability of adverse drug reactions (ADRs) among individuals with tuberculosis, supported by references provided by peer reviewers. Additionally, the discussion emphasizes the urgent need for further exploration, advocating for the development of a system that provides comprehensive guidance on managing ADRs throughout treatment. Furthermore, the study underscores the importance of training frontline healthcare workers and medical officers in health facilities to effectively handle ADRs.

Any further responses from the reviewers can be found at the end of the article

1. Introduction

Tuberculosis (TB) is a communicable disease that remains a major cause of illness and death across low and middle-income countries (LMIC) even after the discovery of novel diagnostic methods and chemotherapeutic drugs. The incidence of TB and rising numbers of multidrug-resistant TB cases are still a concern for countries with high disease burden. As per the global TB report, the incidence of TB in India is approximately 2.8 million cases annually, accounting for almost a quarter of all TB cases worldwide. Even though a six-month drug regimen can successfully treat about 85% of those who develop TB, TB remains a significant threat to public health systems due to difficulties in early detection and the required treatment duration.[1] Over the years, the National TB Elimination Program (NTEP) has expanded the range of anti-tuberculosis therapy (ATT) drugs utilized in daily regimens and revised programmatic guidelines for the management of drug-resistant TB.[2]

The critical component of ATT is the standard directly observed treatment, short course (DOTS) chemotherapy regimen for drug-susceptible TB and the extended multidrug regimen for drug-resistant TB, depending on the culture and drug susceptibility tests. Poor treatment adherence increases the risk of drug resistance, treatment failures, relapses, and deaths. The persistence of infection among TB patients due to poor adherence continues to be a barrier to the success of TB programs.[3] To avoid morbidity, mortality, and the spread of TB, every effort should be made to persuade and motivate patients to continue their treatments despite any discomforts due to adverse drug events (ADEs). Almost all anti-TB medications result in adverse drug reactions (ADRs) that can range in severity from minor to fatal. Compared to second-line treatments, first-line anti-TB medications are often well tolerated by patients. These ADRs can cause TB patients to stop their therapy, resulting in needless morbidity, drug resistance, treatment failure, a decreased quality of life, or even death.[4–6] Comorbid conditions and risk factors influence the incidence of ADR and the outcome of TB treatment.

Between 8 and 85% of patients experience different side effects, ranging from mild to severe.[5] About 10–25% of patients who experience side effects develop significant and deadly medication reactions or serious adverse events (SAEs).[7–9] Treatment failure, relapse, or the formation of resistance are risks for patients who take their drugs inconsistently or stop taking them due to side effects.[10–13] It is crucial that all TB patients receiving therapy effectively manage and keep track of ADRs, especially major ones. Early ADR detection and prompt care can improve drug compliance, improve the treatment outcome, and stop the emergence of drug resistance.[14] Due to their under-recording and under-notification when monitored by the NTEP, the range and characteristics of ADR are not well recognized. With this background, the present study was conducted to assess the prevalence and characteristics of ADRs among TB patients and identify various epidemiological, socio-demographic, and programmatic factors associated with ADRs in the Western state of India, Gujarat.

2. Methods

2.1 Study design and settings

A descriptive observational cross-sectional study was conducted from 3rd May 2021 to 30th July 2021 in the Western state of India, Gujarat. The study was conducted through the district tB centre (DTC) and 32 tuberculosis units (TUs) in Gandhinagar and Surat districts (Gujarat state), with TB patients registered and managed. NTEP has been implemented in all districts of the state. Each district has a district TB center, which monitors the program for the entire district. The district is further divided into sub-districts i.e., TUs, at each block. Under the TUs, outlying peripheral (government and private) health facilities (PHI) provide programmatic management for TB patients.

2.2 Study population and sampling method

The assessment targeted a diverse profile of TB patients, such as drug-sensitive TB (DSTB), drug resistance TB (DRTB), pediatric TB, and extra-pulmonary TB. It included both public and private sector patients. The patients diagnosed with TB are reported on the online digital patient management portal Nikshay in the notification registers by the health facilities.[15] The list of reported TB patients from 1st July 2018 to 31st December 2020 was extracted from Nikshay to

ensure that the study population completed treatment based on the duration of the treatment regimen. A total of 20,668 patients were reported in the Nikshay portal from both districts during that period.

The sample size was calculated based on the formula of N=Z21−α/2P(1−P)/ε2, where N=sample size, Z21−α= confidence interval, P=estimated proportion, ε=desired precision/error, with estimated proportion of 50% of ADR occurrences. Based on sample size calculation, it was derived that over 534 TB patients had to be included in the study to have a confidence level of 98% and a desired error that is within ±5% of the measured/surveyed value. Additionally, the final sample size accounted for around a ~10% non-response rate, bringing the number of study participants to about 593. The eligible TB cases were listed with the inclusion and exclusion criteria below. Inclusion criteria: the TB patients reported through Nikshay, their current state PHI was within the selected geographical areas of Gujarat state, and they were given treatment. Exclusion criteria: TB patients who migrated or were untraceable or did not reside in the current PHI surveyed areas or whose relatives didn't provide consent were excluded from the study.

From each TU, patients were recruited randomly depending on their availability and willingness to participate. Simple random sampling was adopted to select TB cases within the selected geographic areas until the saturation of the sample size. However, a proportionate adjustment based on the type of cases, service facility, and site of disease was considered for the unified distribution across the study geography to ensure the collective representation of the study participants.

2.3 Data variables and data collection

A semi-structured interview followed by a semi-structured, pilot-tested ADR assessment questionnaire was used to collect the data in the vernacular language (Gujarati). A pretested and semi-structured questionnaire tool consisting of information regarding primary socio-demographics, medical history, history of addiction and comorbidity, and information about the grade and type of ADRs was administered by the trained researchers in the vernacular language through personal interviews by undertaking home visits. The researchers were trained to administer the questionnaire with a participatory approach and role play to prepare them to interview the study participants for the required information.

