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Prevalence and Patterns of Drug-Resistant Tuberculosis in India: Evidence From the Last 2.5 Decades

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ABSTRACT

Drug-resistant tuberculosis (DR-TB) is a problem that dissuades the tuberculosis control and prevention efforts worldwide. A big portion of the world's TB burden is seen in India. We aimed to produce valuable evidence on the prevalence and patterns of DR-TB pan India for a period of last 2.5 decades. We systematically searched PubMed, Google Scholar and major TB journals for studies published between 1996 till 2020, which reported the prevalence of DR-TB in India. We included sub-groups of pulmonary, extrapulmonary, and paediatric patients in our analysis considering the paucity of data in these sub-groups. We used random effects to estimate prevalence of DR-TB and its types, and I^2 statistic to assess heterogeneity. A total of 789 studies were screened, of which 132 non-duplicate studies were included. Any drug resistance, multi- and extensive-drug resistance was seen in 33.67%, 11.69% and 1.61% cases, respectively. Multi-drug resistance (MDR) among new TB patients and previously treated patients was 1.03% and 23.87%. MDR prevalence among pulmonary, extrapulmonary, and paediatric groups was 11.43%, 11.91%, 9.06% respectively. There was high heterogeneity between the studies. We conclude that continuous DR-TB surveillance is crucial to ensure programmatic success and to control the spread of DR-TB.

KEYWORDS

Drug-resistant tuberculosis, multi-drug resistant tuberculosis, extensively-drug resistant tuberculosis, epidemiology, prevalence

INTRODUCTION

It was estimated that in the year 2019, 10 million people developed TB globally and in recent years, there has been as very sluggish decline in this figure. According to the same report, two thirds of the total global cases were accounted for in only eight countries, and 26% were seen in India itself (World Health Organization, Global Tuberculosis Report, 2020). A persistent risk to successful TB control is the drug-resistance to anti-tubercular therapy. Treatment failure to the anti-tuberculosis drugs and the ineptness of Directly Observed Treatment-Short Course (DOTS),

are among the principal causes for the emergence of various forms of drug-resistant strains, worldwide (Zhang & Yew, 2015). Resistance at least to the two bactericidal drugs rifampicin and isoniazid together, called multidrug-resistant (MDR) tuberculosis, and this multidrug-resistance with further resistance to any one second-line injectable drug as well as to a fluoroquinolone called extensively drug-resistant (XDR) tuberculosis, have emerged globally and are of additional concern (Shah et al., 2007; Fonseca et al., 2015).

In 2019, rifampicin-resistant tuberculosis (RR-TB) was detected in 500,000 people worldwide, and around 78% of them were diagnosed with multidrug-resistant tuberculosis (MDR-TB). The prevalence of RR/MDR-TB was about 3.3% in newly diagnosed patients; and in previously treated patients, the same was estimated to be about 17.7%, worldwide (World Health Organization, Global Tuberculosis Report, 2020). Among the three countries that share the highest proportion of the global drug-resistance burden are India with 27%, China with 14% and the Russian Federation with 8% (World Health Organization Global Tuberculosis Report, 2020).

Drug resistance may develop despite completion of the first-line treatment, or even develop unexpectedly in a previously drug-susceptible strain before treatment initiation (Colijn et al., 2011). Phenotypically, drug-resistant tuberculosis (DR-TB) is primarily driven by drug resistance acquired during treatment and the subsequent transmission of this drug-resistant bacilli to contacts. Early diagnosis and appropriate, timely, and full treatment are crucial for preventing the spread of drug-resistance (Sloan & Lewis, 2016; World Health Organization, The End TB Strategy, 2015).

Primarily, TB infection occurs when the dendrite cells or alveolar macrophages engulf the bacilli while the bacterium avoids the killing mechanism and persists to reproduce evading the phagosome-lysosome membrane fusion (Siroy et al., 2008; Burian et al., 2012). The Mycobacterium tuberculosis (*Mtb)* bacilli replicates vigorously in a specific site where complementary macrophages and other immune cells are usually contained (granuloma), along with a non-replicating persistent/dormant form of *Mtb*, which is impelled by environmental circumstances such as nutrient deprivation, anorexia, nitric oxide production, etc. (Siroy et al., 2008; Kashyap et al., 2018).

The mycobacterium cytomembrane, comprising of a peptidoglycan-arabinogalactan chemical compound bound with covalent mycolic acids (of up to 90 carbon atoms in length) and a large variety of free lipids is an evolved and complex structure (Barry et al., 1998; Daffé& Draper, 1998). Most of these lipids from an essential part of the intrinsic resistance of mycobacteria to many toxic compounds and antibiotics, as it is these constituents of the cell envelope that provide an extraordinarily efficient permeability barrier (Brennen &Nicaido, 1995). The loss of desired activity of the therapeutic agents is due to this intrinsic drug resistance mechanism by expression of various enzymes and efflux pumps. Thus, Mycobacterium tuberculosis is additionally as

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such immune to the numerous approved bacteriostatic and bactericidal agents via this pharmacokinetic type of resistance. The drugs are made ineffective as a result of several bacterial enzymes that are encoded, which either degrade or modify them (Kashyap et al, 2018).

As per the evolution theory by Darwin, drug-resistant*Mtb* strains spread by overcoming the anti-TB regimens and the selective environmental pressure, by adopting genetic mutations and other mechanisms. Thus, the environmental conditions coupled with long-term unchanging drug combination therapies have caused the evolution of the *Mtb* strains which became gradually resistant to the existing drugs (Palomino & Martin, 2014). Environmental factors also cause mutations or genetic modifications in the *Mtb* genome that in addition to providing the potential threshold for survival to the *Mtb* in any extreme condition, which also reduce the effectiveness of an applied drug (Palomino & Martin, 2014). This survival characterizes the lethal introductions through radical-induced mutagenesis to the anti-bacterial agents and promotes the resistant phenotypes of *Mtb*. When the free radicals and reactive oxygen fail to invade the mycobacterial cell, then it promotes cellular mutagenesis and consequently rise of drug resistance is seen.

Therefore acquired drug resistance in *Mtb* strains result from deletions, insertions or substitutions of nucleotide sequences within the particular resistance-defining regions of the gene targets or their promoters or activating enzymes of anti-TB agents and not as a result of horizontal transfer of resistance-determining genes or region. Mutations have been reported in several genes such as *inhA*, *katG*, and *ahpC* (resistance to isoniazid), *rpoB* (resistance to rifampicin), RIF, *gyrA* or *gyrB* (resistance to flouroquinoloes) and *inhA* (resistance to ethionamide) (Almeida et al., 2007; Palomino and Martin, 2014).

Endorsement of the PMDT or the Programmatic Management of Drug Resistant Tuberculosis services by the World Health Organization (WHO) significantly reduced the economic barriers to effective DR-TB control (Chaudhari, 2020). The Revised National TB Control Program (RNTCP) which is India's TB control program launched its own PMDT in 2007 and it attained national coverage in the year 2013 (Central TB Division. Guidelines on Programmatic Management of Drug Resistant TB (PMDT) in India, 2017).

Several rapid molecular tests like Line Probe Assay (LPA) and cartridge based-nucleic acid amplification tests (CB-NAAT) have already been endorsed for Drug Sensitivity Testing (DST) for first-line drugs (TB India, Revised National Tuberculosis Control Programme Annual Status Report, 2014). WHO has also released recommendations for improving the diagnosis rate of TB, including the use and implementation of molecular methods such as the LPA and Xpert MTB/RIF or GeneXpert assay (World Health Organization, Molecular line probe assays for rapid screening of patients at risk of multi-drug resistant tuberculosis (MDR-TB), Policy statement, Genewa, 2008; Lawn et al., 2013; Li et al., 2012; Ahmed et al., Mani et al., 2001; Hillemann et al., 2007).

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Treatment success for RR/MDR-TB is low in many countries even as per latest reports, only 57% of the total MDR patients completed treatment successfully (World Health Organization, Global Tuberculosis Report, 2020). To address the long treatment duration with toxic drugs and the poor treatment outcomes, WHO released guidelines on the control and treatment of DR-TB incorporating a shorter regimen well as a longer, all-oral MDR-TB regimen with opportunity to tailor the regimen according to the DST reports (World Health Organization, WHO consolidated guidelines on drug-resistant tuberculosis treatment, Geneva: World Health Organization, 2019). The RNTCP updated guidelines 2019 are also in line with the global recommendations as shown in **Table 1**. An all-oral regimen is for isoniazid mono or poly-resistance (without rifampicin resistance) of duration 6 months, with no bifurcation into intensive and continuous phase. Another longer, all oral MDR TB regimen of duration 18-20 months is considered for patients not eligible for the shorter MDR-TB course, and incorporates use of the new drugs like delanamid (Dlm) and bedaquiline (Bdq). For the treatment of XDR-TB patients, the same regimen with treatment duration of 20 months is to be used (Chaudhari, 2020; Central TB Division, Guidelines on Programmatic Management of Drug Resistant TB (PMDT) in India, 2019).

