Original Article

# Prevalence of multidrug resistance tuberculosis in adult patients in India: A systematic review and meta-analysis

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## Abstract

**Background:** Multidrug resistance tuberculosis (MDR-TB) is an important public health problem for India but there is a paucity of data related to the prevalence of MDR-TB in India. This systematic review and meta-analysis was designed to synthesize evidence regarding the prevalence of MDR-TB in adult patients in India. **Methods:** PubMed and Google Scholar were searched to find different observational studies reporting MDR-TB prevalence in India. Data related to MDR-TB prevalence were pooled for the analysis. PubMed was searched by using different MeSH words. Prevalence was reported with 95% confidence interval (CI). A separate analysis was done for new cases and previously treated cases. Random effect model was used and heterogeneity was assessed by $I^2$ and Cochran Q test. **Results:** MDR-TB prevalence in new cases were 3% (95% CI 2%-5%, $I^2$ = 95.3%). There was difference in prevalence between different methods of measurement of MDR-TB and study designs. MDR-TB prevalence in previously treated cases was found to be 35% (95% CI 29%-41%, $I^2$ = 98.7%). Results vary with the method of measurement as well as the study design. **Conclusion:** MDR-TB prevalence in previously treated patients was found higher compared to the reported values in national surveys. There is a need for large scale cross-sectional study to verify the findings observed in this review.

**Keywords:** India, multidrug resistance tuberculosis, prevalence, resistance, tuberculosis

## Introduction

Tuberculosis is one of the major causes of mortality worldwide and the leading cause of death.[1] In WHO 2017 report, 3.5% of new cases and 18% of previously treated cases are estimated to be multidrug-resistant tuberculosis.[2] The treatment of MDR-TB is complex and requires a long duration of therapy and toxic drugs.[3,4] Moreover, facility to diagnose MDR-TB is not readily available in low- and middle-income countries.[5] The success rate of MDR-TB treatment is much lower compared to drug sensitive TB. Only 54% patients with MDR-TB completed treatment and death rate was 16% according to the WHO report.[2] Some patients with MDR-TB may survive for many months, and therefore, the transmission and spread of infection from such patients is a major limiting factor for End TB strategies.[6]

India accounts for the highest number of TB cases in the world and about one-fourth of global TB burden.[6] A total of approximately one hundred and thirty thousand incident multidrug resistant patients with TB emerge annually in India which includes approximately 79,000 patients with MDR-TB among notified pulmonary cases.[6] First National Drug Resistance Survey results showed the rates of MDR among

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new patients with TB to be 2.84% and that in previously treated patients to be 11.60%.[7] In 2002, the Global Fund to Fight AIDS, TB and Malaria (GFATM) started financing TB programs, including DR-TB, thus greatly reducing the economic barrier to India for DR-TB.[8] Detection and treatment of MDR-TB is a priority in National Tuberculosis program in India. Detection of DR-TB through Revised National Tuberculosis Control Program (RNTCP) has been progressively rising with increased access to various forms of drug-sensitivity testing (DST).[9] In 2016, detection and treatment of MDR-TB has been started by RNTCP in more than 30,000 patients. However, completion of treatment and cure from MDR-TB still remain a challenge in India.[10]

To date, the rate of MDR-TB has been reported in various report and surveys from India.[11,12] However, it is likely that

**Table 1: Various studies included in the analysis for systematic review and meta-analysis**

| No | First author | Published time | Enrollment time | Province |
|---|---|---|---|---|
| 1 | Dasarathi Das | 2016 | Jan 2014-Sep 2014 | Bhubaneshwar, Odisha |
| 2 | A. Jain | 2016 | Oct 2012-Mar 2015 | Uttar Pradesh |
| 3 | R.Kumar | 2016 | Aug 2014-Apr 2015 | Lucknow district of Uttar Pradesh |
| 4 | Vithal Prasad Myneedu | 2015 | July 2011-June 2012 | Lala Ram Syrup district, New Delhi |
| 5 | Parshuram Raao | 2015 | Sep 2011-Aug 2014 | Udupi district, Karnataka |
| 6 | N. Selvakumar | 2015 | May 2011-Aug 2012 | Tamilnadu |
| 7 | R.Singhal | 2015 | Oct 2011-Dec 2012 | Delhi |
| 8 | Sunita Tripathy | 2015 | Feb 2014-July 2014 | Bihar |
| 9 | D.Das | 2014 | Feb 2012-Apr 2013 | Rayagada district, Odisha |
| 10 | Harshita Gupta | 2013 | Jan 2010-Mar 2011 | Lucknow district of Uttar Pradesh |
| 11 | Subhakar Kandi | 2013 | Dec 2010-Mar 2011 | Hyderabad |
| 12 | Chhavi Porwal | 2013 | Apr 2007-May 2010 | Delhi |
| 13 | Sunil Sethi | 2013 | Oct 2006-Feb 2010 | Chandigarh |
| 14 | R. Yadav | 2013 | 2008-2010 | Chandigarh |
| 15 | Rajendra Prasad | 2012 | Aug 2003-July 2008 | Uttar Pradesh |
| 16 | Surendra Sharma | 2011 | Feb 2008-Dec 2009 | New Delhi |
| 17 | Surendra Sharma | 2011 | Mar 2005-Mar 2008 | New Delhi |
| 18 | C. Paramasivan | 2010 | 2001-2004 | Across India |
| 19 | Desiree TB D'souza | 2009 | Apr 2004-Jan 2007 | Mumbai |
| 20 | M.Hanif | 2009 | 2006 | New Delhi |
| 21 | B. Joseph | 2009 | 1998-2005 | Kerala |
| 22 | S.Rajasekaran | 2009 | 2004-2007 | Chennai |
| 23 | R. Ramachandran | 2009 | Nov 2005-Oct 2006 | Gujarat |
| 24 | Jagdish Rawat | 2009 | Jan 2002-Dec 2006 | Dehradun, Uttarakhand |
| 25 | R.Singla | 2009 | June 2006-Feb 2008 | South Delhi |
| 26 | Amita Jain | 2008 | Nov 2000-Oct 2002 | Lucknow district of Uttar Pradesh |
| 27 | M. Joseph | 2007 | May 2004-Sep 2004 | Ernakulam district, Kerala |
| 28 | B. Anuradha | 2006 | Jan 2001-Dec 2003 | Hyderabad |
| 29 | B.Mahadev | 2005 | Aug 2000-July 2001 | Hoogli district, West Bengal |
| 30 | B.Mahadev | 2005 | Aug 2000-May 2001 | Mayurbhanj district, Orissa |
| 31 | Mycal Pereira | 2005 | Sep 2000-July 2004 | Pune |
| 32 | Sophia Vijay | 2004 | Apr 1999-Dec 1999 | Banglore, Karnataka |
| 33 | D.Barat | 2003 | Sep 1998-Sep 2000 | Patna, Bihar |
| 34 | C. Deivanayagam | 2002 | Oct 1997-May 2000 | Chennai |
| 35 | C. Paramasivan | 2002 | Feb 1999-Apr 1999 | North Arcot district, Tamilnadu |
| 36 | C. Paramasivan | 2002 | July 1999-Dec 1999 | Raichur district, Karnataka |
| 37 | A.Shah | 2002 | Jan 2000-Aug 2001 | Gujarat |
| 38 | C. Paramasivan | 2000 | Feb 1997-Mar 1997 | Tamilnadu |
| 39 | P.Gopi | 1997 | Nov 1988-Mar 1989 | Raichur district, Karnataka |
| 40 | R. Vasanthakumari | 1997 | NM | Tamilnadu |
| 41 | Manjula Dutta | 1993 | Apr 1986-Mar 1988 | North Arcot district, Tamilnadu |
| 42 | C. Paramasivan | 1993 | May 1985-Apr 1989 | North Arcot district, Tamilnadu |
| 43 | C. Paramasivan | 1993 | July 1985-June 1991 | Pondicherry district |
| 44 | Sujata Chanrasekaran | 1992 | 1985-86 | Banglore (urban), Karnataka |
| 45 | Sujata Chanrasekaran | 1992 | 1987-89 | Kolar district (rural), Karnataka |
| 46 | Sujata Chanrasekaran | 1990 | NM | Banglore, Karnataka |
| 47 | Sunil Trivedi | 1988 | Jan 1983-Dec 1986 | Amargadh, Gujarat |