2.4 Study definition for adverse drug reactions

The World Health Organization (WHO) has defined adverse drug reactions (ADRs) as "A response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or the modification of physiological function".[16] The cornerstones of DSTB therapy continue to be a treatment plan with a minimum duration of six months and numerous first-line medicines (FLDs), such as isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E), and streptomycin (S). Similar to this, NTEP offers streamlined regimens for several forms of DR-TB, including shorter oral bedaquiline-containing MDR/rifampicin resistant-TB regimens and longer oral M/XDR-TB (mono or extreme drug resistant) regimens generally ranging from six to nine months but can reach up to 20 months. The drug dosages are adjusted based on the age, weight, severity of the disease, site of the disease, and type of drug resistance/susceptibility towards ATTs.

2.5 Data analysis

Once the data collection was completed, data sets were scrutinized for completeness and validation by the different sets of the researchers. The study participants were contacted again if any data variables were found to be missing by the researchers who had collected the primary data. The patient data on various variables was tabulated, analyzed, and interpreted by proper statistical methods using IBM SPSS statistics software version 20 (RRID:SCR_019096). The chi-squared test was used to compare groups, while the chi-squared for the trend examined linear trends. Risk measures were determined using odds ratios (OR) and 95% confidence intervals (CI). Crude OR and 95% CI were calculated for the interpretation of univariate analysis, with the level of significance set at $p<0.05$. To identify the independent factors associated with ADRs, adjusted odds ratios (AOR) and 95% CI were calculated by bivariate logistic regression analysis.

3. Results

Based on the study criteria, 105 (18%) TB patients from Gandhinagar and 488 (82%) from Surat were included. There were 536 (90%) patients who completed the treatment and 57 (10%) on treatment.

3.1 Demographic profile of study participants

The mean age of study participants was 34.6±15.6 years, and the median age was 31 years, ranging from 1 to 85 years. The majority of study cases, 517 (87.2%), were in the age group of 15–60. There were 343 (57.8%) male patients and 250 (42.2 %) female patients. There were 99 (16.7%) illiterates, 52 (8.8%) graduates, and 133 (22.4%) daily laborers and 381 (64.2%) of the patients were married. The association between age categories, marital status, and education status and adverse drug reaction was not significant ($p>0.05$). However, among gender and occupation status, it was found to be significant ($p<0.05$) (Table 1).

Table 1. Socio-demographic profile of the TB patients (n=593).

Socio-demographic profile of the TB patients (n=593)							
Characteristics	**ADR (Yes)**	**(%)**	**ADR (No)**	**(%)**	**n**	**(%)**	**Chi-squared and p values**
Age categories							
≤15 Years	8	1.3	23	3.9	31	5.2	Chi-squared=1.329 p value: 0.722
16–30 years	79	13.3	184	31	263	44.4	
31–60 Years	75	12.6	179	30.2	254	42.8	
>61 Years	10	1.7	35	5.9	45	7.6	
Gender							
Male	78	45.3	256	60.8	343	57.8	Chi-squared=15.505 p value: 0.0001
Female	94	54.7	156	37.1	250	42.2	
Marital status							
Divorce/separated/widow	5	2.9	6	1.4	11	2.0	Chi-squared=5.407 p value: 0.067
Married	99	57.6	282	67.0	381	64.2	
Single	68	39.5	133	31.6	201	33.8	
Education status							
Illiterate	30	17.4	69	16.4	99	16.7	Chi-squared=2.466 p value: 0.651
Primary	56	32.6	165	39.2	221	37.3	
Secondary	43	25.0	96	22.8	139	23.4	
Higher secondary	27	15.7	55	13.1	82	13.8	
Graduate and above	16	9.3	36	8.6	52	8.8	
Occupational status							
Daily labourer/farmer/cultivator	28	16.3	147	34.9	175	29.5	Chi-squared=24.5266 p value: 0.0001
Employed	30	17.4	74	17.6	104	17.5	
Housewife	56	32.6	85	20.2	141	23.8	
Business or professional	42	24.4	77	18.3	119	20.1	
Student	16	9.3	38	9.0	54	9.1	

3.2 Clinical profile of the study participants

The study participants were comprised of 147 (25%) extra-pulmonary TB (EPTB) patients and 446 (75%) pulmonary TB patients (PTB), 519 (87%) of whom had contracted the first episode of TB. The distribution of the type of cases as per national guidelines was 492 (83%) new cases and 69 (12%) previously treated cases on the drug-sensitive TB treatment regimen, while 32 (5%) cases were on the drug-resistant treatment regimen. A total of 66 (11%) TB patients were receiving treatment from private providers. The study reported that 268 (44.7%) had a history of addiction, with 91% addicted to tobacco (either smokeless or smoking) and 9% to alcohol. Among them, 41% had an addiction to tobacco and alcohol, while 1.2% had addictions to psychotic substances. Sixty-one (10%) reported the presence of at least

Table 2. Symptoms of adverse drug reactions in TB patients (n=172) during anti-tuberculosis therapy (multiple answers).

Symptoms of adverse drug reactions	n	%
Gastric discomfort (nausea/vomiting/gastric discomfort)	97	56.4
Skin related reactions (itching/redness)	59	34.3
Peripheral nervous system (numbness/tingling)	37	21.5
Joint pain (arthralgia/joint stiffness)	76	44.2
Ophthalmic discomfort (impaired vision/red eyes)	27	15.7
Psychological disturbances (confusion/anxiety)	18	10.5

Table 3. Logistic regression on predictive independent variables: socio-demographic, clinical and programmatic services of adverse drug reactions (n = 593).

