Systematic Review

Prevalence of pulmonary tuberculosis in India: A systematic review and meta-analysis

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ABSTRACT

The Revised National Tuberculosis Control Program was started in India in 1997. There has been no nationwide survey to assess the prevalence of pulmonary tuberculosis. We aimed to conduct a systematic review and meta-analysis of published literature to provide an estimate of the prevalence of pulmonary tuberculosis in India. Several databases including Medline, Embase, Scopus, the Cochrane Library, Web of Science, and Google Scholar were searched for studies published between January 1, 1997, and December 31, 2018, which reported the prevalence of pulmonary tuberculosis. Community-based cross-sectional studies conducted among population aged 15 years and above were included. Summary estimates were calculated using random effects models. We identified 13 articles with 16 individual studies having screened 961,633 individuals for pulmonary tuberculosis. The pooled prevalence of bacteriologically positive pulmonary tuberculosis was 295.9 (95% confidence interval: 201.1–390.6) per 100,000 population. The prevalence was higher among males than females and in rural areas compared to urban areas. The pooled prevalence of culture-positive pulmonary tuberculosis (277.8/100,000 population) was higher than smear-positive pulmonary tuberculosis (196.6/100,000 population). The pooled prevalence of bacteriologically positive pulmonary tuberculosis in sensitivity analysis was 186.6/100,000 population. In all these estimates, heterogeneity remained high and significant publication bias was observed. The prevalence of pulmonary tuberculosis varied based on sex and distribution of population in rural and urban areas. There is a need of nationwide population-based survey to estimate the burden of tuberculosis to inform control measures and facilitate monitoring and evaluation.

KEY WORDS: Meta-analysis, prevalence, systematic review, tuberculosis

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INTRODUCTION

Tuberculosis is caused by *Mycobacterium tuberculosis*. It has affected humans for thousands of years.[1] According to the Global Tuberculosis Report 2018, there are an estimated 10 million incident cases of tuberculosis, equivalent to 133 cases/100,000 population.[2] The developed countries regard tuberculosis as a disease of the past due to the implementation of effective control strategies with social and economic development. For many low- and middle-income countries, the "end" of tuberculosis as a major public health problem is still a reality to achieve. India accounts for 27% of all estimated incident cases worldwide. India under its Revised National Tuberculosis Control Program (RNTCP) adopted the World Health Organization-endorsed Directly Observed Treatment, Short-Course (DOTS) in 1997.[3,4] Since then, the program had its crests and troughs in the control of tuberculosis

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nationwide.[5] The estimated incidence of tuberculosis in India is 204/100,000 population in 2017.[2] Most estimates of the burden of tuberculosis incidence are based on small studies and annual reports of the Central Tuberculosis Division. There has been no nationwide prevalence survey after 1955[6] or published review of community-based epidemiological studies to assess the prevalence of pulmonary tuberculosis after 2005.[7] Estimating the prevalence of pulmonary tuberculosis is crucial to guide intervention policies for program management strategies. We, therefore, conducted a systematic review and meta-analysis of published literature to provide a comprehensive and updated assessment of the prevalence of pulmonary tuberculosis in India.

MATERIALS AND METHODS

Search strategies

In India, the RNTCP was introduced in 1997 with the incorporation of DOTS strategy. Hence, we searched for studies published from January 1, 1997, to December 31, 2018, in the following databases such as Medline, Embase, Scopus, the Cochrane Library, Web of Science, and Google Scholar. Keywords from Medical Subject Headings or titles or abstracts of the studies were searched for with the help of Boolean operators (and, or) without language limitations. Search terms used included "tuberculosis" or "pulmonary tuberculosis" and "cross-sectional study" or "survey" or "prevalence study" and "India." We also reviewed the reference lists of primary studies and review articles.