NM=Not mentioned

surveys undertaken in India might underestimate the true burden of MDR-TB in India. The surveys conducted in India are mostly on smear positive TB thereby excluding smear negative and extra-pulmonary TB. Patients residing in jail and prisons were also not included in survey. Moreover, private sector contributes significantly to TB treatment but has been excluded from survey. These surveys are also limited to few metro cities. A comprehensive analysis of MDR-TB from different parts of India has not yet been performed. In addition, a reliable assessment of MDR-TB burden is needed for programmatic management in context of National tuberculosis program of India. The present systematic review and meta-analysis was designed to determine the prevalence of drug-resistant TB in adult patients in India. Results generated through this systematic review may add to the findings of the nationwide surveys regarding the prevalence of MDR-TB in India.

## Materials and Methods

### Search strategies

PubMed and Google scholar were used to find studies related to the prevalence of MDR-TB in adult patients in India. Search was restricted to the original articles published in English language. Besides references mentioned in the review articles, previously published systematic reviews and meta-analysis etc., were also explored to find any new study which may fulfill the inclusion criteria. Keywords like "tuberculosis, multidrug-resistant", "tuberculosis", "MDR-TB", "MDR Tuberculosis", "Drug Resistance", "Prevalence", "India" etc., were used in Medical Subject Headings (MeSH), titles and abstracts with the help of Boolean operators in PubMed.

### Inclusion and exclusion criteria

Observational studies which includes cross-sectional, cohort and retrospective chart reviews were included in the analysis. Studies which mention MDR-TB prevalence in new and/or previously treated patient with tuberculosis and where standard method of Drug Sensitivity Testing was used for the diagnosis were considered for the review. Review articles, meta-analyses and duplicates were removed from the analysis. Studies, which were conducted by same authors in two different timelines and included different patients, were analyzed as different studies.

### Data extraction

Different data related to the studies and not restricted to the authors, year of publication, study setting, patient sample, prevalence of various types of drug resistances were included in the analysis. Data were extracted by two investigators independently and in the case of any discrepancy the third investigator was consulted to resolve the discrepancy. Data related to MDR-TB only was pooled for the analysis. Standard definitions for new cases, old cases and MDR-TB were used for characterization.

### Statistical analysis

Statistical analysis was done by using STATA software. Data were represented as pooled proportion with 95% CI. Random

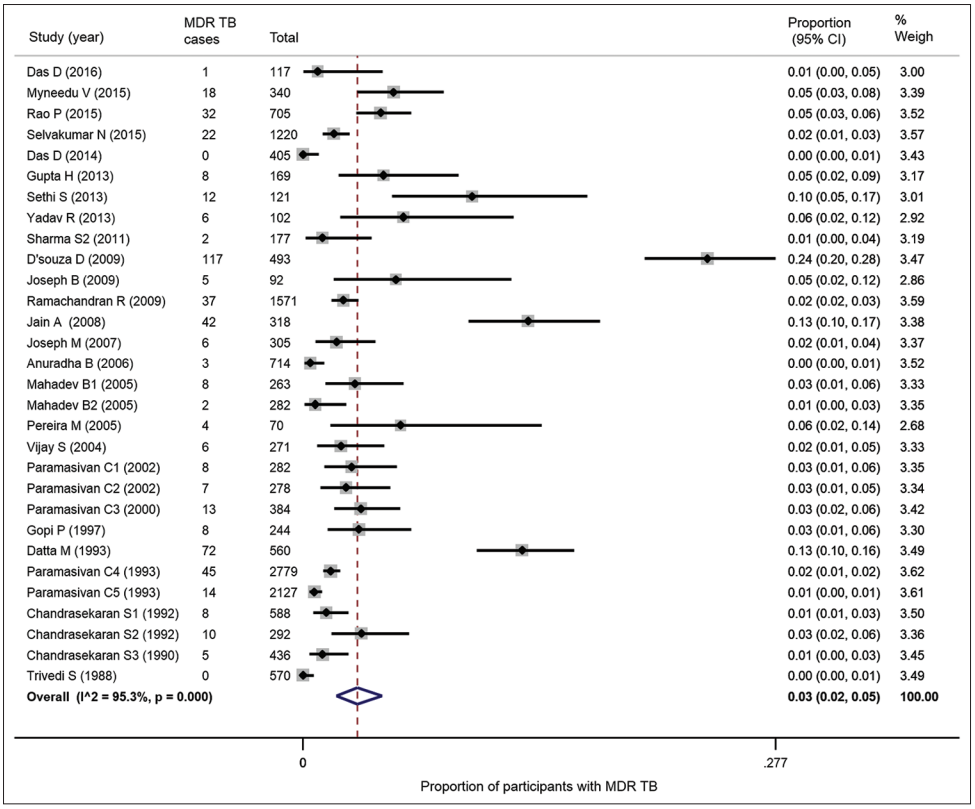



**Figure 1:** Prevalence of MDR-TB in new cases

effect model was used for the analysis considering the chance of heterogeneity. A separate analysis was done for new cases as well as previously treated cases. For each of new and old cases separate analysis was done for the method of DST, sample size less or more than 500, proportion after removal of largest study and prospective or retrospective nature of the studies. Heterogeneity was assessed by $I^2$ and Cochran Q test.