		ADR experienced				Total	%	B	Wald	aOR	(95% CI)	p value
		No	%	Yes	%							
Gender	Female	156	26.3	94	15.9	250	42.2	0.883	19.187	2.419	(1.629–3.592)	0.000
	Male	265	44.7	78	13.2	343	57.8			Reference		
Literacy	Illiterate	69	11.6	30	5.1	99	16.7	0.021	0.006	1.021	(0.612–1.704)	0.937
	Literate	352	59.4	142	23.9	494	83.3			Reference		
Anatomical site	Extra-pulmonary TB	101	24.0	46	26.7	147	24.8	0.119	0.281	1.126	(0.726–1.748)	0.596
	Pulmonary TB	320	76.0	126	73.3	446	75.2			Reference		
Drug susceptibility	DRTB	14	2.4	18	3.0	32	5.4	1.523	14.158	4.587	(2.075–10.141)	0.000
	DSTB	407	68.6	154	26.0	561	94.6			Reference		
Service facility current	Private providers	46	7.8	20	3.4	66	11.1	0.190	0.389	1.209	(0.0665–2.198)	0.533
	Public health facility	375	63.2	152	25.6	527	88.9			Reference		
Episodes of TB	More than one episode	56	9.4	18	3.0	74	12.5	0.528	2.730	1.696	(0.906–3.175)	0.098
	First episode	365	61.6	154	26.0	519	87.5			Reference		
History of addiction	Yes	164	27.7	101	17.0	265	44.7	1.138	30.224	3.121	(2.080–4.684)	0.000
	No	257	43.3	71	12.0	328	55.3			Reference		
History of comorbidity	Yes	42	7.1	19	3.2	61	10.3	0.260	0.630	1.297	(0.682–2.466)	0.427
	No	379	63.9	153	25.8	532	89.7			Reference		
Age (Years)								−0.008	1.285	0.992	(0.978–1.006)	0.257
Constant								−2.220	27.510	0.109		0.000

Number in () indicates the row % across the group and column % in total.
All variables shown here significantly differ across the group with p<0.001.
Cox & Snell R Square 0.097, Nagelkerke R^2 value was 0.139, classification accuracy is of 71% in prediction.

F1000Research 2024, 11:1388 Last updated: 10 FEB 2025

one comorbidity, while the major contribution of comorbidity was diabetes (50%). The number of patients with a HIV co-infection was deficient in numbers to be included in a detailed analysis.

3.3 Adverse drug reactions among the study participants

During the study, it was observed that 172 (29%) patients experienced ADRs with at least one symptom. Out of those, 80% had mild symptoms, and 133 (77%) experienced them during the early (intensive) phase of the treatment initiation. The 18 (56%) drug-resistant TB patients on second-line ATTs reported ADR, 50% of whom reported moderate and severe ADRs. The association between ADR experience and drug susceptibility was significant (p value of 0.005; Chi-squared 12.193) and drug-resistant TB patients experience two times more ADRs than drug-sensitive TB patients (OR 2.049, CI: 1.47–2.86). The TB patients had experienced gastric disturbances, skin-related symptoms, peripheral nervous system symptoms, arthralgia, ophthalmic discomfort, and psychological disorders during ATT (Table 2).

3.4 Logistic regression on predictive independent variables

The study used a binomial logistic regression model to estimate the bivariate odds ratio and a 95% confidence interval to describe the association between predictor variables and the occurrence of ADRs. The study used the dataset's socio-demographic, clinical, and programmatic service delivery variables to develop the predictive model. The model showed that gender, drug susceptibility status, and history of addiction were statistically significant ($p<0.05$). The regression model showed that the Nagelkerke R2 value was 0.139 with a classification accuracy of 71% (Table 3).

4. Discussion

Adverse events, defined as any unfavorable medical occurrence, can also be linked to treatment with these medications but are not always causally related. The study was conducted in only a selected part of the country, but the findings of the study provide insight into the drug reactions observed by TB patients during the course of treatment. The present study revealed that the prevalence of ADRs was 29% among the study population, similar to various worldwide studies ranging from 8% to 85%.[3–6,14,17–20] Several studies reported more ADR prevalence in drug-resistant TB patients, similar to the present study, where 50% of DRTB patients experienced ADRs.[19,21–23] The variance in ADR prevalence between these studies could be due to several data collection variables including the ADR reporting mechanism, patient-reported (subjective) or clinician-detected (objective), and variations in the use of particular anti-tubercular drugs such as dosage and ancillary medications used for ADR management.

The study observed 71% mild grade ADRs, 77% of which occurred in the early period (intensive phase) of treatment. Several studies also reported that major or severe ADRs were less common (occurring in approximately 2% of the cases, reaching 8% in specialized clinics), and ADRs were more prevalent in the intensive phase than in the continuation phase.[24–27] Many studies have reported the frequency of symptoms and types of ADRs, which can range in severity from mild to severe, caused by both first-line and second-line anti-TB medications. The drug-specific ADRs may cause either a reduction of dosage or termination of the offending drug(s) and lead to common ADRs up to organ-specific toxicity in severe cases.[3,21] The present study reported that the most common ADRs were gastric discomfort and arthralgia, followed by cutaneous ADRs, peripheral neuropathy, ophthalmic photosensitivity, and psychiatric disorders (headache/anxiety/confusion), similar to various studies conducted in India.[22,28–30] When compared to other adverse events, patients report gastrointestinal adverse events and arthralgia more frequently, which can contribute to subjective variation and a high prevalence of these events. Similar findings were observed in a study that showed gastrointestinal symptoms as the most common among persons with TB treated with DSTB regimen, followed by arthralgia, cutaneous drug reactions, and peripheral neuropathy. Gastrointestinal reactions are likely due to the oral administration of medications. These findings highlight the common adverse effects of TB medications and emphasize the need for effective management strategies to improve patient outcomes.[31]

A study from Uttar Pradesh by Prasad *et al.* and Gujarat by Jakasania *et al.* reported that there was no statistically significant difference in patients suffering from ADRs concerning variables such as age group, gender, educational and occupational status, history of addiction, and presence of a comorbidity, episodes of TB, and healthcare facility opted for services.[19,29] According to the study, one of the associated factors for ADR is the female gender. However, we may not have observed this since most participants in our study cohort were men. The logistic regression model of the present study identified that gender, drug susceptibility, and history of addiction were each predisposing risk factors for ADRs.