Table 1: Standard DR-TB Regimen as per latest PMDT guidelines in India

Regimen Class*	**Intensive phase**	**No bifurcation into IP/CP**	**Continuation Phase**
All oral H mono-poly DR-TB regimen (R resistance not detected and H resistance)	-	6/9 Levofloxacin, Rifampicin, Ethambutol, Pyrazinamide	-
Shorter MDR TB regimen	4-6 Moxifloxacin[hd], Kanamycin/Amikacin[1], Ethionamide, Clofazimine, Pyrazinamide, Isoniazid[hd], Ethambutol		5 Moxifloxacin[hd], Clofazimine, Pyrazinamide, Ethambutol
All Oral MDR TB Regimen/XDR TB Regimen	-	18-20 Bedaquiline (6) Levofloxacin Linezolid[2] Clofazimine Cycloserine	-

[hd]– High dose

[1] – If the intensive phase is prolonged, the injectable agent is only given three times a week in the extended phase

[2] – reduction of Linezolid to 300 mg per day after 6-8 months

*– Pyridoxin to be given to all DR-TB patients as per weight band

The prevalence of drug-resistant tuberculosis (DR-TB) has not been estimated in India as nationwide prevalence surveys are not always feasible in a resource limited setting. Evidence generation relies largely on assessments from various smaller scale epidemiological studies. For example, a pivotal study was conducted in the western Indian state of Gujarat that had estimated

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the prevalence of pulmonary MDR-TB as 2.4% and 17.4% in new and previously treated patients, respectively (Burian et al., 2012).

A national level survey (carried out only in designated public health facilities) in 2014–2016 estimated the prevalence of MDR-TB to be 2.8% and 11.6% among new and previously treated patients, respectively (Ministry of Health and Family Welfare. Report of the First National Anti Tuberculosis Drug Resistance Survey: India 2014–16. 2018). The scope of this study was restricted because of two reasons: the private sector was not included, and it caters to as high as 50% of TB patients in India in a relatively unregulated manner. Further this survey was undertaken in the health centres and hence the population covered included only care-seekers who reported to the TB clinics and not the entire population and facility-based estimates are likely to be biased from the true prevalence estimates. Also to be noted is the fact that the surveys in India predominantly exclude smear negative and extrapulmonary cases, and are mostly centred around estimating only the sputum smear positive TB burden (Charan et al. 2019).

Data on drug-resistance patterns in extrapulmonary tuberculosis (EPTB) are scarce and the lack of facilities and expertise for image-guided sampling as well as non-availability of rapid tests at most centres compound the diagnostic challenge posed by EPTB (Sharma & Mohan, 2004). The main challenge to EPTB is its paucibacillary nature and the relative lack to accessibility to obtain diagnostic specimens from sites such as nervous system, bones and joints, pleura, or even eyes, etc. which warrants strong clinical suspicion to be diagnosed and leads to empirical treatment in most cases. Drug-resistant EPTB is also a tough challenge due to the high morbidity associated with it and despite causing a major burden on the health system it has frequently been neglected. Of all the new TB cases, 15% are reported to be EPTB cases. In patients also infected with human immunodeficiency virus or HIV, this number may be as high as 50%. Even in the reports published by WHO, studies focus more on microbiologically confirmed cases of TB and that too in the adult population thereby excluding the burden in the paediatric population and that of extrapulmonary TB. TB elimination efforts and surveillance should concentrate on all forms of TB equally.

MATERIALS AND METHODS

The present study was therefore designed to profile the drug resistance patterns in pulmonary as well as extrapulmonary cases tested, and to provide pooled estimates in the overall clinical samples for DR-TB, including any drug resistance or ADR, mono-resistance to any of the first line drug, MDR-TB, pre-XDR and XDR-TB in India, from a body of published studies conducted across the last 25 years. Period prevalence in clinical isolates across five-yearly intervals (1996-2000, 2001-2005, 2006-2010, 2011-2015, 2016-2020) was calculated. Data was assessed collectively (across all the clinical samples) and also in the sub-groups or cohorts of pulmonary, extrapulmonary, and paediatric patients. In scenarios of healthcare disruption, such analysis can

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provide valuable estimates to plan the further course of action in coming years. Mathematical models can be developed to further predict incidence and actual prevalence in coming years.

PubMed, Google scholar as well as major TB journals and other databases were systematically searched to find studies published in English language, reporting to the prevalence of DR-TB within India. Citations or references were also explored to find any studies that could be included as per the inclusion and exclusion criteria. Keywords like “Multi-drug resistance”, “Extensively-drug resistant tuberculosis”, “MDR”, “XDR”, “Drug Resistance”, “Prevalence”, “India” etc., were used. Duplicates, meta-analyses, and systematic review studies were removed from our analysis. Same studies conducted in locations of more than one state were analysed as separate; so were studies conducted by the same authors in two different timelines, including different set of patients.

Selection criteria

Primary or secondary studies reporting the prevalence of drug resistance in TB patients in India published in English from January 1996 till December 2020 were included in the review. Studies reporting duplicate data, and those which did not provide the estimates in the required format (number of resistant patients and total number tested), studies that did not report resistance data on any of the five first line drugs were excluded from the analysis.

Statistical analysis

We performed statistical analysis for this study using the MedCalc software. Random effects model was used for meta-analysis. Pooled prevalence for the various forms of drug-resistance (mono-resistance, DR-TB, MDR-TB, pre-XDR TB and XDR-TB were estimated across five-year periods, overall study period, region and study sub-groups along with their 95% confidence intervals. Heterogeneity was estimated using the I^2 statistic, where the higher I^2 values signify increased heterogeneity.

RESULTS

A total of 789 were considered for inclusion in this review. After full text assessment screened studies, 657 were excluded leaving 132 non-duplicate studies for the final analysis (**Figure 1** below). If a study reported PTB and EPTB cases separately, or if a study was conducted in more than one district/state and provided location-wise results, they were considered as separate studies: giving a total number of 150 analysable estimates according to the above criteria. A majority of these estimates were from hospitals (n=91) and less than half (n=59) were from centres across both rural and urban areas combined. The most common diagnostic method employed was phenotypic (Löwenstein-Jensen or LJ method, 52%) and rest were genotypic i.e., BACTEC, MGIT, GeneXpert, etc.). Overall, of the 150 estimates, 106 studies tested 70,411

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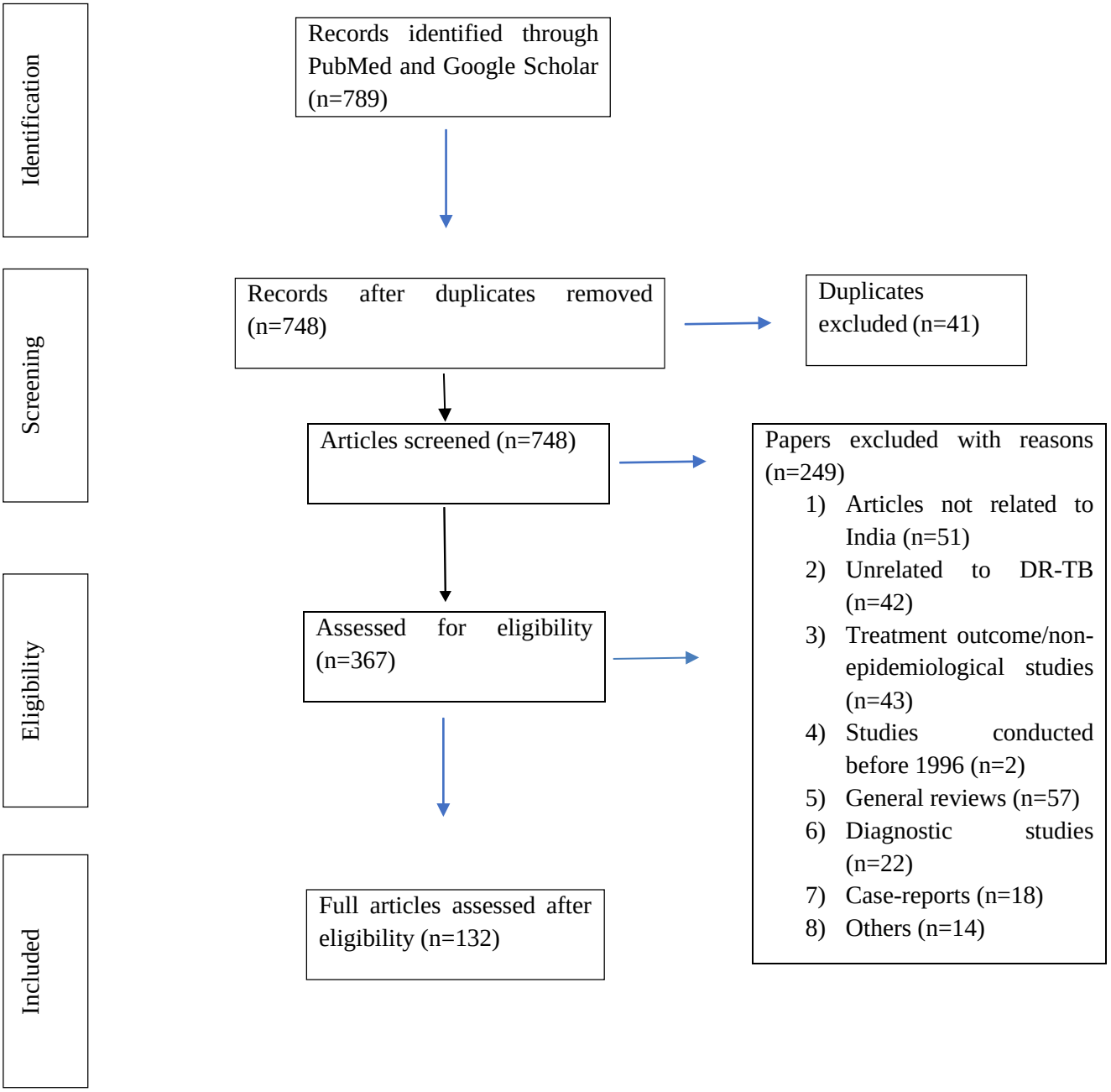
isolates for possible suspicion of any any resistance and over 33% isolates were confirmed positive with any resistance to any of the first-line anti-TB drugs.

