

Original Research Article**Incidence of Diagnosed Drug Resistant Tuberculosis Cases in India As Reported by Central TB Division since 2007: Ecological Study**Pritam Sakhare^{1*}, Anuradha Chivate², Sunita Ramanand³, Shivashakti Pawar⁴¹Assistant Professor, Dept. of Pharmacology, RSCM GMC Kolhapur²Assistant Professor, Dept. of Pharmacology, Krishna Institute of Pharmacy, Karad³Professor & Head, Dept of Pharmacology, RSCM GMC Kolhapur⁴Medical Officer, Dept. of Health, Govt of Maharashtra

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Abstract:

Background: India has maximal load of the tuberculosis in the world. Drug-resistant pulmonary tuberculosis is an important factor that determines the outcomes of the TB elimination efforts in India. Along with the advent of anti-TB drugs, drug-resistant tuberculosis (DR TB) has existed in India. This study would provide an insight about incidence of diagnosed DR TB cases based on Central TB Division reports and additionally help to avoid duplication of data reported through the various case reports, case series and reviews, as TB has been a notifiable disease in India since 2012.

Objectives: To determine the incidence of diagnosed DR TB cases in India as reported by Central TB Division.

Method: Various publications by Central TB Division Ministry of Health and Family Welfare, Govt of India, notably: Programmatic Management of Drug-Resistant TB 2021, India TB report 2022 and India TB report 2023 have reported data on diagnosed DR TB cases in India since 2007. The annual number of DR TB cases as per Central TB Division and population of India as per World Bank population projections are used to calculate the Incidence of DR TB cases in India.

Results: The incidence of diagnosed DR TB patients in India is increased from 0.5 per Lakh Population for the period 2007-2010 to 4.49 per Lakh Population in the year 2022.

Conclusion: There is gradual increase in the incidence of diagnosed DR TB patients in India between the periods of 2007 to 2022.

Keywords: Diagnosed drug resistant tuberculosis, NAAT, Incidence, India TB report, Central TB Division.

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Introduction

There are various reports about the estimations for projected DR TB cases in India; however little information on actually diagnosed DR TB cases in India. Considering this limitation, current study to report diagnosed DR TB cases in India is conducted. Mycobacterium tuberculosis bacilli cause an airborne pulmonary disease, and less commonly extrapulmonary disease.

The tubercle bacilli enter the body by droplets (< 5µm overcome defences) dissemination during coughing, sneezing or talking by infected person and institution of tubercle bacilli in human body initiates infection (on an avg. up to 2 months from the entry). First time infection in susceptible individuals is primary infection and indicated by release of interferon gamma.

Regional lymph nodes are the site of secondary bacillary growth to result in tubercle bacillaemia leading to the establishment of developing forms of

bacilli (seedlings) around the body. After a long latency, post-primary tuberculosis disease might occur as consequence of reactivation of primary dormant tubercle bacilli or by re-infection exogenously.

Anyone can be affected by TB. However, vulnerable population at higher risk of acquiring TB are the patients with immunocompromised state (HIV, Immunosuppressants), health care staff, and people in overcrowded areas with low ventilation. [1] Over the years TB is an important public health issue more in developing countries, causing significant mortality from an infectious micro-organism.

As per 'Causes of death Statistics 2017-2019', Govt of India, mortality due to Tuberculosis in India is contributing about 2.9% of all deaths, and 4.2% at age group 30-69 years. TB is preventable and mostly manageable disease. But the number

deaths from TB could be higher in absence of treatment. [2] As per World Health Organization (WHO) approximate calculations about 74 million deaths due to TB were prevented between 2000 and 2021 as result of successful TB management efforts. [3] TB disease wherein the bacilli are resistant to one or multiple anti TB drugs is DR TB.

TB disease in which the bacilli are resistant to isoniazid (H), rifampicin (R), with or without resistance to remaining first line drugs is defined as Multi Drug Resistance (MDR-TB). One-fourth of the global load of MDR-TB is estimated to be in India.

A sub group of MDR-TB in which the bacilli is resistant to R, H, fluoroquinolones and any of the second-line injectable drugs (namely Kanamycin, Capreomycin or Amikacin) is Extensively Drug Resistant TB (XDR-TB).