Limitations

The present study recorded ADRs or adverse events from the history of patients that could lead to subjective variations and recall bias. The type and grade of ADRs were also recorded from the patient's perspective, limiting the researchers to identify the drug-specific symptom of ADRs. In the absence of patients' medical records, the study could not assess or record the nutritional status at the time of ATT, the severity of comorbidity, drug specific ADRs or confirm hospitalisation due to severe ADRs. This was one of the reasons that during the study, researchers had not considered the history of

stoppage of the offending drug(s), alterations in the treatment regimen, or management received for the discomfort. The study excluded one TB patient who was non-traceable at the time of the data collection. The excluded TB patient could have provided additional information that support the results.

5. Conclusions

The present study focused on adverse events pertaining to TB patients missed by the health system. The analysis delivered crucial conclusions that could direct policymakers to educate and train all healthcare professionals and high-risk patients on how to solicit and manage ADRs among patients receiving programmatic treatment effectively. It is crucial to strengthen the program by carefully examining treatment plans based on medical history, ensuring treatment compliance, managing adverse events aggressively and proactively, and establishing a training cascade for health care providers and treatment supporters.

Ethics and informed consent

Ethical approval for this study was obtained from the Indian Institute of Public Health Gandhinagar- Institutional Ethics Committee (TRC-IEC No:18/2020-21). The administrative approval to conduct the study was received from the State TB cell, Department of Health and Family Welfare, Government of Gujarat.

Written informed consent for publication of the patients' details was obtained from the patient or the parents/guardian of the participant if they were under 18 years of age.

Author contributions

All authors contributed equally to the development of this study. All authors contributed to data analysis, drafting, or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Data availability

Underlying data

Figshare: A Study on Adverse Drug Reaction Among TB Patients, https://doi.org/10.6084/m9.figshare.21185875.v1.[32]
The project contains the following underlying data:

- Gujarat Baseline Data for Online Publication.xlsx
- Protocol Methodology for the study assessing the Adverse Drug Reactions among TB patients.docx
- ADR Questionnaire Tool - Gujarati.docx (in the language in which the questionnaire was distributed)
- ADR Questionnaire Tool.docx (in English)

Reporting guidelines

Figshare: STROBE checklist for 'Characteristics and contributing factors of adverse drug reactions: an analytical study of patients with tuberculosis receiving treatment under the National TB Program of India', https://doi.org/10.6084/m9.figshare.21185875.v1.[32]

Acknowledgments

We wish to extend our gratitude to the Health and Family Welfare, the Government of Gujarat & Jharkhand, and State TB Training and Demonstration Center (STDC) team and the National Tuberculosis Elimination Program (NTEP) staff for their kind support during the project activities. We are thankful to the Dr Satish Makwana (State TB Officer), Dr Dipak Patel and Dr Sheladia (District TB Officers), all the NTEP staff and all the participants of Gujarat for providing the necessary information for this study. We are also thankful to the research team of the Indian Institute of Public Health Gandhinagar (IIPHG) for their support during the field activities. We thank the World Health Partners (WHP) for their continuous support in the Closing the Gaps in TB Care Cascade (CGC) project. We express our sincere thanks to USAID New Delhi, India, for funding this study as a part of the larger project, namely, Closing the gaps in the TB care cascade.

References

1. Singh S, Dey B, Sachdeva K, *et al.*: **Challenges in Tuberculosis Diagnosis and Management: Recommendations of the Expert Panel.** *J. Lab. Physicians.* 2015; **7**(01): 001–003.
Publisher Full Text

2. Khaparde S: **The national strategic plan for tuberculosis step toward ending tuberculosis by 2025.** *J. Mahatama Gandhi Inst. Med. Sci.* 2019; **24**(1): 17.
Publisher Full Text

3. Singla R, Sarin R, Khalid UK, *et al.*: **Seven-year DOTS-Plus pilot experience in India: results, constraints and issues.** *Int. J. Tuberc. Lung Dis.* 2009; **13**: 976–981.
PubMed Abstract

4. Jayapriya B, Antony LJ, Balamurugan PV, *et al.*: **Pattern of adverse drug reactions of antitubercular drugs in tuberculosis patients with comorbidities and risk factors in South Indian government health-care facilities.** *Natl. J. Physiol. Pharm. Pharmacol.* 2021.

5. Singh A, Prasad R, Balasubramanian V, *et al.*: **Prevalence of adverse drug reaction with first-line drugs among patients treated for pulmonary tuberculosis.** *Clin. Epidemiol. Glob. Health.* 2015; **3**: S80–S90.
Publisher Full Text

6. Borisov S, Danila E, Maryandyshev A, *et al.*: **Surveillance of adverse events in the treatment of drug-resistant tuberculosis: First global report.** *Eur. Respir. J.* 2019 Dec 1; **54**(6): 1901522.
PubMed Abstract | Publisher Full Text

7. Saha A, Margaret Shanthi FX, Blessed Winston A, *et al.*: **Prevalence of hepatotoxicity from antituberculosis therapy: A five-year experience from South India.** *J. Prim. Care Community Health.* 2016; **7**(3): 171–174.
PubMed Abstract | Publisher Full Text

8. Tost JR, Vidal R, Caylà J, *et al.*: **Severe hepatotoxicity due to anti-tuberculosis drugs in Spain.** *Int. J. Tuberc. Lung Dis.* 2005; **9**(5): 534–540.
PubMed Abstract

9. Yee D, Valiquette C, Pelletier M, *et al.*: **Incidence of Serious Side Effects from First-Line Antituberculosis Drugs among Patients Treated for Active Tuberculosis.** *Am. J. Respir. Crit. Care Med.* 2003 Jun 1; **167**(11): 1472–1477.
PubMed Abstract | Publisher Full Text