Inclusion and exclusion criteria

This systematic review and meta-analysis were carried out using PRISMA guidelines.[8] All studies in which the prevalence of pulmonary tuberculosis was reported in the given time period among population aged 15 years and above were included. Furthermore, the included original articles must be a community-based cross-sectional study and report on some or all of the following: the sputum smear-positive pulmonary tuberculosis or culture-positive pulmonary tuberculosis or bacteriologically positive pulmonary tuberculosis. Only those studies in which individuals were examined for pulmonary tuberculosis through initial screening of standard tuberculosis symptoms such as cough for >2 weeks, fever for >2 weeks, hemoptysis, or chest pain were included. Studies with the following characteristics were excluded from the analysis: studies reporting on the prevalence of childhood tuberculosis, extrapulmonary tuberculosis, or drug-resistant tuberculosis and studies on nontuberculous mycobacterium. Editorials, narrative review articles, case reports, and conference abstracts, as well as duplicate publications, were excluded from the analysis.

Study selection, data extraction, and quality assessment

Two reviewers independently screened the studies by title and abstract. After screening, full texts of the selected articles were obtained. Of the studies included, the following data were extracted: author, year of publication, study period, study setting, study population, sample size, study procedure, and prevalence estimates. There was a complete agreement between the two reviewers.

Operational definitions

Sputum smear-positive pulmonary tuberculosis was defined as having at least one sputum sample showing acid-fast bacilli on direct smear microscopy, irrespective of sputum culture result. Culture-positive pulmonary tuberculosis was defined as having at least one sputum culture showing growth of *M. tuberculosis*, irrespective of sputum smear result. Anyone sputum sample showing acid-fast bacilli on direct smear microscopy and/or growth of *M. tuberculosis* considered a bacteriologically positive pulmonary tuberculosis.

Data synthesis and statistical analyses

The prevalence was reported as the ratio between the total numbers of reported pulmonary tuberculosis individuals over the study population. It is presented as the number of pulmonary tuberculosis cases per 100,000 population. Of the 16 studies, four reported age- and sex-standardized prevalence.[9] To maintain uniformity in the meta-analysis, the crude prevalence was calculated from the data presented in the tables of these four studies. The pooled prevalence and 95% confidence intervals (95% CIs) were calculated using random effects model based on the DerSimonian and Laird method[10] using Metan in STATA 12.0 (StataCorp, College Station, Texas, USA). The χ^2-based Q statistic and I^2 test were used to assess the between-study heterogeneity using two-sided P values.[11] Subgroup analyses were done for sex and distribution of population in urban and rural areas. Sensitivity analysis was undertaken by removal of three studies which reported a high prevalence of bacteriologically positive pulmonary tuberculosis. Funnel plot was used to assess the publication bias. Quality of studies is reported by an assessment of the risk of bias.

RESULTS

Characteristics of included studies

A total of 346 articles were retrieved by literature search [Figure 1]. Of these, 320 articles were retained after duplicates were removed; 288 of them were excluded as they did not meet the inclusion criteria based on their title and abstract. Thirty-two articles were retained for full-text evaluation. After a detailed full-text evaluation, 13 articles published between 1997 and 2018 were included in the quantitative synthesis.[9,12-23] One article reported four cross-sectional studies of different time periods.[9] These were analyzed as four separate studies. Thus, a total of 16 studies were included in the meta-analysis. The distribution of the studies and relevant data retrieved for this analysis is summarized in Table 1. A total of 961,633 individuals were screened for pulmonary tuberculosis between 1999 and 2010. Half the studies were reported