1 in 106 bacilli are inherently resistant to Isoniazid & 1 in 108 bacilli are inherently resistant to Rifampicin, thus the possibility of naturally H and R resistant bacilli is very rare. [4]

More the bacterial load, more the chances of resistant variants are present. Excess of 100 million viable tubercle bacilli could be in the cavities sized around 2 cms in diameter. On contrary, smear negative and extra pulmonary lesions have lower number of bacilli.

DR TB could be propagated from a drug resistant index case (Primary transmission) or resistance emerge during treatment (Acquired Resistance).

Genetic mutation is the basis of emergence of drug resistance which leads to anti TB drug ineffective against the resistant bacilli. Inappropriate treatment regimen (single drug therapy, treatment noncompliance) for TB facilitates dominance of drug resistant strain in a TB infected patient.

Prevention of drug resistance is essential for the TB control. Early diagnosis of resistance avoids air borne resistant infection spread & increases chances of cure in the patient.

Presumptive DR-TB involves the patients in order of their risk: follow-up sputum smear examination positive TB patients on treatment, treatment failures concerning first line drugs; paediatric TB non-responders; TB patients in contacts with DR-TB patient; previously treated TB patients; new HIV TB co-infection patients; all notified new TB patients.

The earliest recognition of presumptive DR-TB cases is the initial step in detection of DR-TB cases. In India all notified new patients are tested for resistance to Rifampicin by Cartridge Based Nucleic Acid Amplification Test (CBNAAT) and termed as universal Drug susceptibility testing

(DST) for Rifampicin. All TB patients are planned for specimen for CBNAAT at baseline.

Currently dysregulated availability of first and second-line anti-TB, and its irrational, injudicious administration is the impeding threat for drug resistant TB (DR-TB). [4]

Drug-resistant tuberculosis (DR-TB) cases are steadily increasing globally. [5]

Rifampicin mono-resistance is infrequent and mostly detected with Isoniazid resistance. Multi-drug-resistant TB (MDR-TB) constitutes almost 90% of Rifampicin-resistant Pulmonary Tuberculosis (PTB) cases.

As per National Drug Resistance Survey (NDRS) India - 2014-16, DR TB was up to 21.10 - 24.1 % in new cases and up to 34.64 – 39.04 % in previous cases.

Globally, MDR-TB incidence in new cases is 3.4% and in previously treated cases is 18%. [6]

DR TB management is difficult and is associated with high cost. Prolonged treatment with multiple antimicrobial agents, extended transmission of the bacilli, impending fear of treatment failure, increased risk of relapse, chances of developing physical sequelae, adverse effects of the anti TB agents and death are the challenges in the management of DR TB. [7,8]

Indian Council of Medical Research (ICMR) had been carrying out progressive surveys for DR TB since more than four decades. [9,10] One of Drug Resistance Surveillance was done in India in 2007 as part of WHO global surveillance of drug resistance project.

As per National TB Prevalence Survey in India 2019 – 2021, the rifampicin resistance was 7.6% with CBNAAT. Relatively higher Rifampicin resistance was found in patients with normal chest X-ray and symptomatic patients. [11] India has 27% of the universal load of multi-drug resistant TB (MDR-TB). As per WHO global estimates around 191 000 (range 119 000–264 000) fatalities were due to MDR/RR-TB in 2021.

As per estimations on global level in 2022, 410 000 patients (95% UI: 370 000–450 000) had multidrug-resistant or rifampicin resistant TB (MDR/RR-TB). However, diagnosed and started on treatment number was lower: 175 650 patients (2022), which is less than the before pandemic level of 181 533 (2019) diagnosed and started on treatment patients. [5]

National level TB disease burden quantification is a challenging task for TB control activities. [11] Early diagnosis of TB disease is critical to interrupt the progression of M. tuberculosis transmission. Rational treatment will limit exposure to contact

and decrease the bacillary load in the ambient air. These steps are essential to achieve tuberculosis elimination.

Objectives

This study is undertaken to evaluate the existing Central TB Division, Ministry of Health and Family Welfare, Govt of India data on diagnosed cases of DR TB in India. The study intends to determine the year wise incidence of diagnosed DR TB cases in India. The study outcomes would be relevant for policy, and future research.