## Results

A total 86 original articles were included for the screening. After going through the abstracts, 36 studies were excluded and remaining 50 articles were selected for full text reading. Out of these 50 studies, 47 were selected for the analysis [Table 1]. Among the excluded studies, two were review articles/meta-analysis and one study was related to the specific tribal population [Flow chart 1]. In almost all studies, data related to new cases as well as previously treated cases were extractable.

### MDR-TB in new cases

Thirty studies enrolled 16,275 participants and reported on new cases of MDR-TB. A pooled analyses of 30 studies (16,275 participants) showed 3% new cases of MDR-TB (95% CI 2%-5%). The heterogeneity between pooled studies was high ($I^2$ = 95.3%) [Figure 1].

Among studies which used the proportion method, the pooled proportion of MDR-TB cases was 3% (95% CI 2%-4%) and heterogeneity between pooled studies was high ($I^2$ = 88.0%). Among studies using the BACTEC method, the pooled proportion of MDR-TB cases is 21% (95% CI 18%-24%) and the heterogeneity between pooled studies was high ($I^2$ = 99.3%). The single study which used the Alamar blue dye reduction assay reported 5% (95% CI 2%-12%) proportion of MDR-TB cases. Among studies using the MIC method, the pooled proportion of MDR-TB cases was 1% (95% CI 1%-2%) and the heterogeneity between studies was high ($I^2$ = 85.9%). Finally, among studies where the method used was not reported, the pooled proportion of MDR-TB cases was 9% (95% CI 7%-11%) and the heterogeneity between studies was high ($I^2$ = 98.0%). There was a statistically significant difference between the subgroups ($p < 0.001$) [Figure 2].

Among studies with less than 500 participants, the pooled proportion of MDR-TB cases was 4% (95% CI 2%-6%) while in the studies with more than 500 participants enrolled, the pooled proportion of MDR-TB cases was 2% (95%