10. Alipanah N, Jarlsberg L, Miller C, *et al.*: **Adherence interventions and outcomes of tuberculosis treatment: A systematic review and meta-analysis of trials and observational studies.** *PLoS Med.* 2018; **15**(7): e1002595.
PubMed Abstract | Publisher Full Text

11. Nahid P, Dorman SE, Alipanah N, *et al.*: **Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis.** *Clin. Infect. Dis.* 2016; **63**: 853–867.
PubMed Abstract | Publisher Full Text

12. Pettit AC, Cummins J, Kaltenbach LA, *et al.*: **Non-adherence and drug-related interruptions are risk factors for delays in completion of treatment for tuberculosis.** *Int. J. Tuberc. Lung Dis.* 2013; **17**(4): 486–492.
PubMed Abstract | Publisher Full Text

13. Awofeso N: **Anti-tuberculosis medication side-effects constitute major factor for poor adherence to tuberculosis treatment.** *Bull. World Health Organ.* 2008; **86**: 240–24D.
PubMed Abstract | Publisher Full Text | Free Full Text

14. Prasad R, Singh A, Gupta N: **Adverse drug reactions in tuberculosis and management.** *Indian J. Tuberc.* 2019; **66**: 520–532.
Publisher Full Text

15. Kumar S: **STDHIDNGovt of I. NIKSHAY- A Web-based Solution for Monitoring of TB Patients.** [cited 2022 May 27].
Reference Source

16. WHO: *Safety of Medicines: A guide to detecting and reporting adverse drug reactions.* Geneva: World Health Organization; 2002. 2002.2 (2002).

17. Sant´Anna FM, Araújo-Pereira M, Schmaltz CAS, *et al.*: **Adverse Drug Reactions Related to Treatment of Drug-Susceptible Tuberculosis in Brazil: A Prospective Cohort Study.** *Frontiers in Tropical Diseases.* 2022; **2**: 2.
Publisher Full Text

18. Phillipson J, Kuruppu N, Chikura T, *et al.*: **Adverse effects and duration of treatment of TB in Canterbury, New Zealand.** *Int. J. Tuberc. Lung Dis.* 2021; **25**(12): 990–994.
PubMed Abstract | Publisher Full Text

19. Jakasania A, Shringarpure K, Kapadia D, *et al.*: **"Side effects--part of the package": a mixed methods approach to study adverse events among patients being programmatically treated for DR-TB in Gujarat, India.** *BMC Infect. Dis.* 2020 Dec 1; **20**(1).
Publisher Full Text

20. Ausi Y, Santoso P, Sunjaya DK, *et al.*: *Between Curing and Torturing: Burden of Adverse Reaction in Drug-Resistant Tuberculosis Therapy.* Patient Preference and Adherence; 2021; vol. 15: 2597–2607.
Publisher Full Text

21. Joseph P, Desai VBR, Mohan NS, *et al.*: **Outcome of standardized treatment for patients with MDR-TB from Tamil Nadu, India.** *Indian J. Med. Res.* 2011; **133**(5).

22. Isaakidis P, Varghese B, Mansoor H, *et al.*: **Adverse events among HIV/MDR-TB co-infected patients receiving antiretroviral and second line anti-TB treatment in Mumbai, India.** *PLoS One.* 2012; **7**(7): e40781.
PubMed Abstract | Publisher Full Text

23. Akshata JS, Chakrabarthy A, Swapna R, *et al.*: **Adverse Drug Reactions in Management of Multi Drug Resistant Tuberculosis, in Tertiary Chest Institute.** *J. Tuberc. Res.* 2015; **03**(02): 27–33.
Publisher Full Text

24. Vieira DEO, Gomes M: **Adverse effects of tuberculosis treatment: Experience at an outpatient clinic of a teaching hospital in the city of São Paulo, Brazil.** *J. Bras. Pneumol.* 2008; **34**(12): 1049–1055.
PubMed Abstract | Publisher Full Text

25. Arbex MA, Varella M d CL, de Siqueira HR, *et al.*: **Antituberculosis drugs: Drug interactions, adverse effects, and use in special situations. Part 1: First-line drugs.** *J. Bras. Pneumol.* 2010; **36**.

26. Lan Z, Ahmad N, Baghaei P, *et al.*: **Drug-associated adverse events in the treatment of multidrug-resistant tuberculosis: an individual patient data meta-analysis.** *Lancet Respir. Med.* 2020 Apr 1; **8**(4): 383–394.
PubMed Abstract | Publisher Full Text

27. Prafulbhai Rupani M, Dave JD, Parmar VB: **THE NATIONAL MEDICAL JOURNAL OF INDIA Adverse drug reactions and risk factors for discontinuation of multidrug-resistant tuberculosis regimens in Gujarat, western India.** 2020.
Reference Source

28. Prasad R, Verma SK, Sahai S, *et al.*: **Efficacy and safety of kanamycin, ethionamide, PAS and cycloserine in multidrug-resistant pulmonary tuberculosis patients.** *Indian J. Chest Dis. Allied Sci.* 2006; **48**(3): 183–186.
PubMed Abstract

29. Prasad R, Singh A, Srivastava R, *et al.*: **Frequency of adverse events observed with second-line drugs among patients treated for multidrug-resistant tuberculosis.** *Indian J. Tuberc.* 2016; **63**(2): 106–114.
PubMed Abstract | Publisher Full Text

30. Shinde KM, Pore SM, Bapat TR: **Adverse reactions to first-line anti-tuberculous agents in hospitalised patients: pattern, causality, severity and risk factors.** *India. J. Med. specialities.* 2012; **4**(1).
Publisher Full Text

31. Mate K, Mishra G, Munje R: **Adverse Drug Reactions to a Daily Fixed-dose Combination Based Antituberculosis Treatment Regime in India's National Tuberculosis Elimination Programme: A Prospective Cohort Study.** *J. Clin. Diagn. Res.* 2022; **16**(8): OC14–OC19.
Publisher Full Text

32. Shah H, Yasobant S, Patel J: A Study on Adverse Drug Reaction Among TB Patients.xlsx. figshare. Dataset. 2022.
Publisher Full Text

Open Peer Review

Current Peer Review Status: ✔ ✘ ? ?