Methods

Study design

The RECORD (Reporting of studies Conducted using Observational Routinely-collected Data) statement for pharmacoepidemiology: RECORD-PE guidelines are used for this study. [12]

It is an ecological study based on data analysis of India TB report 2022, India TB report 2023, Central TB Division, Ministry of Health and Family Welfare, Govt of India.

The number of diagnosed DR TB cases as reported by Central TB Division, Ministry of Health and Family Welfare, Govt of India (<https://tbcindia.gov.in/WriteReadData/IndiaTBReport2022/TBAnnulReport2022.pdf>, <https://tbcindia.gov.in/showfile.php?lid=3680>) from year 2007 to 2022 are included.

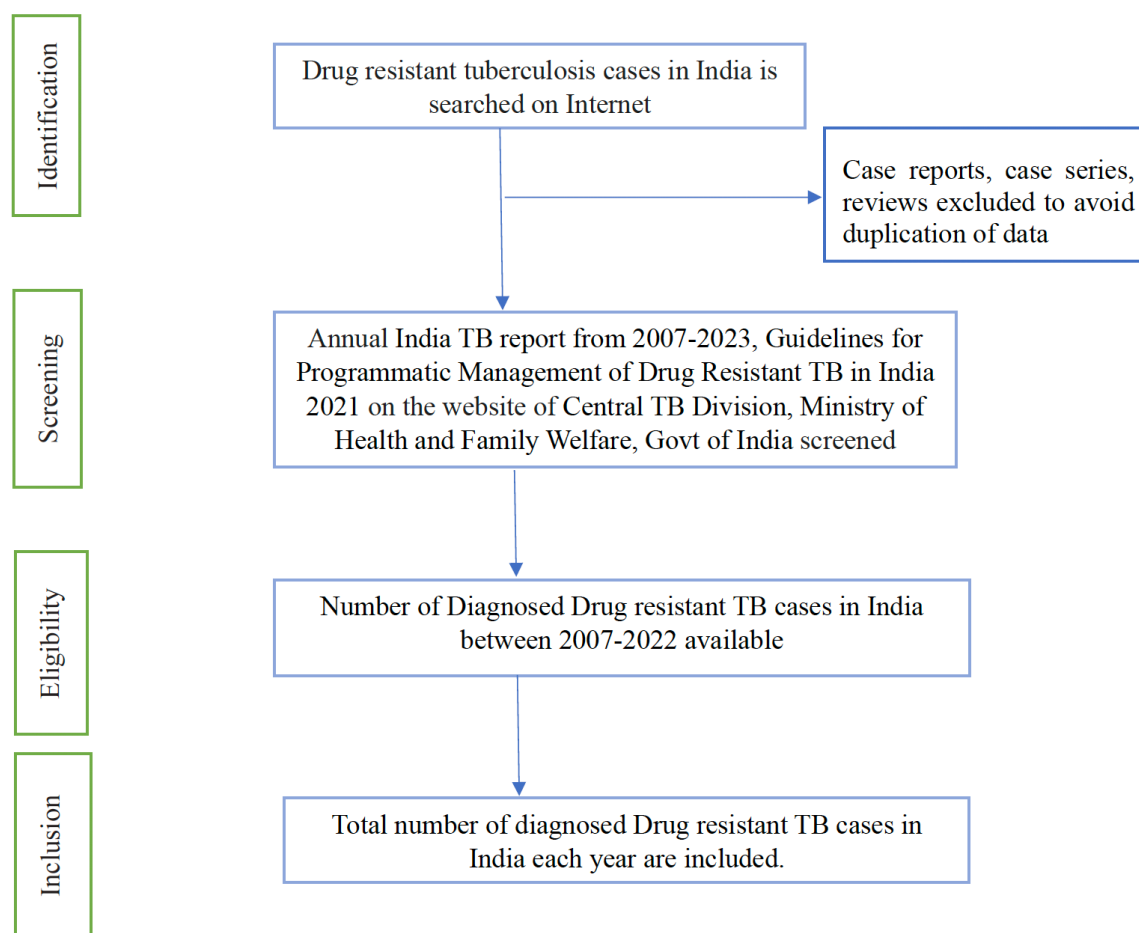


Figure 1: Flowchart for methodology of data inclusion

Setting

This is a Longitudinal Ecologic study classified on two dimensions: (a) exploratory: primary group is measured for incidence of diagnosed DR TB; and (b) patients grouped by time: 2007-2022. [13,14] The Aggregated measure of diagnosed DR TB patients was reported from all over the India. [15]