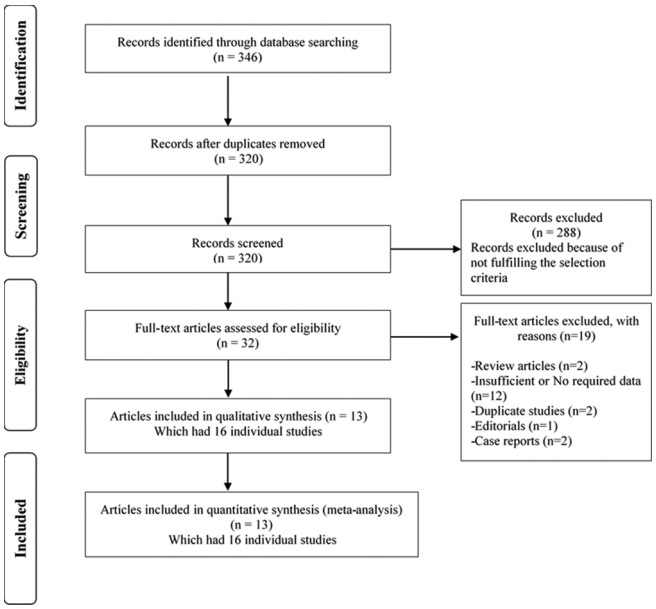

Figure 1: Flowchart depicting the study selection process

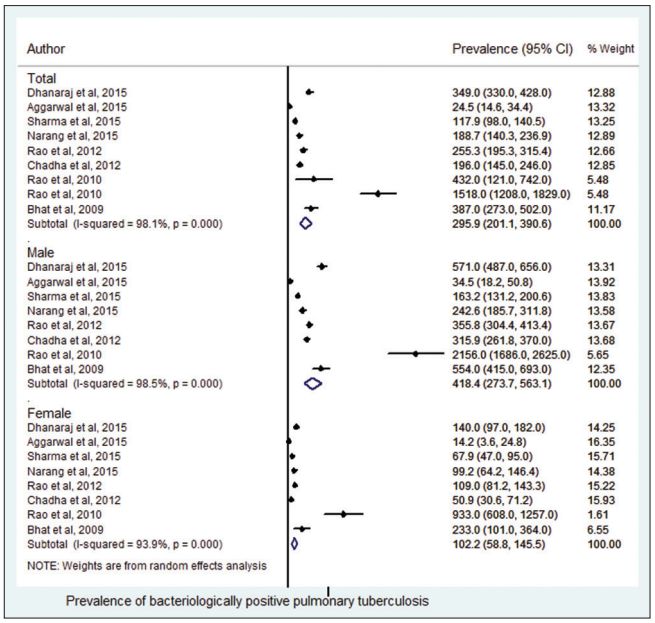

Figure 2: Forest plot of the meta-analysis for the prevalence of total bacteriologically positive pulmonary tuberculosis and its distribution among males and females

from South[9,12,17,22,23] India. Majority of the studies were from the states of Tamil Nadu and Madhya Pradesh. There were ten studies from rural area, one from urban area, and five from both rural and urban areas. The response rate of the studies ranged from 88.2% to 97.4%. All 16 studies had the participants screened with tuberculosis symptoms. In addition to screening of tuberculosis symptoms, six studies also used radiographic examination and two studies used mass miniature radiography. All studies did sputum smear and culture examination except two studies that did only sputum smear examination.[20,22]

Prevalence of bacteriologically positive pulmonary tuberculosis and its stratification by sex

Nine studies reported the prevalence of bacteriologically positive pulmonary tuberculosis [Table 2].[12-19,21] Overall prevalence of bacteriologically positive pulmonary tuberculosis ranged from 24.5 to 1518/100,000 population. The pooled prevalence of bacteriologically positive pulmonary tuberculosis was 295.9/100,000 population (95% CI: 201.1–390.6) [Figure 2]. Significant heterogeneity was observed (I^2 = 98.1%, $P < 0.001$). The prevalence of bacteriologically positive pulmonary tuberculosis was reported for male and female population separately, by eight studies. The prevalence of bacteriologically positive pulmonary tuberculosis among males ranged from 34.5 to 2156/100,000 population. The prevalence of bacteriologically positive pulmonary tuberculosis among females ranged from 14.2 to 933/100,000 population. The pooled prevalence of bacteriologically positive pulmonary tuberculosis was higher among males (418.4/100,000 population, 95% CI: 273.7–563.1) compared to the pooled prevalence of females (102.2/100,000 population, 95% CI: 58.8–145.5). There was an evident heterogeneity for the pooled estimates of both male (I^2 = 98.5%, $P < 0.001$) and female (I^2 = 93.9%, $P < 0.001$) population.