Figure 1: Process of screening of the articles for literature review.



The maximum number of studies were reported from the Northern part of India (n = 62), followed by South India (n = 38), West India (n = 28), East India (n = 15) and Central India (n = 5). Two studies reported samples from across different states. Drug resistance forms (including mono-resistance, ADR-TB, MDR, pre-XDR and XDR) was reported in a total of 1,19,242 *Mtb* isolates during the entire study period of 25 years, which were subjected to drug susceptibility

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testing (DST). Of these total isolates, studies reported 26,392 (22.13%) isolates from previously treated patients and 32,117 (26.93%) from newly diagnosed cases. For the remaining 60,733 (50.93%) isolates, a bifurcation of sample derived from new versus previously treated patients was not specified.

Drug-resistance in Overall Clinical samples

The prevalence for ADR across the complete study period of 25 years was 33.67% (95% CI: 33.32–34.01, n = 24450). The proportion of MDR was 11.69% (95% CI: 11.50–11.87, n = 17818) in overall; and 1.03% (95% CI: 0.922–1.148, n = 724) and 23.87% (95% CI: 23.36–24.385, n = 7124) in new and previously treated patients, respectively. Among the individual drugs, mono-resistance to isoniazid (INH) was highest 8.59% (95% CI: 8.38–8.80, n = 6639) followed by streptomycin 4.08% (95% CI: 3.86–4.31, n = 1767). Mono-resistance to rifampicin was 2.83% (95% CI: 2.71–2.96, n = 2707). Significant heterogeneity was observed between the studies as indicated by high I^2 values (93.08–99.45%) (**Table 2**). The nationwide prevalence of pre-XDR TB was estimated to be 2.94% (95% CI = 2.61–3.29, n = 479) over the 25-year study period, of which 162 were due to additional resistance to a fluoroquinolone. Nationwide prevalence of XDR-TB was estimated to be 1.61% (95% CI: 1.45–1.78, n= 488) and as reported from 30 odd studies.

Table 2: Drug resistance pattern for overall clinical samples across complete study period

Total isolates	No. of Studies	N (No. detected)	Isolates tested	Proportion percent (95% CI)	I^2	P	Tau square	P
Any DR Overall	106	24450	70411	33.668 (33.319-34.018)	99.45%	<0.0001	0.1071	0.1039
MDR_Total	143	17818	117415	11.688 (11.505 - 11.873)	99.47%	<0.0001	0.00493	0.9304
MDR_Prev Treated	58	7124	26731	23.87 (23.36-24.385)	99.17%	<0.0001	0.08783	0.3301
MDR_New	44	724	31489	1.031 (0.922-1.148)	97.76%	<0.0001	0.1037	0.3211
Isoniazid mono-resistance	100	6639	70193	8.594 (8.388-8.803)	97.16%	<0.0001	0.06612	0.3297
Rifampicin mono-resistance	87	2707	68992	2.833 (2.710-2.959)	97.72%	<0.0001	0.1370	0.0602
Pyrazinamide mono-resistance	13	61	7140	0.345 (0.223-0.510)	93.08%	<0.0001	0.4359	0.0381
Ethambutol mono-resistance	47	596	24330	0.959 (0.84-1.089)	97.47%	<0.0001	0.3571	0.0004
Streptomycin mono-resistance	58	1767	30385	4.082 (3.862-4.310)	97.75%	<0.0001	0.0533	0.5543
Pre-XDR	13	479	9770	2.939 (2.613-3.293)	98.87%	<0.0001	0.333	0.1127

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Extensive drug resistance (XDR)	30	488	23179	1.613 (1.455-1.784)	94.56%	<0.0001	0.1912	0.1378

Drug-resistance in pulmonary isolates

The prevalence of ADR in pulmonary samples across the study period was 34.14% (95% CI: 33.982–34.70, n = 23402) and MDR overall was 11.43% (95% CI: 11.24–11.62, n = 16326). In new and previously treated pulmonary cases, MDR was seen 0.89% (95% CI: 0.78–1.0, n = 618) and 24.06% (95% CI: 23.54–24.60, n = 6759) respectively. Mono-resistance was highest to isoniazid 8.63% (95% CI: 8.42–8.84, n = 6489), followed by streptomycin 4.21% (95% CI: 3.98–4.44, n = 1752), rifampicin 2.77% (95% CI: 2.65–2.90, n = 2568), ethambutol 0.89% (95% CI: 0.78–1.03, n = 552), and pyrazinamide 0.32% (95% CI: 0.20–0.48, n = 55). Pre-XDR was seen in 3.02% (95% CI: 2.68–3.38, n=473) and XDR in 1.16% (1.01–1.33, n = 265) (**Table 3**).

Table 3: Drug resistance pattern in pulmonary samples for complete study period

Pulmonary	**No. of Studies**	**N (No. detected)**	**Isolates tested**	**Proportion percent (95% CI)**	**I^2**	**P**	**Tau square**	**P**
Any DR Overall	88	23402	66379	34.140 (33.982-34.705)	99.51%	<0.0001	0.1088	0.1334
MDR_Total	116	16326	108220	11.434 (11.245-11.625)	99.56%	<0.0001	0.0178	0.7763
MDR_Prev Treated	51	6759	25095	24.065 (23.538-24.598)	99.24%	<0.0001	0.06206	0.5204
MDR_New	37	618	30323	0.891 (0.788-1.003)	97.85%	<0.0001	0.01953	0.8649
Isoniazid mono-resistance	84	6489	68194	8.63 (8.421-8.843)	97.58%	<0.0001	0.02641	0.7221
Rifampicin mono-resistance	74	2568	66535	2.776 (2.652-2.903)	97.98%	<0.0001	0.133	0.0936
Pyrazinamide mono- resistance	11	55	7063	0.320 (0.202-0.481)	93.38%	<0.0001	0.3818	0.1021
Ethambutol mono-resistance	41	552	23282	0.895 (0.778-1.025)	97.68%	<0.0001	0.3568	0.0010
Streptomycin mono-resistance	50	1752	29310	4.212 (3.985-4.446)	98.02%	<0.0001	0.0245	0.8016
Pre-XDR	11	473	9438	3.017 (2.681-3.382)	99.04%	<0.0001	0.3818	0.1021
Extensive drug resistance (XDR)	22	265	17238	1.16 (1.005-1.331)	93.28%	<0.0001	0.1696	0.2694

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Drug-resistance in extrapulmonary isolates

The prevalence of overall MDR among extrapulmonary patients was 11.92% (95% CI: 10.11–13.92, n = 140) with 5.27% (95% CI: 3.28–7.96, n=22) in new and 15.52% (95% CI: 11.32–20.19, n=39) in previously treated cases. ADR was seen in 32.48% cases (95% CI: 29.364–35.712, n=285) and XDR in 0.83% cases (95% CI: 0.07–3.29, n=1). Mono-resistance was seen in isoniazid, ethambutol, rifampicin and streptomycin: 7.25% (95% CI: 5.64–9.14, n=68), 3.05% (95% CI: 1.99–4.43, n=40), 2.63% (95% CI: 1.68–3.92, n=25), and 0.87% (95% CI: 0.36–1.76, n=8), respectively. Drug-resistance pattern in EPTB is depicted in **Table 4**.