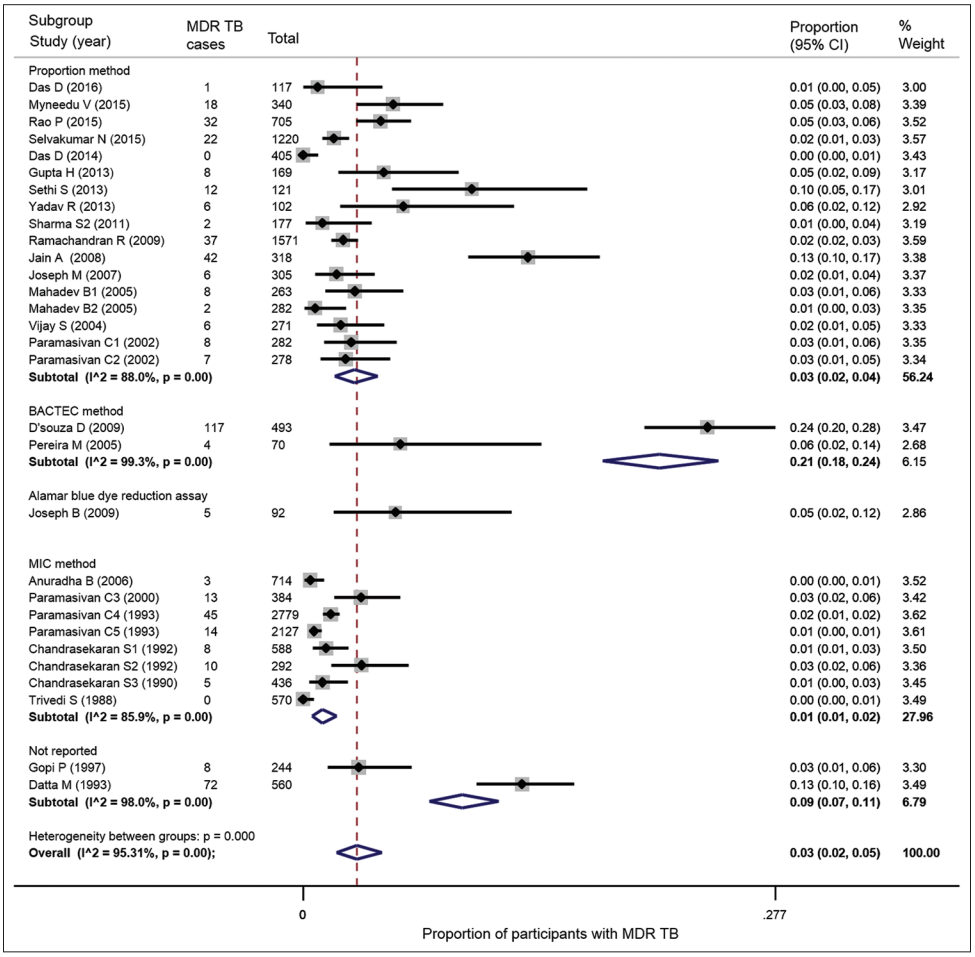



**Figure 2:** Prevalence of MDR-TB as per method of measurement

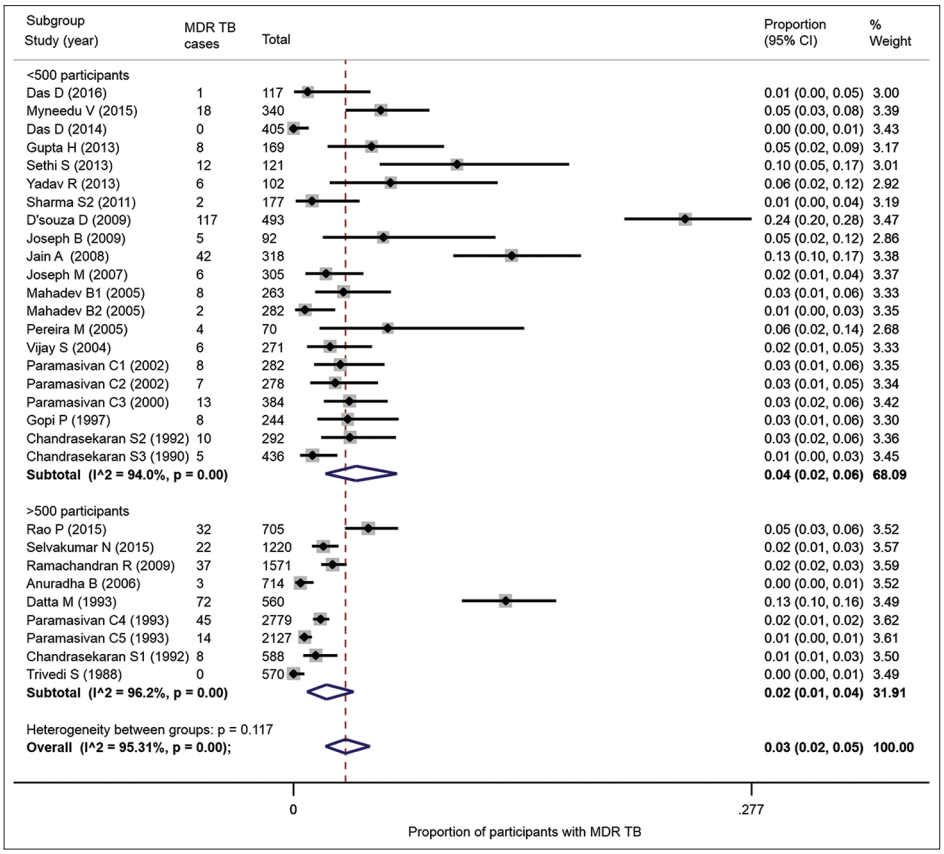



**Figure 3:** Prevalence of MDR-TB in new cases in sample size of the study <500 versus >500

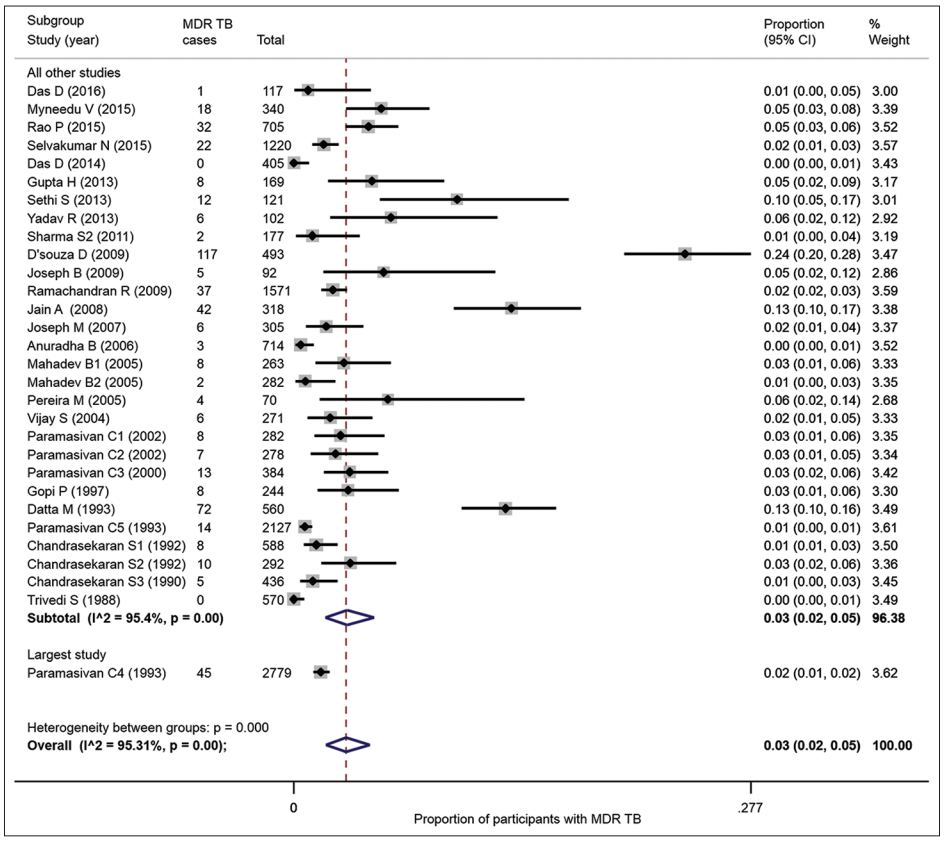



**Figure 4:** Prevalence of MDR-TB when largest study excluded vs included

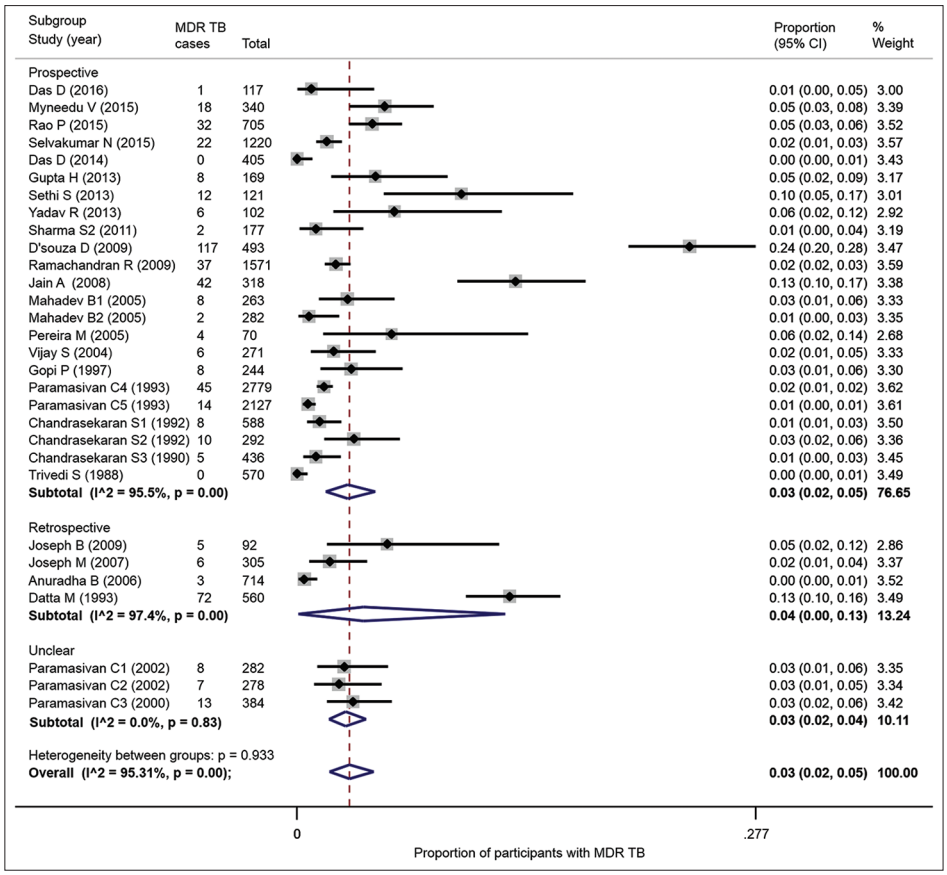



**Figure 5:** Prevalence of MDR-TB as per the study designs

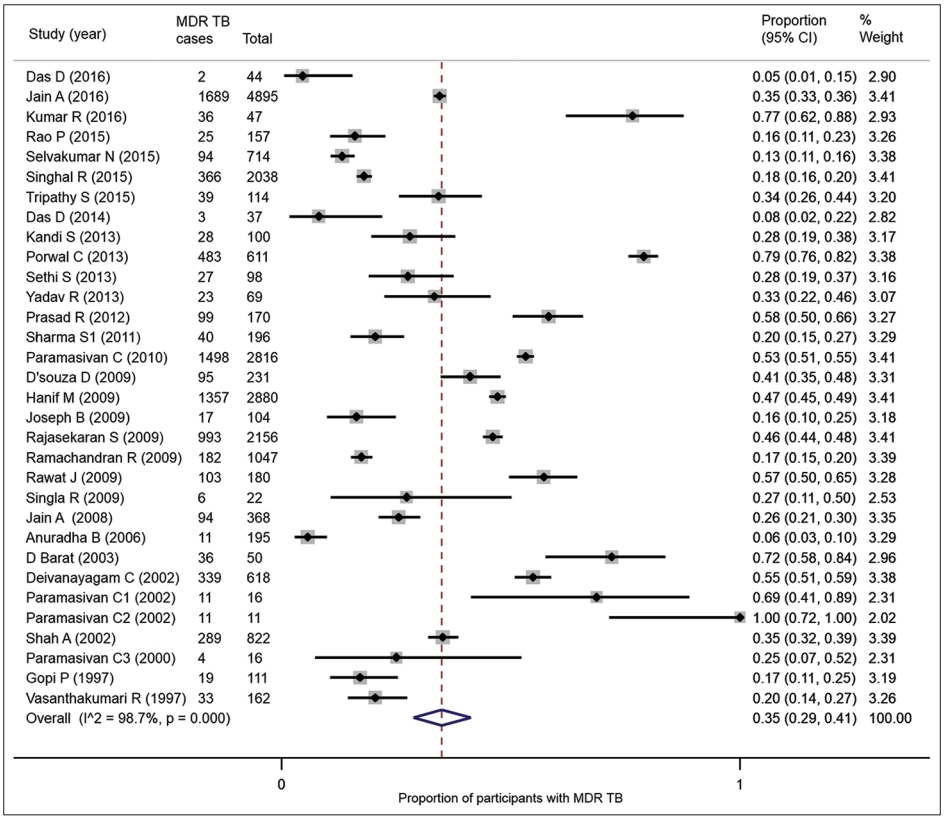



**Figure 6:** Prevalence of MDR-TB in previously treated cases

CI 1%-4%). The heterogeneity between studies was high for both groups, $I^2$ = 94.0% and 96.2%, respectively. There was no statistically significant difference between the two groups ($p$ = 0.117) [Figure 3].

The proportion of MDR-TB cases in the largest included study was 2% (95% CI 1%-2%). Without the largest study, the pooled proportion of MDR-TB cases was 3% (95% CI = 2%-5%) and heterogeneity between studies was high ($I^2$ = 95.4%). There was a statistically significant difference between the largest included study and the remaining studies ($p$ < 0.001) [Figure 4].

A sensitivity analysis performed according to the timing of the studies shows that in prospective studies, the pooled proportion of MDR-TB cases was 3% (95% CI 2%-5%) while in retrospective studies the pooled proportion of MDR-TB cases was 4% (95% CI 0%-13%). In both subgroups, the heterogeneity between studies was high: $I^2$ = 95.5% and 97.4%, respectively. Meanwhile, in studies where the timing of the study could not be evaluated the pooled proportion of MDR-TB cases was 3% (95% CI 2%-4%) and there was no heterogeneity between these studies ($I^2$ = 0%). There was no significant difference between subgroups ($p$ = 0.933) [Figure 5].

## MDR-TB in previously treated cases

Thirty two studies which enrolled 21,095 participants reported on previously treated cases of MDR-TB. A pooled analyses of 32 studies (21,095 participants) showed 35% cases of MDR-TB among the previously treated population (95% CI 29%-41%). There was significant heterogeneity between pooled studies ($I^2$ = 98.7%) [Figure 6].

Among studies which used the proportion method, the pooled proportion of MDR-TB cases was 28% (95% CI 20%-37%) and

