Running 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

# **Introduction**

Tuberculosis (TB) is a communicable disease that remains a major cause of illness and death across low and middle-income counties (LMIC) even after the discovery of newer diagnostic methods and chemotherapeutic drugs. The incidence of TB and rising numbers of multidrug-resistant TB are still a concern for the high disease burden countries. As per the global TB report, the incidence of TB in India is a TB approximately 2.8 million cases annually, accounting for almost a quarter of all TB cases worldwide (1). Even though a 6-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 (2). 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 (3,4).

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 (5). 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 (6–8). 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 (7). About 10–25% of patients who experience side effects develop significant and deadly medication reactions or serious adverse events (SAEs) (9–11). 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 (12–15). 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 (16). 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.

# **Methods**

## ***Study design and settings***

A descriptive observational cross-sectional study was conducted from May 3rd 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.

## ***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 (17). The list of reported TB patients from July 1st, 2018, to December 31st, 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 derived that over 534 TB patients to be included into the study to have a confidence level of 98% and desired error 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. Final eligible TB cases were listed with the inclusion and exclusion criteria below.

* Inclusion criteria: the TB patients were 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 till 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.

##  ***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. 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 on questionnaire with participatory approach and role plays to collect the information from the study participants by interviewing for the required information available with the patients including medical records.

## ***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” (18).

The cornerstones of the therapy of DSTB continue to be a treatment plan with a minimum duration of 6 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 lengthier oral M/XDR-TB (Mono or Extreme Drug Resistant) regimens ranging from 6-9 months 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 resistant / susceptibility towards ATTs.

## ***Data analysis***

Once the data collection was completed, data sets were scrutinized for completeness and validation by the different set of the researchers. The study participants were contacted again if any data variables found 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-square for trend examined linear trends. Risk measures were determined using odds ratios (OR) and 95% confidence intervals (CI). Crude odds ratios (OR) and 95% confidence intervals (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% CIs were calculated by bivariate logistic regression analysis.

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