Table 4: Drug resistance pattern in extrapulmonary samples across complete study period

Extrapulmonary	No. of Studies	N (No. detected)	Isolates tested	Proportion percent (95% CI)	I^2	P	Tau square	P
Any DR Overall	5	285	860	32.478 (29.364-35.712)	95.81%	<0.0001	0.000	>0.0001
MDR_Total	7	140	1152	11.919 (10.109-13.925)	78.45%	<0.0001	0.0476	0.8806
MDR_Prev Treated	2	39	255	15.52 (11.319-20.193)	0.00%	<0.0001	1	0.3173
MDR_New	2	22	393	5.271 (3.284-7.958)	89.95%	<0.0001	1	0.3173
Isoniazid mono-resistance	5	68	898	7.245 (5.641-9.135)	82.32%	0.0002	-0.20	0.6242
Rifampicin mono-resistance	4	25	875	2.632 (1.678-3.919)	83.16%	0.0005	0.333	0.4969
Pyrazinamide mono- resistance	Not reported	Not reported	Not reported	NA	NA	NA	NA	NA
Ethambutol mono-resistance	3	40	837	3.045 (1.991-4.443)	97.20%	<0.0001	0.333	0.6015
Streptomycin mono-resistance	3	8	837	0.874 (0.362-1.765)	76.52%	0.0141	1	0.1172
Pre-XDR	1	4	10	NA	NA	NA	NA	NA
Extensive drug resistance (XDR)	2	1	199	0.831 (0.0739-3.289)	0.00%	0.6730	1	0.3173

Drug-resistance in isolates from paediatric patients

ADR was seen in 9.94% paediatric cases (95% CI: 8.60–11.42, n=184). The prevalence of overall MDR among paediatric sub-group of patients was 9.06% (95% CI: 7.91–10.33, n = 223). Mono-resistance was observed to be maximum in isoniazid, followed by rifampicin: 7.82% (95% CI: 5.80–10.27, n=46), and 7.62% (95% CI: 6.13–9.34, n=102), respectively. Prevalence in XDR was seen in 0.95% cases (95% CI: 0.54–1.54, n=16). **Table 5** depicts the prevalence pattern in paediatric patients.

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Table 5: Drug resistance pattern in paediatric patients for complete study period

Paediatric samples	No. of Studies	N (No. detected)	Isolates tested	Proportion percent (95% CI)	I^2	P	Tau square	P
Any DR Overall	5	184	1796	9.943 (8.599-11.419)	91.77%	<0.0001	0.40	0.3272
MDR_Total	7	223	2236	9.063 (7.907-10.328)	95.19%	<0.0001	0.333	0.2931
MDR_Prev Treated	2	115	440	26.235 (22.191-30.599)	0.00%	0.5528	-1.0	0.3173
MDR_New	1	5	127	NA	NA	NA	NA	NA
Isoniazid mono-resistance	5	46	591	7.822 (5.796-10.277)	55.63%	0.0607	0.40	0.3272
Rifampicin mono-resistance	5	102	1106	7.623 (6.131-9.343)	95.70%	<0.0001	0.00	>.0001
Pyrazinamide mono-resistance	1	5	17	NA	NA	NA	NA	NA
Ethambutol mono-resistance	1	2	127	NA	NA	NA	NA	NA
Streptomycin mono-resistance	2	4	144	3.197 (0.994-7.501)	0.00%	0.5816	-1.00	0.3173
Pre-XDR	NR	NR	NR	NA	NA	NA	NA	NA
Extensive drug resistance (XDR)	2	16	1645	0.948 (0.538-1.544)	81.63%	0.0194	-1.00	0.3173

Zone-wise prevalence

The prevalence of ADR-TB for the clinical samples examined was highest in Central followed by the Eastern region as reported by 5 and 14 studies: 53.87% (95% CI = 51.06–56.69, n = 1411) and 53.69% (95% CI = 50.94–56.44, n = 1447) respectively. The same was lowest in the Northern region with estimated prevalence of 38.54% (95% CI = 37.62–39.46, n = 6727) during the entire study period. The Eastern states were estimated to have the maximum prevalence of MDR-TB with 36.38%, (95% CI = 34.05; 38.70, n = 1082) followed by the Northern zone, 25.65% (95% CI = 22.59–28.71, n = 7692); and while the Central states reported the least with 13.91% (95% CI = 12.43−15.39, n = 339).

Period-prevalence estimates

There was a significantly increasing trend in the prevalence of ADR and MDR (total) types of resistance in the first 3 periods (1996-2000, 2001-2005, 2006-2010) and the reverse in the last 2 periods (2011-2015, 2016-2020). Country-wide estimates for ADR-TB was 22.30% (95% CI: 20.39–24.30, n=410) for the period 1996-2000, 45.75% (95% CI: 44.61–46.90, n= 3377) for 2001-2005, 45.00% (95% CI: 47.20–48.80, n= 7428) for the period 2006-2010, 37.52% (95% CI: 36.87–38.18, n= 8055) for the period 2011-2015, and 20.41 (95% CI: 19.91–20.91, n= 5180) for the period 2016-2020. Likewise, for MDR-TB (total) the estimates were 4.78% (95% CI: 3.84–

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5.87, n= 95) for 1996-2000, 13.40% (95% CI: 12.66–14.17, n= 1283) for 2001-2005, 27.55% (95% CI: 26.85–28.27, n= 4773) for 2006-2010, 20.46% (95% CI: 19.98–20.95, n= 6165) for 2011-2015, and 6.30% (95% CI: 6.121–6.493, n= 5502) for 2016-2020. Forest Plots for ADR and MDR across the five study periods are depicted in **Figures 2-11**.

Figure 2: Forest plot showing ADR prevalence across all clinical samples for the period 1996-2000

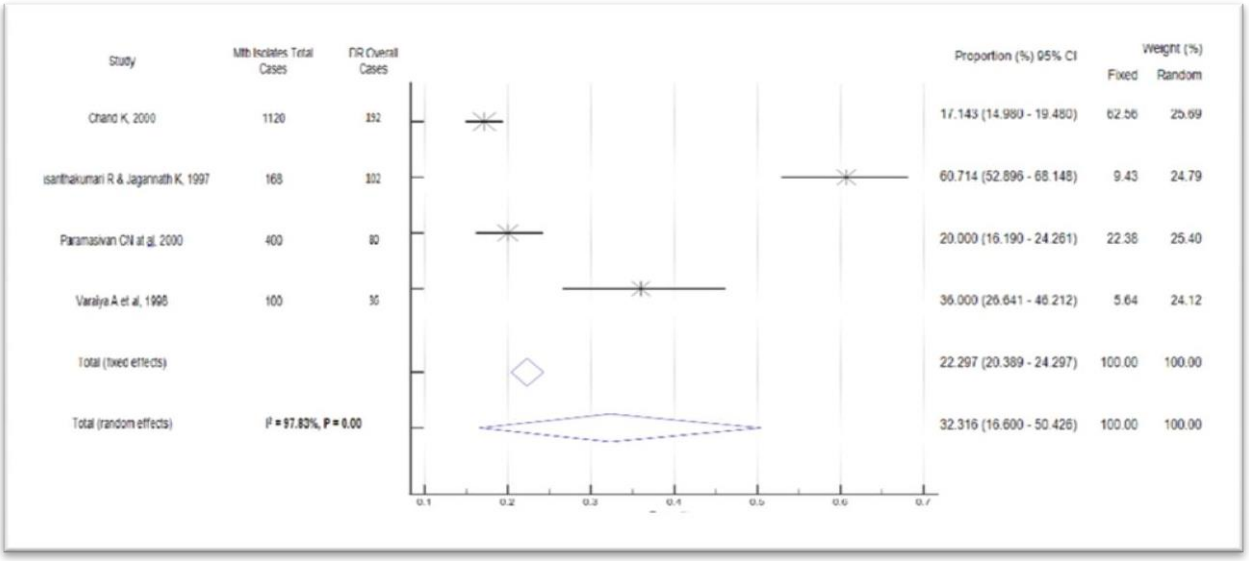

Figure 3: Forest plot showing ADR prevalence across all clinical samples for the period 2001-2005

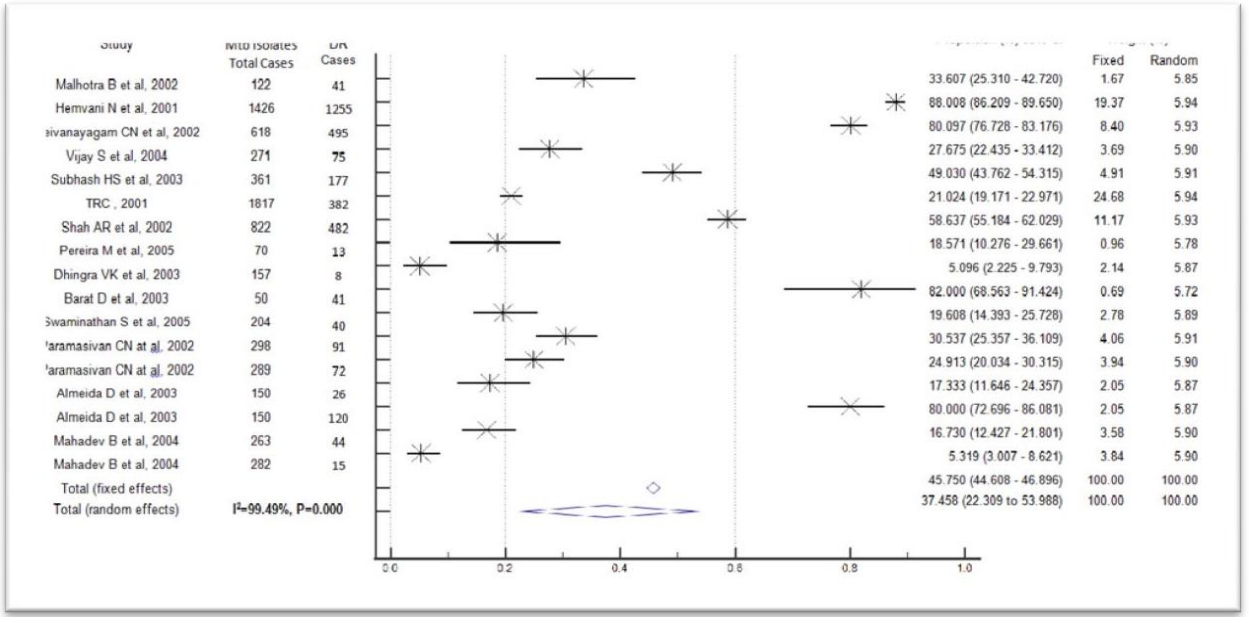

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Figure 4: Forest plot showing ADR prevalence across all clinical samples for the period 2006-2010