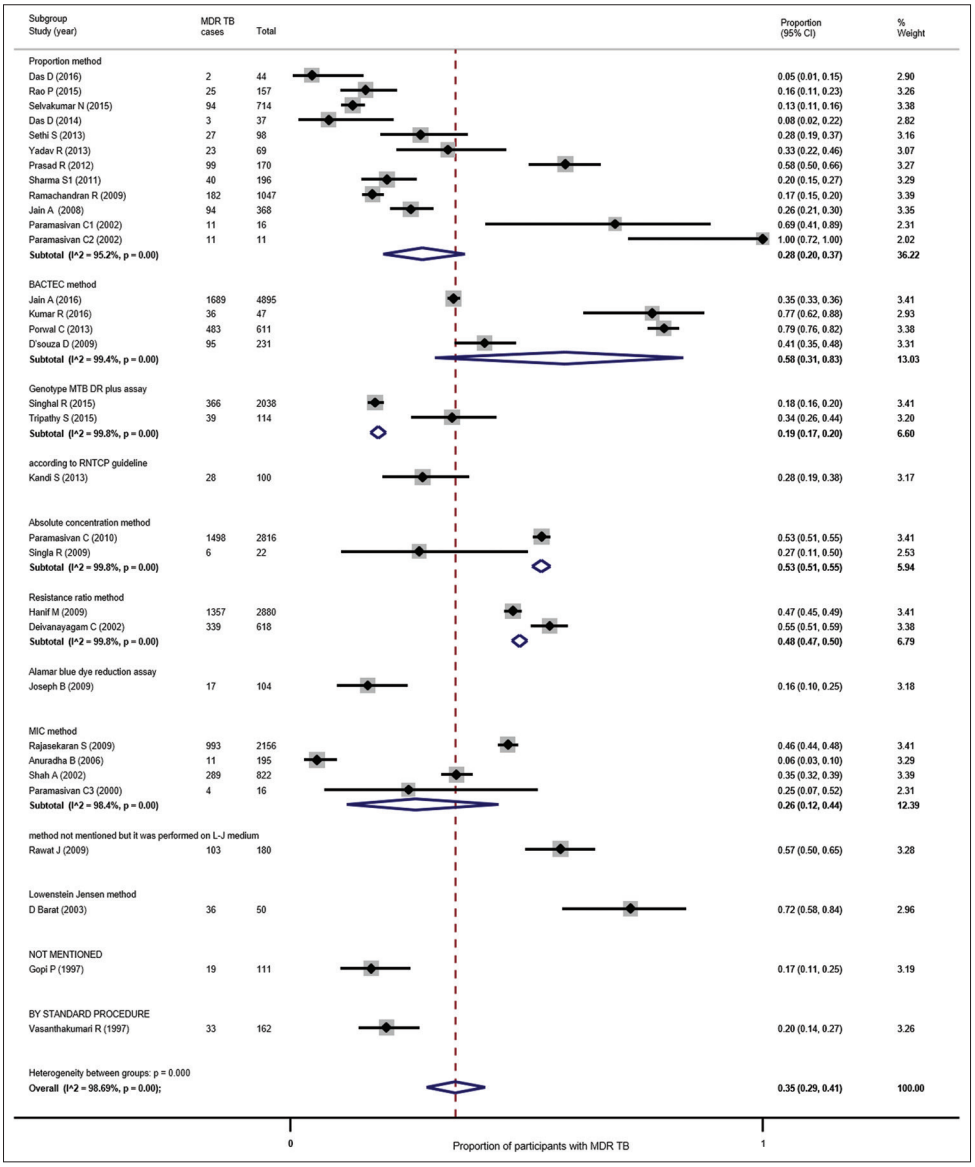



**Figure 7:** Prevalence of MDR-TB in previously treated patients as per the methods of measurement

heterogeneity between studies was high ($I^2$ = 95.2%). Among studies using the BACTEC method, the pooled proportion of MDR-TB cases was 58% (95% CI 31%-83%) and the heterogeneity between pooled studies was high ($I^2$ = 99.4%). Among studies using the genotype MTB DR plus assay method, the pooled proportion of MDR-TB cases was 19% (95% CI 17%-20%) and the heterogeneity between pooled studies was high ($I^2$ = 99.8%). The single study which used the RNTCP guideline reported proportion of MDR-TB cases at 28% (95%CI 19%-38%). Among studies using the absolute concentration method, the pooled proportion of MDR-TB cases was 53% (95% CI 51%-55%) and the heterogeneity between pooled studies was high ($I^2$ = 99.8%). Among studies using the resistance ratio method, the pooled proportion of MDR-TB cases was 48% (95% CI, 47%-50%) and the heterogeneity between studies was high ($I^2$ = 99.8%). The single study which used the Alamar blue dye reduction assay reported proportion of MDR-TB cases at 16% (95% CI 10%-25%). Among studies using the MIC method, the pooled proportion of MDR-TB cases was 26% (95% CI 12%-44%) and the heterogeneity between studies was high ($I^2$ = 98.4%). The single study, which did not report a method but used L-J medium, reported proportion of MDR-TB cases at 57% (95% CI, 50%-65%). The single study which used the Lowenstein Jensen method reported proportion of MDR-TB cases at 72% (95% CI 58%-84%). The single study which did not report the method used had 17% (95% CI 11%-25%) cases of MDR-TB. The single study which used the standard procedure reported proportion of MDR-TB cases at 20% (95% CI 14%-27%). There was a statistically significant difference between the subgroups ($p < 0.001$) [Figure 7].

Among studies with less than 500 participants, the pooled proportion of MDR-TB cases was 33% (95% CI 25%-42%) while in the studies with more than 500 participants enrolled, the pooled proportion of MDR-TB cases was 39% (95% CI 29%-50%). The heterogeneity between studies was high for both groups, $I^2$ = 95.1% and 99.5%, respectively. There was no statistically significant difference between the two groups ($p = 0.417$) [Figure 8].

The proportion of MDR-TB cases in the largest included study was 35% (95% CI 33%-36%). Without the largest study, the pooled proportion of MDR-TB cases was 35% (95% CI 28%-42%) and the heterogeneity among pooled studies is high ($I^2$ = 98.7%). There was a statistically significant difference between the largest included study and the remaining studies ($p < 0.001$) [Figure 9].

A sensitivity analysis performed by the timing of the studies showed that in prospective studies, the pooled proportion