Version 2

Reviewer Report 07 February 2025

https://doi.org/10.5256/f1000research.169379.r361948

?

Anurag Agarwal
Maulana Azad Medical College & Associated Hospitals, New Delhi, India

This study was conducted to assess the prevalence and characteristics of ADRs among TB patients and identify various epidemiological, socio-demographic, and programmatic factors associated with ADRs in the Western state of India, Gujarat.
I have the following observations:
1. First line ATT and 2nd line ATT adverse effects are not comparable and should be handled separately. This is so as drugs, duration of treatment and number of drugs too are different and not comparable.
2. A comparison of ADRs within weight bands could have been made. That is, patients lying in which part of weight band had more adverse events. Was there any relation to weight in the individual weight band?
3. Was there an increase in adverse events after shifting to daily ATT vs previous alternate day ATT?
4. Hospitalization and temporary or permanent drug stoppage, mortality should have been recorded.
5. How was it concluded that " The analysis delivered crucial conclusions that could direct policymakers to educate and train all healthcare professionals and high-risk patients on how to solicit and manage ADRs among patients receiving programmatic treatment effectively. It is crucial to strengthen the program by carefully examining treatment plans based on medical history, ensuring treatment compliance, managing adverse events aggressively and proactively, and establishing a training cascade for health care providers and treatment supporters."
This was not the aim or purpose of the study nor was it looked at in the 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?
Yes

Are the conclusions drawn adequately supported by the results?
No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious diseases, rabies, 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.

Reviewer Report 19 August 2024

https://doi.org/10.5256/f1000research.169379.r306199

Gyanshankar Mishra
Indira Gandhi Government Medical College, Nagpur, Maharashtra, India

With the revisions incorporated, the article now offers a comprehensive overview, discussing key points and proposing potential policy recommendations for diagnosing and managing adverse drug reactions (ADRs) to anti TB drugs in programmatic settings.

Is the work clearly and accurately presented and does it cite the current literature?
No

Is the study design appropriate and is the work technically sound?
No

Are sufficient details of methods and analysis provided to allow replication by others?
No

If applicable, is the statistical analysis and its interpretation appropriate?
No

Are all the source data underlying the results available to ensure full reproducibility?
No

Are the conclusions drawn adequately supported by the results?
No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Respiratory diseases, 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.

Reviewer Report 25 July 2024

https://doi.org/10.5256/f1000research.169379.r305305

Aditi Gupta
Pulmonary Medicine, BRAIMS, Mohali, India

Previous suggestions are not being considered.

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?
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?
Yes

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

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

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.

Author Response 25 Jul 2024

Harsh Shah

Greetings, Reviewer

We appreciate your input, however we would like you to review the response that addresses the comments you expressed regarding the manuscript. We believe that the evidence that this article generates will be necessary to improve India's ADR surveillance system as part of the National TB Elimination Program.

1. Kindly elaborate Serious adverse events (SAE) and ADR categories also need to be explained
    - The study had classified ADRs into various categories based on severity, including mild, moderate, and severe, with SAEs defined as those resulting in significant health risks, requiring hospitalization, or leading to long-term consequences. This classification is based on the guidelines and protocols defined in context with the National TB Elimination Program (NTEP).
2. It has been proven that elderly develop more ADR but this is not the case with your study.
    - While literature indicates a higher prevalence of ADRs among elderly patients, the findings may reflect demographic variances or differences in treatment regimens that could mitigate these risks. It is crucial to consider that the elderly in the study may have had different TB comorbidities or medication profiles compared to the general population. The results provide valuable insights into the complexity of ADRs and underscore the need for targeted interventions in vulnerable groups.
3. BMI, age, comorbidity have strong association with ADR. Given tables and text do not support this.
    - While the study did not establish significant correlations in the reported data, it is important to consider that these associations can vary based on geographical and socioeconomic factors affecting the patient population. The findings contribute to the broader understanding of ADRs in TB treatment and highlight the necessity for ongoing research to explore these relationships further, particularly in public health settings where such data can inform resource allocation and management strategies. We made references supporting this evidences, however we believe there should be more in depth operational research or longitudinal case control study will provide more structured findings in alignment of the NTEP in India.
4. Kindly elaborate, how did you reach private patients for interview.
    - We reached out the private patients through the National Tuberculosis Elimination Program (NTEP) staff, project staff and through various stakeholders, to ensure a comprehensive representation of persons with TB across both public and private healthcare sectors.
5. Since, there is lot of recall bias, results cannot be generalized.
    - While we acknowledge that recall bias can affect data accuracy, we have already

mentioned and narrated it under the limitation of the study. In order to reduce the recall bias, we had further employed a semi-structured questionnaire designed to mitigate these issues by prompting patients to recall their experiences in the context of their ongoing / completed treatment. We ensured that the interviewed study subjects have the medical records available in Ni-kshay or with treatment report card at health facilities in case of requirement to check bias.

6. At what time of treatment, did you interview the patient? Time of interview is very important in assessing ADR and decreasing recall bias. Ideally different groups at different time point of treatment must be evaluated or even same group at different time points if feasible.
   - The study interviews were conducted from the individuals with TB on post completion / on going of their TB treatment. We have tried to incorporate various representative of patients in the study to understand the occurrence of ADRs at various phase of treatment. We could not make separate groups in absence of budgetary restriction to repeat visits for periodic timeframe. The study design was cross sectional and interview was one time event. This is limitation that we have mentioned into the manuscript.
7. Design of the study makes it very less informative.
   - While the design may appear limited, it was intentionally developed to capture data from a diverse patient population. The findings provide critical insights into ADRs experienced by individuals undergoing TB treatment at point interval (with cross sectional design), which is vital for program policies aimed at improving drug safety and efficacy.
   - The study highlights the importance of monitoring ADRs during various treatment phases, which is essential for developing effective TB interventions that ensure patient safety and optimize treatment outcomes.