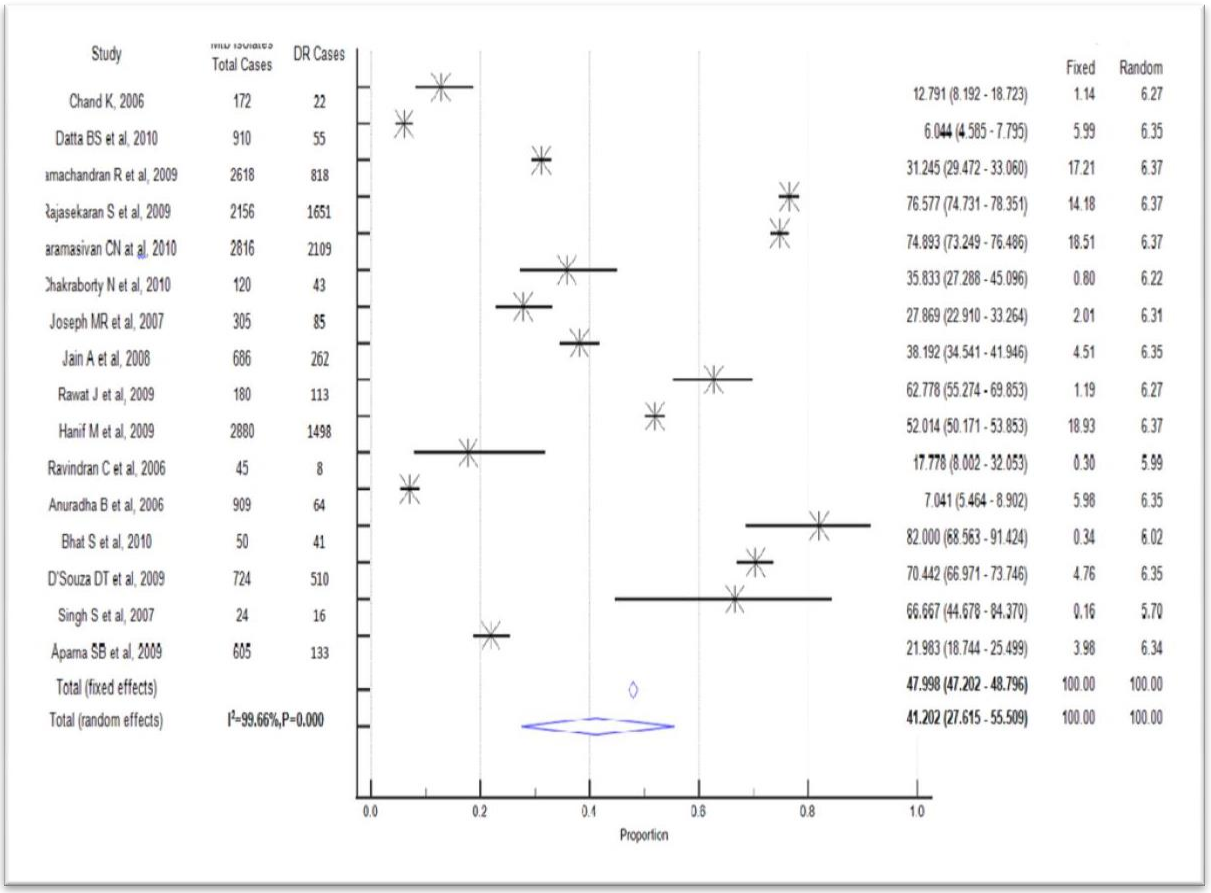

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Figure 5: Forest plot showing ADR prevalence across all clinical samples for the period 2011-2015

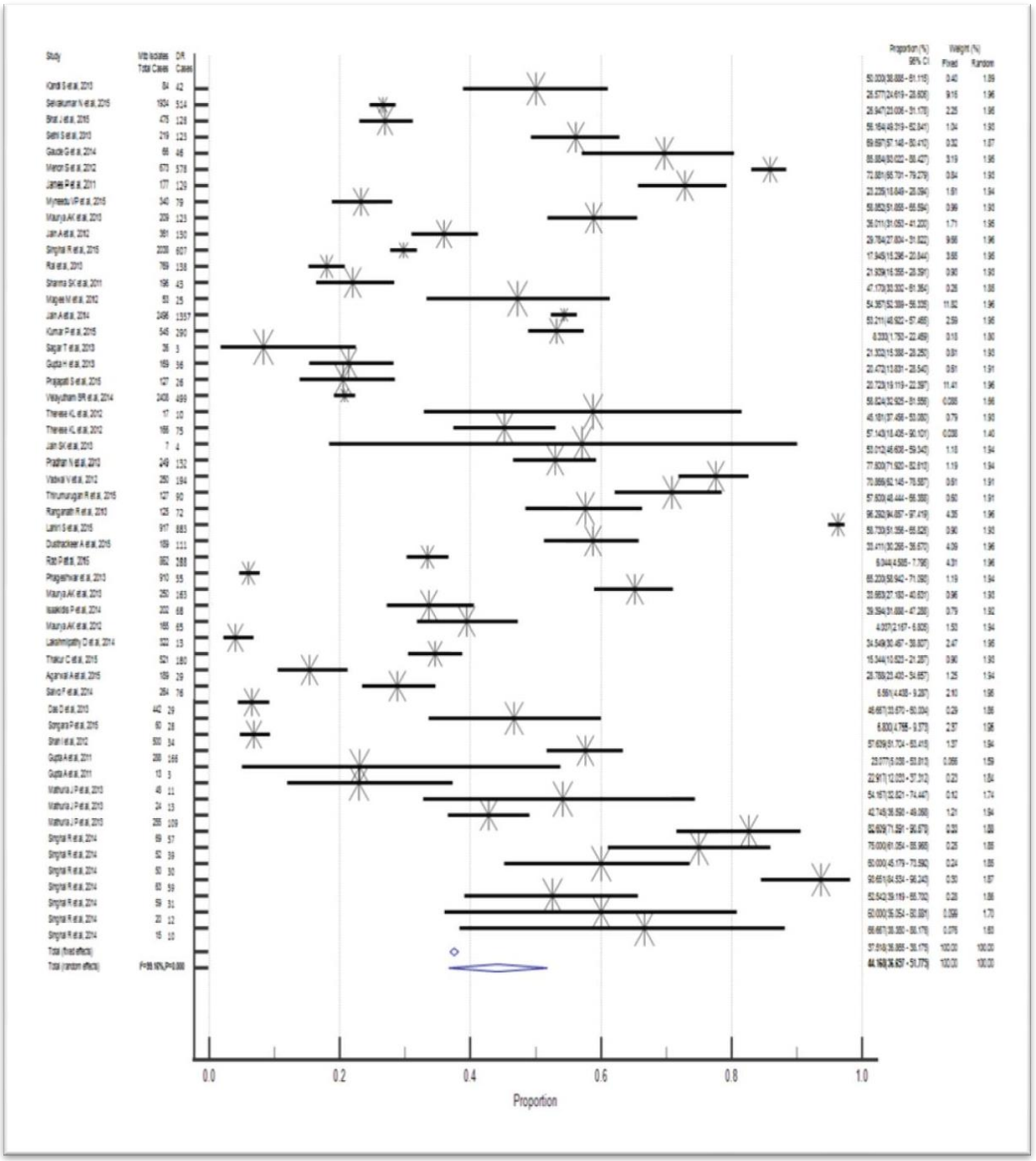

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Figure 6: Forest plot showing ADR prevalence across all clinical samples for the period 2016-2020