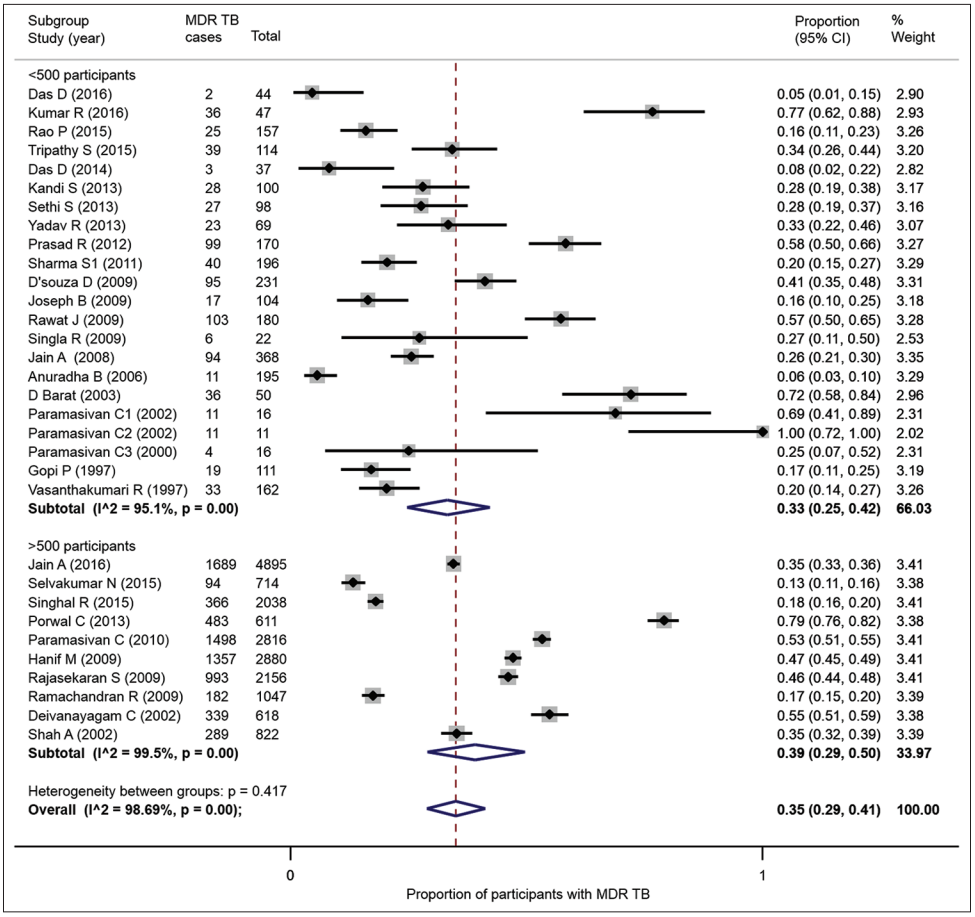



**Figure 8:** Prevalence of MDR-TB in previously treated patients when sample size is <500 versus >500

of MDR-TB cases was 33% (95% CI, 25%-43%) while in retrospective studies the pooled proportion of MDR-TB cases was 31% (95% CI, 22%-41%). In both groupings the heterogeneity between pooled studies was high, $I^2 = 98.7\%$ and 99.0%, respectively. Meanwhile, in studies where the timing of the study could not be evaluated the pooled proportion of MDR-TB cases was 69% (95% CI 20%-100%) and the heterogeneity between studies was high ($I^2 = 90.6\%$). There was no significant difference between the three subgroups ($p = 0.317$) [Figure 10].

## Discussion

The current analysis showed a prevalence of 3% and 28% MDR-TB in new and previously treated TB cases, respectively. The prevalence of MDR-TB in new cases was similar to the survey conducted at the National level. The national survey reported prevalence of MDR-TB in new cases as 2.8%. The prevalence of MDR-TB in previously treated patients is found to be higher in the current study compared to the National level survey. Current study found the prevalence to be 35% as compared with 11.6% estimated by the National level survey.[13] The of prevalence in any National program is based on sample presented to government health facility for drug sensitivity testing in MDR-TB suspects which might not be true representative of real situation.[14,15]

A study by Goyal *et al.* (2017) estimated the prevalence of MDR-TB 1%-2% higher in new cases as compared to our study while prevalence of MDR-TB in previously treated cases is almost similar to our study.[16] Such kind of systematic reviews always have the component of heterogeneity looking at the different kinds of studies pooled together but sensitivity analysis/subgroup analysis shows that estimates for each subgroups falls within the CIs of primary estimate. So even if we consider lower end of CI for MDR-TB in new and previously treated patients that is 2% and 29%, respectively, the values of previously treated patients is higher than national survey.

The low rate of MDR-TB in new patients and the high rate in previously treated patients indicates that most of the newly diagnosed TB patients are sensitive to first line drugs but there is an issue with the process of treatment which induces secondary resistance. This may be either due to inappropriate dosing, duration and variability in prescription of anti-tubercular drugs by clinicians particularly from private sector.[17,18] Moreover, intermittent therapy under Directly Observed Treatment Short Course (DOTS) strategy may also lead to increase in resistance which has now been shifted to daily therapy under new RNTCP guidelines.[19] In India, one of the important factor for the development of MDR-TB is the rampant use of antibiotics due

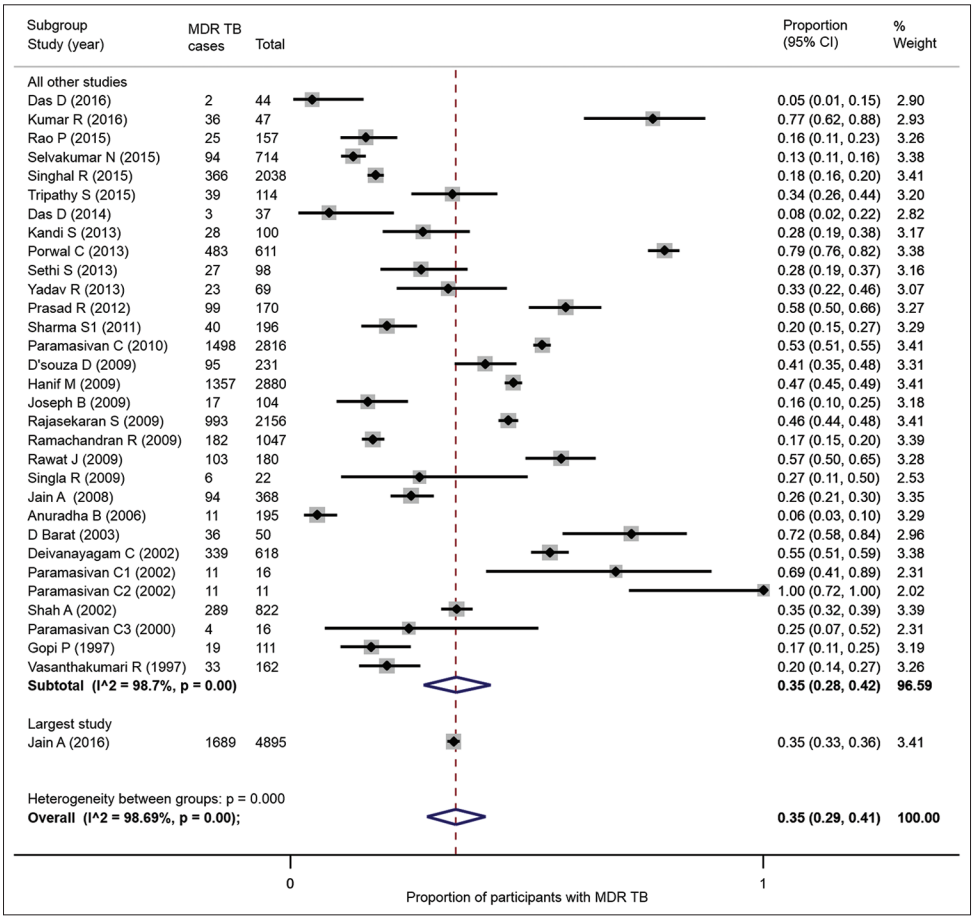



**Figure 9:** Prevalence of MDR-TB in previously treated patients when largest study excluded versus included in the analysis