Kindly do revisit the manuscript and comments that we addressed here.

Regards

Competing Interests: NIL.

Version 1

Reviewer Report 10 February 2025

https://doi.org/10.5256/f1000research.138161.r235640

?

Yogendra Shah

[1] Province Public Health Laboratory, Kailali, Nepal
[2] Infectious Disease, National One Health Alliance for Nepal, Kathandu, Bagmati, Nepal
[3] Province Public Health Laboratory, Kailali, Nepal
[4] Infectious Disease, National One Health Alliance for Nepal, Kathandu, Bagmati, Nepal

Title: Characteristics and Contributing Factors of Adverse Drug Reactions: An Analytical Study of Patients with Tuberculosis Receiving Treatment under the National TB Program of India

Reviewer: I would like to suggest some improvements to enhance the manuscript's acceptability. Please find below point-wise comments to refine the manuscript:

Title: Revise the title to align more closely with the manuscript's research objectives.

Abstract: Summarize only the significant findings of the manuscript, including background, rationale, and justification of the study. Include information on research objectives, methods, findings, and recommendations.

Keywords: Select crucial keywords from the abstract.

Introduction:
- Provide a brief overview of the global situation concerning *Mycobacterium tuberculosis* complex, with a specific focus on the current status in India.
- Discuss the utility of phenotypic and genotypic techniques in diagnosing TB globally. Address questions such as the prevalence of MDR and pan-susceptible strains, predominant lineages among MDR and non-MDR strains, mechanisms of drug resistance, and the challenges of detecting transmission dynamics without epidemiological data.
- Explore possible contributing factors to adverse drug reactions among tuberculosis patients. Justify the feasibility of combining epidemiological, phenotypic, genotypic, and WGS data for spatial analysis of TB transmission dynamics.
- Examine drug-resistant genes' mechanisms through genotypic techniques, explaining principles and applications for diagnosing TB and other diseases.
- Clearly justify the research objective and rationale for the current study.

Materials and Methods:
- Define inclusion and exclusion criteria for confirming TB patients using phenotypic and genotypic methods.
- Concisely outline procedures for phenotypic methods (sputum collection, microscopic examination, GeneXpert, culture) and genotypic methods. Consider creating a flowchart illustrating the study design and procedures.
- Provide a straightforward discussion of procedures and statistical analyses in an easily understandable format.
- Elaborate on the procedure for studying drug-resistant TB isolates and the use of artificial intelligence software for vaccine development against TB.

Results:
- Restructure and discuss results in a sequential order for better comprehension.
- Compare various databases for studying mutations in resistance genes to first and second-line anti-TB drugs.
- Highlight key findings in tables and provide brief explanations. Use asterisks to denote

P<0.05 significance in tables.

Discussion:

- Revise the entire discussion section, comparing the current paper's findings with those of previous global studies. Offer logical explanations to enhance understanding.
- Include a discussion on the limitations of the research study.
- Conclude with comprehensive recommendations grounded in practicality rather than theory.
- Implementing the current study involves carefully following the research plan outlined in your manuscript. Here is a step-by-step guide on how to implement the study:

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?
Partly

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

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious diseases with Zonootic and vector borne diseases

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 23 July 2024

https://doi.org/10.5256/f1000research.138161.r301300

Aditi Gupta
1

Pulmonary Medicine, BRAIMS, Mohali, India
[2] Pulmonary Medicine, BRAIMS, Mohali, India

1. Kindly elaborate Serious adverse events (SAE) and ADR categories also need to be explained
2. It has been proven that elderly develop more ADR but this is not the case with your study.
3. BMI, age, comorbidity have strong association with ADR. Given tables and text do not support this.
4. Kindly elaborate, how did you reach private patients for interview.
5. Since, there is lot of recall bias, results cannot be generalized.
6. At what time of treatment, did you interview the patient? Time of interview is very important in assessing ADR and decreasing recall bias. Ideally different groups at different time point of treatment must be evaluated or even same group at different time points if feasible.
7. Design of the study makes it very less informative.

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?
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?
Yes

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

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

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.

Author Response 25 Jul 2024

Harsh Shah

Dear Reviewer,

We request you to approve this article as we have incorporated your suggestions in our manuscript. Kindly do needful for its wider dissemination.

Regards

Competing Interests: NIL.

Author Response 25 Jul 2024

Harsh Shah

Greetings, Reviewer

We appreciate your input, however we would like you to review the response that addresses the comments you expressed regarding the manuscript. We believe that the evidence that this article generates will be necessary to improve India's ADR surveillance system as part of the National TB Elimination Program.

1. Kindly elaborate Serious adverse events (SAE) and ADR categories also need to be explained
    - The study had classified ADRs into various categories based on severity, including mild, moderate, and severe, with SAEs defined as those resulting in significant health risks, requiring hospitalization, or leading to long-term consequences. This classification is based on the guidelines and protocols defined in context with the National TB Elimination Program (NTEP).
2. It has been proven that elderly develop more ADR but this is not the case with your study.
    - While literature indicates a higher prevalence of ADRs among elderly patients, the findings may reflect demographic variances or differences in treatment regimens that could mitigate these risks. It is crucial to consider that the elderly in the study may have had different TB comorbidities or medication profiles compared to the general population. The results provide valuable insights into the complexity of ADRs and underscore the need for targeted interventions in vulnerable groups.
3. BMI, age, comorbidity have strong association with ADR. Given tables and text do not support this.
    - While the study did not establish significant correlations in the reported data, it is important to consider that these associations can vary based on geographical and socioeconomic factors affecting the patient population. The findings contribute to the broader understanding of ADRs in TB treatment and highlight the necessity for ongoing research to explore these relationships further, particularly in public health settings where such data can inform resource allocation and management strategies. We made references supporting this evidences, however we believe there should be more in depth operational research or longitudinal case control study will provide more structured findings in alignment of the NTEP in India.
4. Kindly elaborate, how did you reach private patients for interview.
    - We reached out the private patients through the National Tuberculosis Elimination Program (NTEP) staff, project staff and through various stakeholders, to ensure a comprehensive representation of persons with TB across both public and private healthcare sectors.
5. Since, there is lot of recall bias, results cannot be generalized.