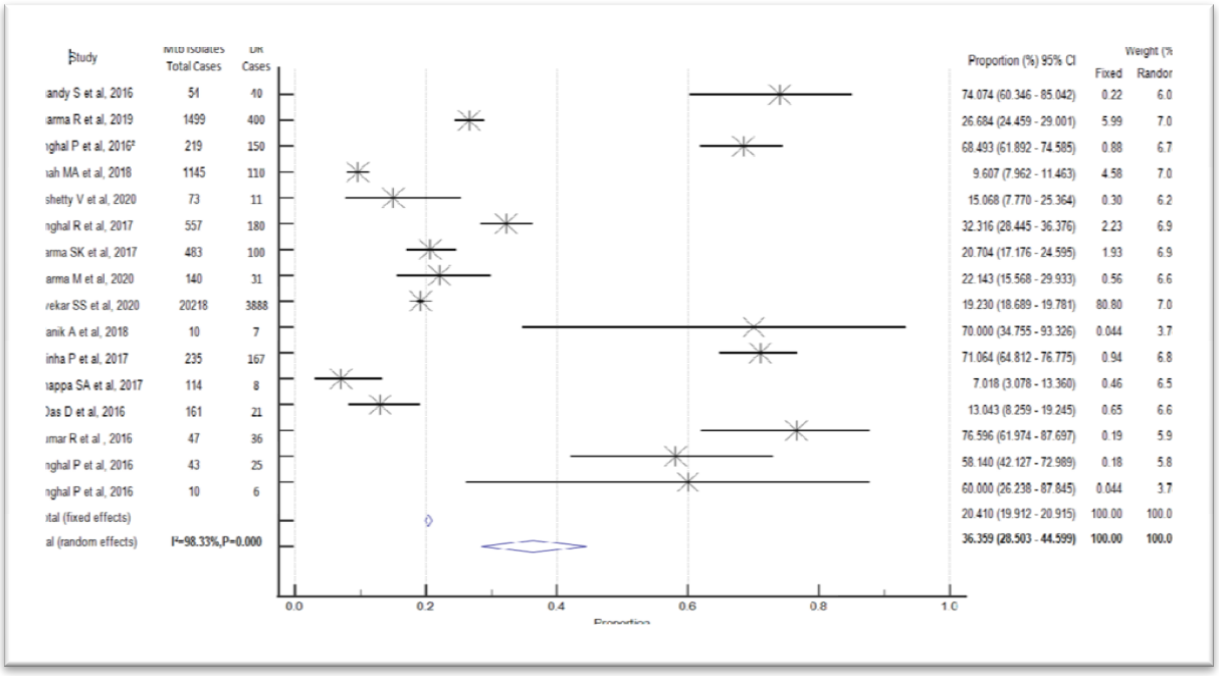

Figure 7: Forest plot showing MDR prevalence across all clinical samples for the period 1996-2000

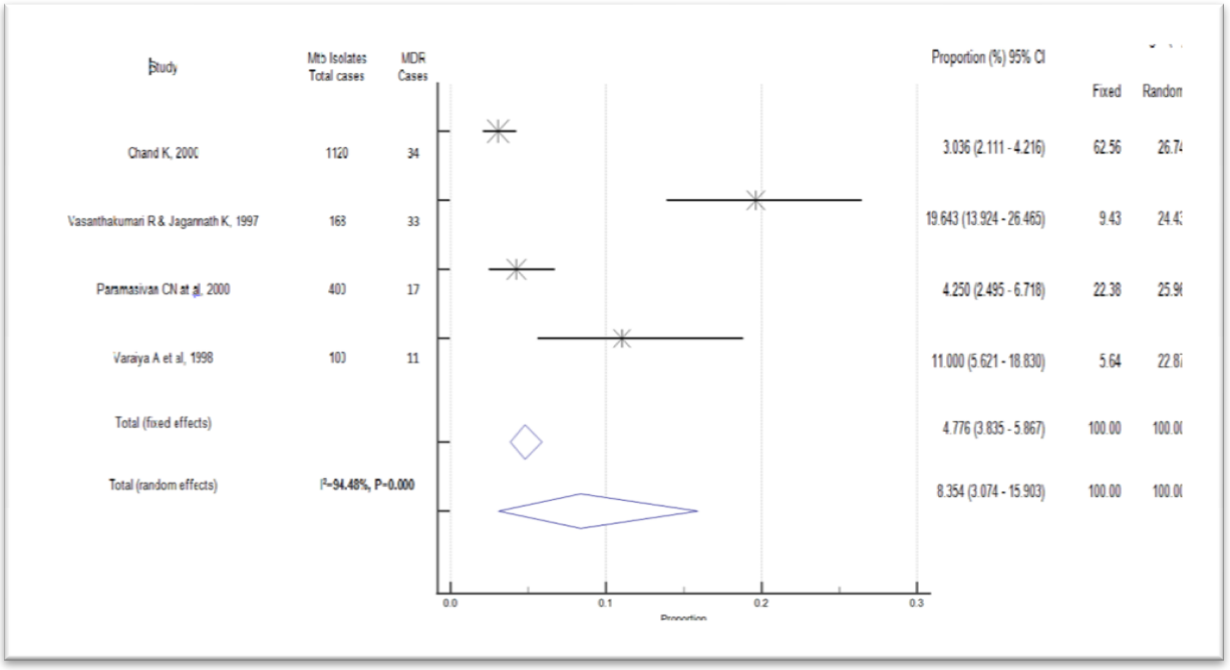

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Figure 8: Forest plot showing MDR prevalence across all clinical samples for the period 2001-2005

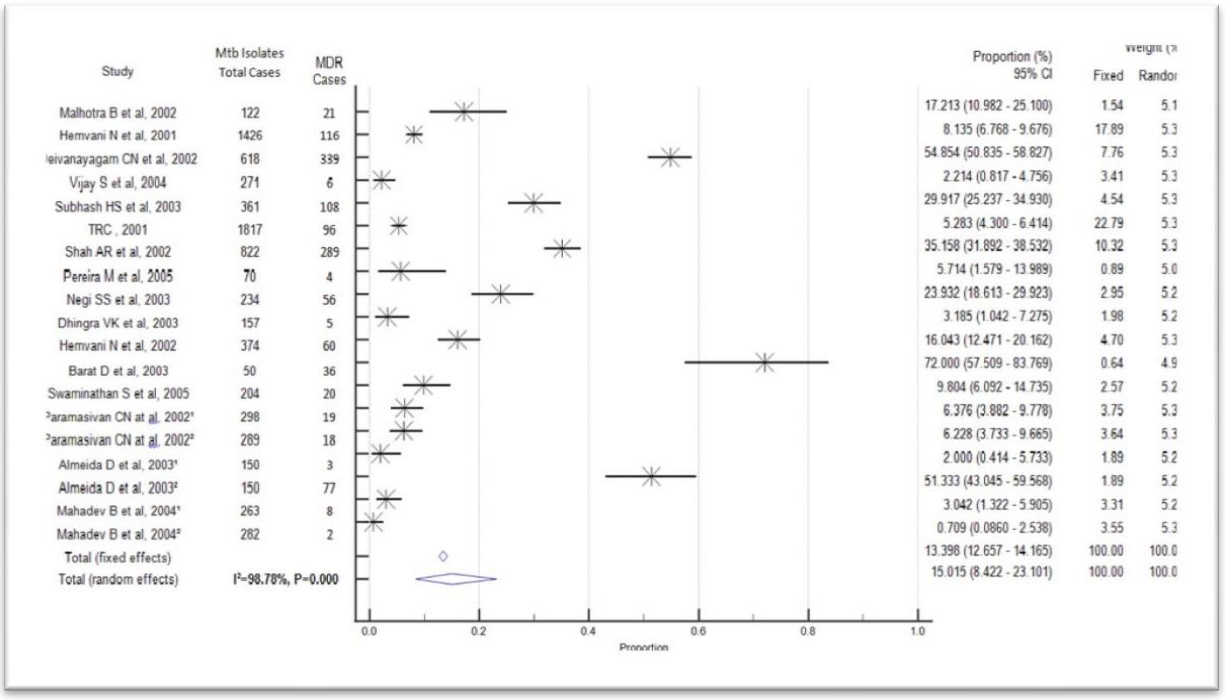

Figure 9: Forest plot showing MDR prevalence across all clinical samples for the period 2006-2010

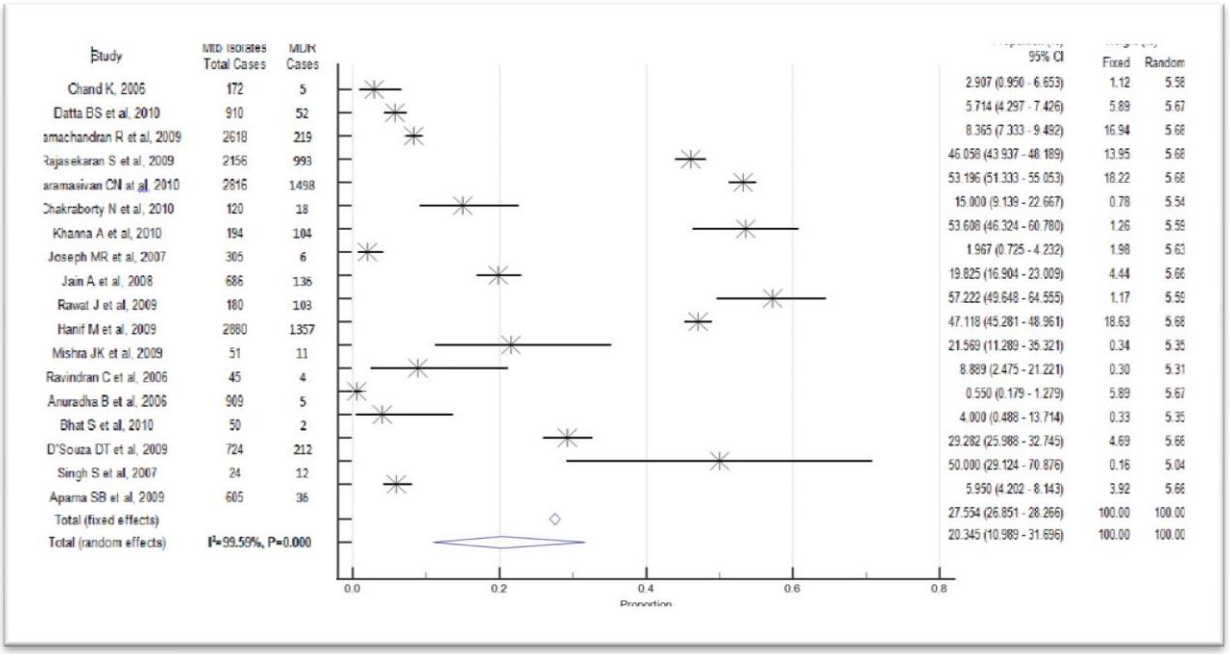

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Figure 10: Forest plot showing MDR prevalence across all clinical samples for the period 2011-2015