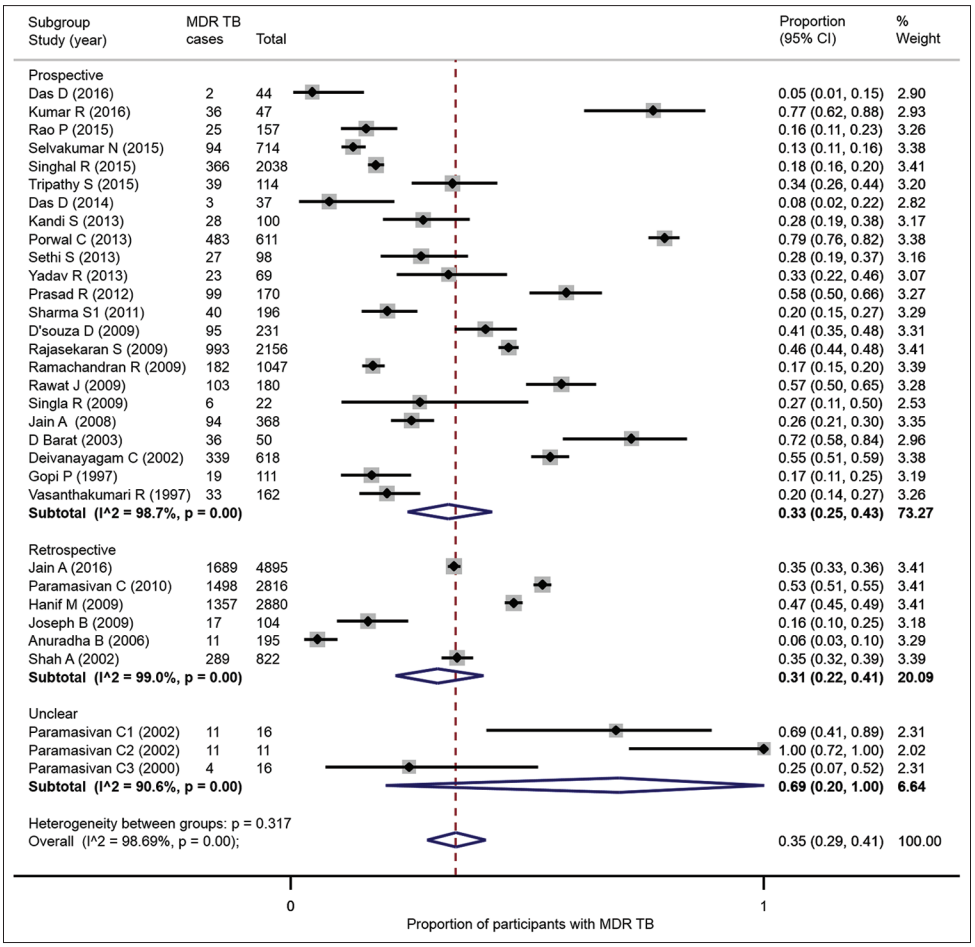
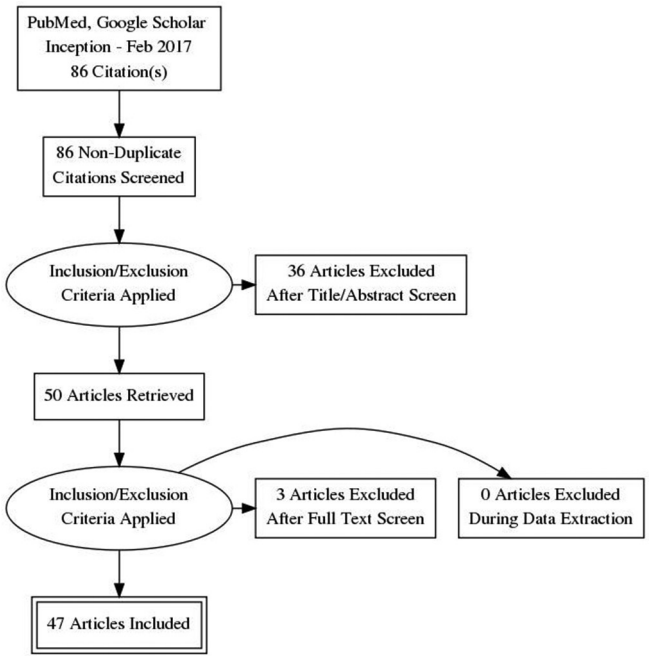



**Figure 10:** Prevalence of MDR-TB in previously treated patients as per the study designs




**Flow chart 1:** PRISMA Flow chart for inclusion of studies

to over the counter availability with no regulatory mechanism for the pharmacy shops.

This review is not devoid of potential limitations. Looking at the chances of heterogeneity in such studies, the random model was used for the analysis but mere using this model does not remove every influence of heterogeneity on estimates. There may be many confounders which could be adjusted to remove heterogeneity but not possible in aggregate data meta-analysis. The results obtained in this study as well in the national survey may be bit overestimated as compared to real situation as in both the cases MDR-TB was assessed in suspected drug resistant cases and not random or consecutive patients. A survey on patients of TB selected randomly without considering risk for resistance need to be planned to get true picture.

There are some very interesting observations from this review. Firstly, there is a lack of standard method for drug sensitivity testing (DST) across the country which government of India has also realized and started universal DST with WHO recommended rapid diagnostic testing. Secondly, a large part of care for TB patients is provided by private practitioners and patients are not followed under DOTS which may lead to inadequate and irregular treatment.[20] To support TB notification and strengthen TB surveillance in general, a case-based, web-based TB notification system NIKSHAY was established to provide platform for notification from both public and private sector. By making TB

notification mandatory by the treating doctor this problem might be resolved and in future more robust follow-up of patient with TB may happen. Since newer and effective drug like bedaquline, delamanid, etc., are made available under RNTCP program, MDR-TB now be treated more effectively.

To conclude, there is a growing prevalence of MDR-TB in India which may be an obstacle to End TB strategy adopted by WHO and government of India. The results from this review supports the priority need of having a continuous surveillance of MDR-TB. The role of primary care physician and primary health center (PHC) is of paramount importance. The staff at primary care should be trained with latest guideline on MDR-TB and made aware when to send sputum culture and DST for patients with TB, since patients' first encounter is with them. There should also be a link between PHC provider and TB services at district level. Good communication between PHC provider and TB services can be useful for detecting and treating patients with MDR-TB. It would also help the clinicians as well as public health experts to remain alert as well as vigilant for the timely response to MDR-TB cases occurring in an area. Future research in evidence-based diagnosis, management and prevention will help to eradicate TB.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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