Participants

Patients of all ages, gender who are diagnosed of DR TB and reported by Central TB Division, Ministry of Health and Family Welfare, Govt of India are included. The diagnosed patients were mostly from the group Presumptive DR-TB patients. Diagnosed DR TB cases reported from case reports, case series and reviews are excluded

as TB is notifiable disease from 2012 and hence all cases in private health set up should be reported to concerned Govt authorities.

National Policy for Diagnosis (<https://tbcindia.gov.in/WriteReadData/IndiaTBReport2022/TBAnnualReport2022.pdf>)

◀ Drug-Resistant TB (DR TB)

▼ Nucleic acid amplification test (NAAT) for TB patients (Microbiologically diagnosed) to determine resistance to Rifampicin.

▼ Rifampicin Sensitive (RS) TB Patients are offered to Line Probe Assay (LPA – First Line).

▼ Rifampicin-resistant (RR) and Isoniazid (H) resistant TB patients are offered First- and Second-Line LPA.

▼ Liquid Culture (LC) & DST is performed for determining amplification of resistance to drugs used for managing DR TB.

▼ Determination of amplification of resistance to drugs used for treating DR TB done with Liquid Culture (LC) & DST.

▼ LC is used for monitoring response to DR TB treatment.

▼ DR TB treatment surveillance with LC.

Results

Incidence of diagnosed DR TB patients=

$$\frac{\text{Annual diagnosed DR TB patients} \times 100000}{\text{Population of India that year}}$$

Incidence of diagnosed DR TB is calculated with observational data of annual diagnosed DR TB cases reported by Central TB Division, Ministry of Health and Family Welfare, Govt of India and respective annual population of India as estimated by World Bank (<https://data.worldbank.org/indicator/SP.POP.TOTL?end=2022&locations=IN&start=2007>). The data for 2007-2010 is reported as combined number of diagnosed DR TB patients for 3 years, thus average of population for these 3 years is considered for the calculation of incidence of 2007-2010. Similarly, 2011-2012 combined number of patients of diagnosed DR TB for 2 years and additionally for 2012 diagnosed DR TB patients were reported separately thus for year 2011 diagnosed DR TB patients are calculated by subtraction.