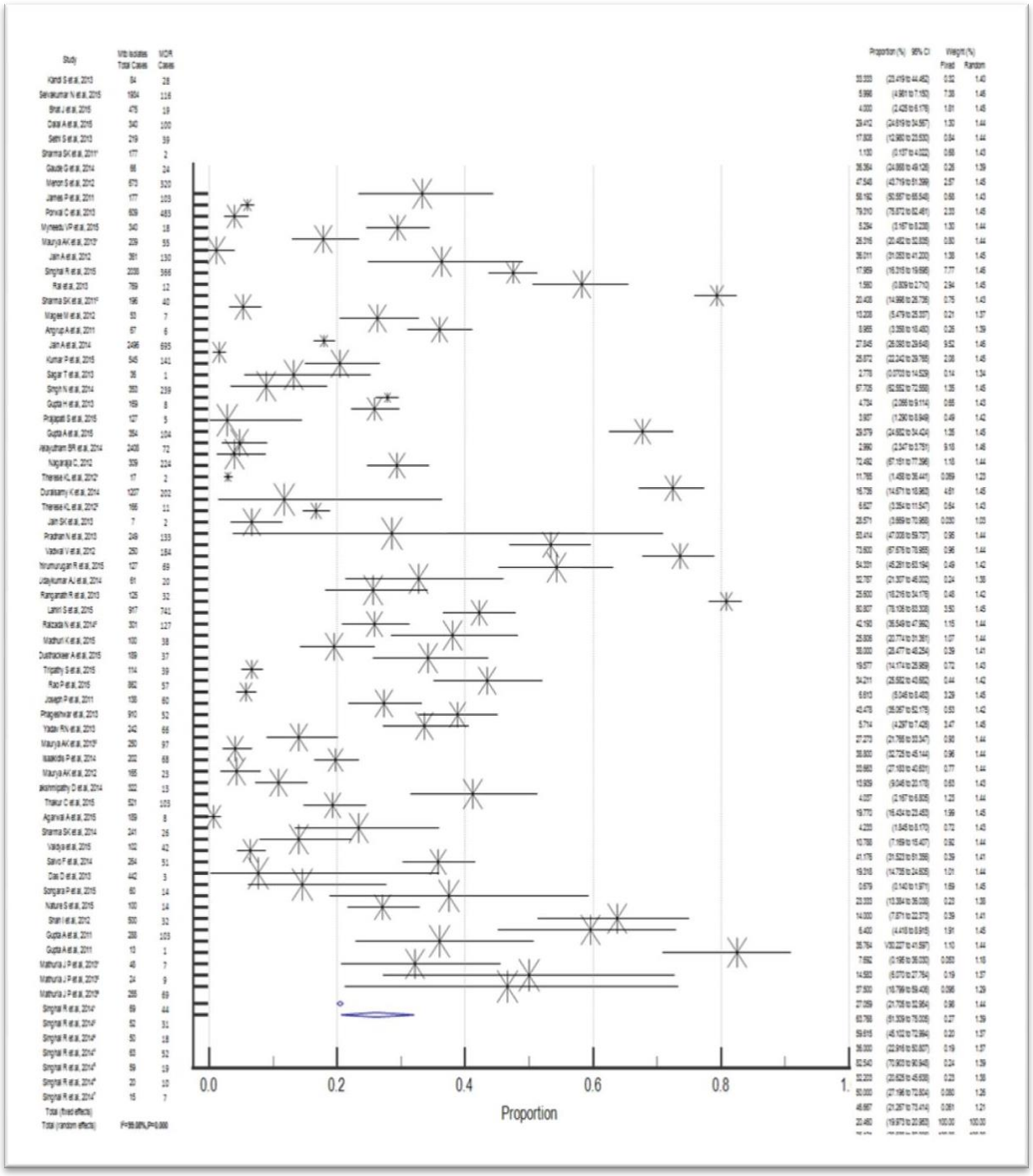

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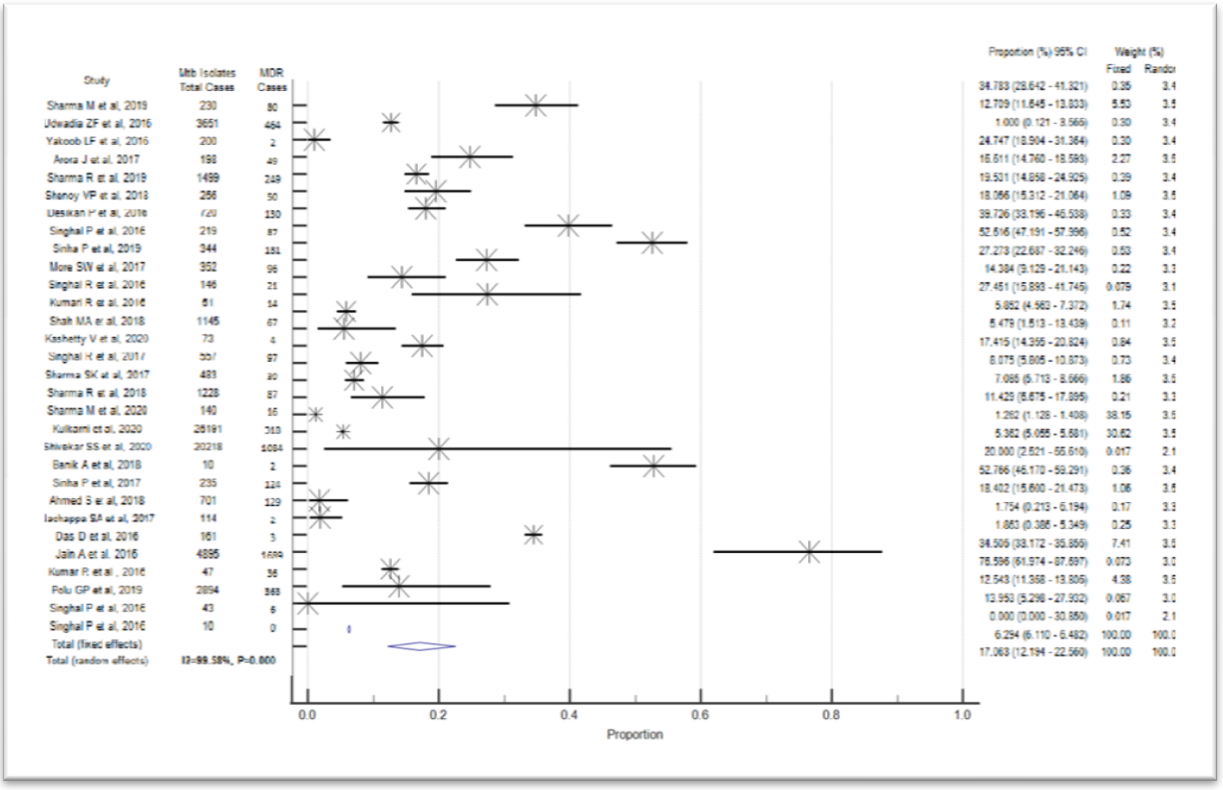
Figure 11: Forest plot showing MDR prevalence across all clinical samples for the period 2016-2020



In newly diagnosed MDR cases, a rise in prevalence was seen in the periods 2001-2005, 2006-2010, and 2011-2015 while for the previously diagnosed, the reverse was seen in the periods 2006-2010, 2011-2015, and 2016-2020. Among the individual drugs, mono-resistance to isoniazid (INH) was highest 8.59% (95% CI: 8.38–8.80, n = 6639) in the country-wide prevalence for the 25-year study period. Lowest mono-resistance was seen in pyrazinamide (Z) with 0.345% (95% CI: 0.22–0.51, n= 61). Period prevalence for the five-yearly spans for various types of drug-resistance is provided in **Table 6**.

Table 6: Period prevalence estimates for various types of drug-resistance across all clinical samples.