- While we acknowledge that recall bias can affect data accuracy, we have already mentioned and narrated it under the limitation of the study. In order to reduce the recall bias, we had further employed a semi-structured questionnaire designed to mitigate these issues by prompting patients to recall their experiences in the context of their ongoing / completed treatment. We ensured that the interviewed study subjects have the medical records available in Ni-kshay or with treatment report card at health facilities in case of requirement to check bias.

6. At what time of treatment, did you interview the patient? Time of interview is very important in assessing ADR and decreasing recall bias. Ideally different groups at different time point of treatment must be evaluated or even same group at different time points if feasible.
   - The study interviews were conducted from the individuals with TB on post completion / on going of their TB treatment. We have tried to incorporate various representative of patients in the study to understand the occurrence of ADRs at various phase of treatment. We could not make separate groups in absence of budgetary restriction to repeat visits for periodic timeframe. The study design was cross sectional and interview was one time event. This is limitation that we have mentioned into the manuscript.
7. Design of the study makes it very less informative.
   - While the design may appear limited, it was intentionally developed to capture data from a diverse patient population. The findings provide critical insights into ADRs experienced by individuals undergoing TB treatment at point interval (with cross sectional design), which is vital for program policies aimed at improving drug safety and efficacy.
   - The study highlights the importance of monitoring ADRs during various treatment phases, which is essential for developing effective TB interventions that ensure patient safety and optimize treatment outcomes.

Kindly do revisit the manuscript and comments that we addressed here.

Regards

Competing Interests: NIL.

Reviewer Report 27 February 2024

https://doi.org/10.5256/f1000research.138161.r235642

?

Gyanshankar Mishra
[1] Indira Gandhi Government Medical College, Nagpur, Maharashtra, India
[2] Indira Gandhi Government Medical College, Nagpur, Maharashtra, India

" This manuscript provides a thorough analysis of adverse drug reactions (ADRs) associated with first and second line anti-tuberculosis (TB) treatment drugs. It offers valuable insights into the ADRs experienced by patients in the National TB Program of India, making a significant contribution to the existing body of literature.

One key finding is the increased incidence of ADRs in patients with drug-resistant TB compared to those with drug-sensitive TB. This observation is crucial for a deeper understanding of the challenges in treating drug-resistant TB. I recommend enhancing the discussion on this point at the end of the first paragraph following the line addressing the variance in ADR prevalence. It would be pertinent to include a statement that emphasizes the doubling of ADRs in patients with drug-resistant TB compared to those with drug-sensitive TB, reflecting the lesser efficacy and increased toxicity of second-line drugs. This insight underscores the necessity for prolonged treatment durations and a higher expectation of ADRs during the course of second-line drug therapy.

Additionally, the study's identification of the most common ADRs, including gastric discomfort, arthralgia, and cutaneous reactions, is consistent with findings from other studies in India. In the discussion section following the mention of these ADRs, I suggest incorporating a reference to a significant study involving 750 TB patients who received the daily fixed-dose combination anti-TB treatment under the National TB Elimination Program (NTEP) [1]. This study provides important context on peripheral neuropathy, particularly in drug-resistant TB cases treated with second-line drugs. Emphasizing the importance of early recognition and management of linezolid-associated peripheral neuropathy to prevent irreversible progression would be valuable [2]. Furthermore, the role of arthralgia, especially in relation to pyrazinamide use, warrants additional discussion. Highlighting the importance of serum uric acid estimation in differentiating hyperuricemic from normouricemic arthralgia and the potential role of uric acid-lowering drugs, in addition to standard therapies, in managing anti-TB treatment-induced hyperuricemic arthritis, is crucial for a comprehensive understanding of these ADRs [1].

The inclusion of these points will enhance the depth and comprehensiveness of the discussion in the manuscript, ensuring it provides a detailed and nuanced understanding of the ADRs associated with TB treatment in India. The manuscript, with these additions, will be an invaluable resource for healthcare professionals and researchers in the field of TB treatment.

References

1. Mate K, Mishra G, Munje R: Adverse Drug Reactions to a Daily Fixed-dose Combination Based Antituberculosis Treatment Regime in India's National Tuberculosis Elimination Programme: A Prospective Cohort Study. *JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH*. 2022. Publisher Full Text

2. Mishra G, Alffenaar J, Munje R, Khateeb S: Adverse drug reactions due to linezolid in the programmatic management of drug-resistant tuberculosis in India: A retrospective multicenter study. *Indian Journal of Tuberculosis*. 2023. Publisher Full Text

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?

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?
I cannot comment. A qualified statistician is required.

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

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Respiratory diseases, 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 18 Jul 2024

Harsh Shah

Dear [Reviewer/Editor],

The revised manuscript has incorporated the feedback from the peer review process. The suggestions from the mentioned study have been integrated into the discussion sections.

One limitation of the study was that drug-specific adverse drug reactions (ADRs) were not established, and general considerations of ADRs were taken into account, particularly in drug-resistant tuberculosis (DR-TB) cases, due to the absence of specific case records. Therefore, linezolid-specific ADRs or those related to second-line drugs were not explored, as the primary intention was to identify general characteristics and contributing factors.

However, the feedback received highlights the necessity for further exploration to address the continuum of treatment by creating a system that offers more detailed guidance on ADRs. In the same direction, the present study underscores the need to equip frontline workers and medical officers in health facilities with the knowledge and skills to manage ADRs efficiently.

Thank you for your valuable insights and suggestions, which have significantly contributed to improving the manuscript.

Competing Interests: NIL.