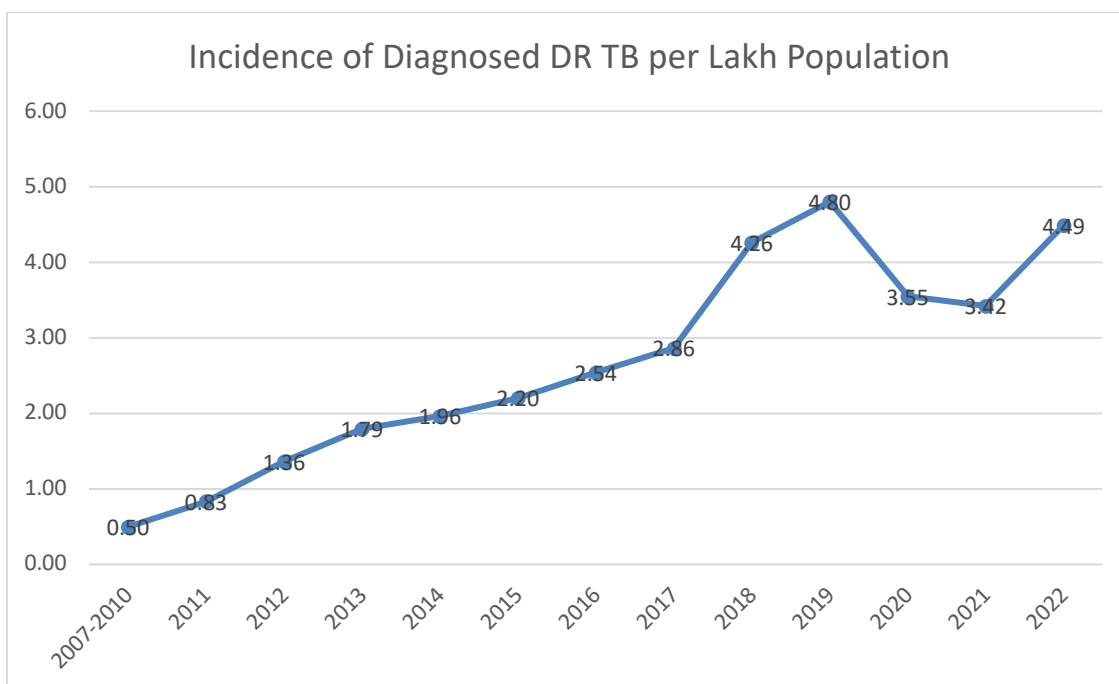


Figure 2: Graphical representation of Incidence of DR TB per Lakh Population year wise

Table 1: Incidence of DR TB per Lakh Population yearwise

Year	No. of DR TB patient detected	India Population in Billions	Incidence of DR TB per Lakh Population
2007-2010	6046	1.215	0.50
2011	10501	1.26	0.83
2012	17274	1.27	1.36
2013	23148	1.29	1.79

2014	25727	1.31	1.96
2015	29057	1.32	2.20
2016	34016	1.34	2.54
2017	38605	1.35	2.86
2018	58347	1.37	4.26
2019	66255	1.38	4.80
2020	49679	1.4	3.55
2021	48232	1.41	3.42
2022	63,801	1.42	4.49

Discussion

The incidence of diagnosed DR TB cases increased from 0.5 per Lakh Population for the period of 2007-2010 to 4.5 per Lakh Population for 2022.

There is significant dip of 3.55 per Lakh Population (2020) and 3.42 per Lakh Population (2021) which has been attributed to operational limitations because of COVID-19 Pandemic. However again in year 2022, the incidence of diagnosed DR TB cases increased to 4.49 per Lakh Population.

To start with in 2007 there were a smaller number of Nucleic acid amplification test (NAAT) sites. In year 2013 there were 18 sites which grew gradually to 3147 NAAT sites in year 2020. [16] Thus, earlier there were lesser resources to detect DR TB cases that might have an impact on diagnosis of DR TB cases in India from 2007.

As per Guidelines for Programmatic Management of Drug Resistant Tb in India 2021, all presumptive TB, all TB patients, non-responders, People living with HIV, presumptive EP (extra pulmonary)-TB cases, presumptive pediatric TB, contacts, smear-ve X-ray suggestive of TB undergo NAAT.

These factors might be the source of bias for diagnosing the cases of DR TB. As per different estimations from WHO and Central TB Division there are a greater number of DR TB patients than actually diagnosed cases of DR TB.

Cases from private set up before 2012 might not have been reported to health authorities as it was not notifiable disease in India before 2012.

Strengths

This study involves significant number of diagnosed DR TB cases reported around the India, allowing to determine the incidence of diagnosed DR TB cases and its trend in India over the period of 2007-2022.

Limitations:

1. Data characteristic for each patient is not available and difficult to quantify how each risk factor is actually contributing to the disease. For e.g. DR TB cases in new patients and drug resistant Tb cases in previously treated

patients could be not separated. Additionally, DR pulmonary and extrapulmonary TB cases not differentiated.

2. Confounders not possible to control. Heterogeneous health factors like diabetes might contribute to drug resistance in TB.
3. Variations of diagnostic tests, methodology, criteria and technological advances over the period of 10-15 years.
4. Disease distribution in the population can't be studied.
5. The denominator for calculating incidence is estimated population of India each year; as census is done every 10 years.

Interpretation

It is interpreted that the incidence of diagnosed DR TB per Lakh Population is increasing. COVID-19 substantially affected the TB care in 2020 with improvements in TB care from 2021 onwards. The ecological fallacy is applicable to this study as well. Potential confounding by other variables is difficult to assess. As per various projections of WHO and Central TB Division, Ministry of Health and Family Welfare, Govt of India, the estimated number of DR TB patients is more than actually diagnosed patients of DR TB patients.

The purpose of this study is to determine the incidence of diagnosed DR TB. National TB Elimination Program (NTEP) has developed effective public health strategies and are being implemented to reduce the DR TB cases in India.

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