Period	Drug resistance	N	Prevalence estimate (95% CI)	Heterogeneity test (I^2)
1996 to 2000	Any drug-resistance	410	22.297 (20.389-24.297)	97.83%
	Multidrug resistance-total	95	4.776 (3.835-5.867)	94.48%
	MDR-Previously treated	33	NR	NR
	MDR-Newly diagnosed	NR	NR	NR
	Isoniazid mono-resistance	45	2.50 (1.776-3.415)	97.07%

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	Streptomycin mono-resistance	58	3.763 (2.864-4.845)	86.40%
	Rifampicin mono-resistance	31	1.967 (1.331-2.798)	88.09%
	Pyrazinamide mono-resistance	4	NR	NR
	Ethambutol mono-resistance	3	0.223 (0.0525-0.614)	53.31%
	Pre-XDR	NR	NR	NR
	XDR	NR	NR	NR
2001 to 2005	Any drug-resistance	3377	45.75 (44.608-46.896)	99.49%
	Multidrug resistance-total	1283	13.398 (12.657-14.165)	98.78%
	MDR-Previously treated	909	21.354 (20.039-22.715)	99.06%
	MDR-Newly diagnosed	90	3.756 (2.991-4.650)	84.86%
	Isoniazid mono-resistance	763	11.564 (10.723-12.447)	98.93%
	Streptomycin mono-resistance	410	6.189 (5.552-6.875)	97.73%
	Rifampicin mono-resistance	362	3.375 (2.849-3.967)	99.45%
	Pyrazinamide mono-resistance	NR	NR	NR
	Ethambutol mono-resistance	296	4.983 (4.190-5.877)	99.22%
	Pre-XDR	NR	NR	NR
	XDR	NR	NR	NR
2006 to 2010	Any drug-resistance	7428	47.998 (47.202-48.796)	99.66%
	Multidrug resistance-total	4773	27.554 (26.851-28.266)	99.59%
	MDR-Previously treated	3252	41.708 (40.60-42.822)	99.25%
	MDR-Newly diagnosed	221	3.962 (3.375-4.618)	98.11%
	Isoniazid mono-resistance	674	4.714 (4.335-5.117)	98.12%
	Streptomycin mono-resistance	524	2.455 (2.167-2.770)	99.34%
	Rifampicin mono-resistance	185	0.604 (0.470-0.765)	98.30%
	Ethambutol mono-resistance	136	0.334 (0.232-0.466)	98.24%
	Pyrazinamide mono-resistance	8	0.0705 (0.0132-0.215)	89.33%
	Pre-XDR	51	0.935 (0.377-1.739)	85.89%
	XDR	151	1.472 (1.234-1.742)	92.19%
2011 to 2015	Any drug-resistance	8055	37.518 (36.865-38.175)	99.16%
	Multidrug resistance-total	6165	20.460 (19.973-20.953)	99.08%
	MDR-Previously treated	1622	33.664 (32.307-35.041)	97.99%
	MDR-Newly diagnosed	301	4.931 (4.319-5.60)	96.27%
	Isoniazid mono-resistance	1507	7.028 (6.673-7.396)	93.22%
	Streptomycin mono-resistance	756	5.159 (4.774-5.566)	95.25%
	Rifampicin mono-resistance	896	3.499 (3.246-3.766)	95.54%
	Pyrazinamide mono-resistance	49	1.323 (0.882-1.904)	93.12%
	Ethambutol mono-resistance	155	1.34 (1.113-1.601)	88.21%
	Pre-XDR	385	6.432 (5.712-7.212)	98.98%
	XDR	101	1.085 (0.844-1.372)	92.11%
	Any drug-resistance	5180	20.410 (19.912-20.915)	98.33%
	Multidrug resistance-total	5502	6.305 (6.121-6.493)	99.57%
	MDR-Previously treated	1308	10.877 (10.291-11.484)	99.02%

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2016 to 2020	MDR-Newly diagnosed	112	0.216 (0.158-0.288)	97.64%
	Isoniazid mono-resistance	3650	11.217 (10.875-11.566)	88.72%
	Streptomycin mono-resistance	19	1.632 (0.927-2.656)	83.62%
	Rifampicin mono-resistance	1233	3.518 (3.320-3.724)	96.08%
	Pyrazinamide mono-resistance	NR	NR	NR
	Ethambutol mono-resistance	6	0.761 (0.310-1.550)	0.00%
	Pre-XDR	43	43.119 (33.396-53.248)	16.28%
	XDR	236	2.305 (1.985-2.662)	97.14%

DISCUSSION

According to us, this is the most comprehensive and updated review on anti-TB drug resistance in India on clinical isolates including pulmonary as well as extrapulmonary samples tested (Hanif et al., 2005; Sharma et al., 2011).

The pooled prevalence of any drug resistance for overall clinical samples was 33.67%. MDR was 1.01% among new and 23.87 % among previously treated patients. Among the primary drugs, the highest mono-resistance was for INH followed by pyrazinamide. We also found that the pooled prevalence of MDR among paediatric patients was 9.94%. For pulmonary cases, ADR overall was found to be around 34.14% and the MDR (total) prevalence was found to be 11.43%. In new and previously treated pulmonary patients, prevalence of MDR was found to be 0.89% and 24.07% respectively. As compared to the estimates from the national survey, ADR in pulmonary cases estimated by us was found to be higher than the national survey (28%); and likewise, for MDR (total) and previously treated MDR patients also (6.19% and 11.62%, respectively). Among new patients our estimate was lower to that reported by the national survey (2.84%) (Ministry of Health and Family Welfare. Report of the First National Anti Tuberculosis Drug Resistance Survey: India 2014–16. 2018). MDR among previously treated patients from our analysis was similar to the WHO Global TB report and findings reported in other studies (Goyal et al., 2019; Nasiri et al., 2014; Dual et al., 2016; Onyedum et al., 2017).

Several factors have been shown to be associated with DR-TB: previous history of treatment, delay in treatment initiation, male sex, treatment side effects, and insufficient duration of treatment being are some of them (Liang et al., 2012; Garg et al., 2014). In our analysis, prevalence of ADR was significantly higher as it is known that hospital-based studies tend to include a higher risk pool of patients, especially those with complications. Totally drug resistant (TDR)-TB have also been reported by AA Velayati et al in a study from Mumbai (Velayati et al., 2013).

With more priority given to MDR and XDR in programmatic conditions, resistance to individual drug estimates is often ignored. In our analysis, we only assessed mono-resistance in individual drugs, and among the total sample, INH mono-resistance was reported as more than 8.5%. This indicates a worrying trend as individual drug resistances often go hand-in-hand and unnoticed, when treatment and diagnosis is more focussed on MDR.

We attempted to estimate the burden of DR-TB using standard WHO indicators and definitions so that estimates can be compared with other countries over time. Many policy outcomes stem

from the findings of this review, including estimates on mono-drug resistance and the time trends or period prevalence of combined clinical samples for the first time. We could also provide included estimates for extrapulmonary TB in this study, which previous studies have not reported.
The review suffers from certain limitations important epidemiological determinants such as residence (rural or urban), age and sex could not be examined in this review, because the primary studies rarely reported such information in a standard manner. Further, as most of the studies were hospital based the possibility of selection bias could not be ruled out, but our estimates are likely to be less biased than the national survey which was solely based out of hospitals and clinics.

The burden of drug resistance among TB patients in India is staggering and the prevalence of tuberculosis among new patients is particularly worrisome. Accurate estimates of the increasing primary bacterial resistance, which is a grave threat to TB control should be sought and prioritized. The burden of DR-TB in vulnerable sub-populations such as HIV and paediatric patients is of particular concern and should be researched further. Generating awareness within the community regarding DR-TB burden and its prevention and consequences can also help in reducing the transmission and improve the diagnosis and treatment rates of DR-TB. It has been understood that for TB elimination, control of DR-TB is imperative. Role of the private sector stakeholders should also be examined, and services incorporated to the national control programs to ensure coverage to an additional group of patients that seek medical help from private practitioners. Their role in operational research in providing valuable data through development of new tools should also be explored.

CONCLUSIONS

Ours is an analysis of data on various forms of drug-resistance from epidemiological studies which aimed to estimate the prevalence of drug-resistance in clinical samples. These results do not reflect the real-world situation as samples were obtained from patients suspected with drug-resistance, following varied inclusion criteria across the primary studies. Overall, we feel that using novel diagnostic tools, proper surveillance methods, and providing readily available treatment to all patients with high risk like previous exposure to anti-TB drugs can help control the problem of DR-TB. Indiscriminate use of chemotherapeutic drugs should be prevented, and induction of novel drugs should be considered in the national programs in a phased manner. The present study reports a high prevalence of DR-TB across the 25-year study period and highlights the gaps in the present programmatic treatment. The need for newer formulations or regimens having unique mode of action is also necessary. In a country like India, where conducting cross-sectional surveys are costly and time consuming, programmatic activities should be overseen critically for proper implementation and emphasis should be laid on innovation and usage of newer tools for rapid diagnosis as well as and for proper estimation of the epidemiological burden. Drug-resistance estimates reported from national programs are often based on samples of population that are already at high risk or for which incidence and recurrence are already monitored and treatment provided. Survey on TB patients recruited pan India without considering the risk of resistance should be conducted for a true picture. As the private sector is also heavily involved as a major part of the healthcare system, government approved standardized regimens and novel treatments options should be propagated to the private sector as well. Position of the

private sector in development of novel strategies for disease control and to track and report the burden of disease can be further explored. Registries that are already in place can be further developed to provide real-world figures of the incidence and prevalence of the disease area-wise.

APPENDIX/SUPPLEMENT

The Appendix containing attributes of the included studies can be made available on request.

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CONFLICT OF INTEREST

There is no conflict of interest to be pronounced by the authors for this study.

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