Prevalence of bacteriologically positive pulmonary tuberculosis in urban and rural areas

There were five studies each in urban[12-16] and rural areas[13-17] that reported the prevalence of bacteriologically positive pulmonary tuberculosis [Table 2]. The prevalence of bacteriologically positive pulmonary tuberculosis in the urban areas ranged from 11.7 to 349.0/100,000 population. The prevalence of bacteriologically positive pulmonary tuberculosis in the rural areas ranged from 32.9 to 348.9/100,000 population. The pooled prevalence of bacteriologically positive pulmonary tuberculosis was higher in rural areas (184.0/100,000 population, 95% CI: 74.3–293.6) than in urban areas (144.9/100,000 population, 95% CI: 49.0–240.8) [Figure 3]. There was a significant heterogeneity in the pooled estimates of both urban (I^2 = 98.3%, $P < 0.001$) and rural areas (I^2 = 97.7%, $P < 0.001$).

Prevalence of smear-positive and culture-positive pulmonary tuberculosis

Thirteen studies reported the prevalence of smear-positive pulmonary tuberculosis.[9,12-17,20,22,23] The prevalence ranged from 4.7 to 728.5/100,000 population [Figure 4]. Eleven studies reported the prevalence of culture-positive pulmonary tuberculosis.[9,12-17,23] The prevalence ranged from 23.1 to 605.0/100,000 population. The pooled prevalence of culture-positive pulmonary tuberculosis (277.8/100,000 population, 95% CI: 176.2–379.3) was higher than smear-positive pulmonary tuberculosis (196.6/100,000 population, 95% CI: 130.7–262.5). There was a significant heterogeneity in the pooled estimates of both smear-positive (I^2 = 98.9%, $P < 0.001$) and culture-positive (I^2 = 99.3%, $P < 0.001$) pulmonary tuberculosis.

Table 1: Characteristics of studies included in the meta-analysis

Author	Publication years	Place	Location	Study period	Response rate (%)	Methodology
Dhanaraj *et al*.[12]	2015	Chennai, Tamil Nadu	Urban	2010-2012	93.0	Screening with tuberculosis symptoms and mass miniature radiography, followed by sputum smear examination and culture
Aggarwal *et al*.[13]	2015	Mohali, Punjab	Mixed	2008-2010	94.2	Screening with tuberculosis symptoms, followed by sputum smear examination and culture
Sharma *et al*.[14]	2015	Faridabad, Haryana	Mixed	2008-2009	93.7	Screening with tuberculosis symptoms, followed by sputum smear examination and culture
Narang *et al*.[15]	2015	Wardha, Maharashtra	Mixed	2007-2009	91.4	Screening with tuberculosis symptoms and mass miniature radiography, followed by sputum smear examination and culture
Kolappan *et al*.[9]	2013	Tiruvallur, Tamil Nadu	Rural	2006-2008	NR	Screening with tuberculosis symptoms and/or radiographic examination, followed by sputum smear examination and culture
Kolappan *et al*.[9]	2013	Tiruvallur, Tamil Nadu	Rural	2004-2006	NR	Screening with tuberculosis symptoms and/or radiographic examination, followed by sputum smear examination and culture
Kolappan *et al*.[9]	2013	Tiruvallur, Tamil Nadu	Rural	2001-2003	NR	Screening with tuberculosis symptoms and/or radiographic examination, followed by sputum smear examination and culture
Kolappan *et al*.[9]	2013	Tiruvallur, Tamil Nadu	Rural	1999-2001	NR	Screening with tuberculosis symptoms and/or radiographic examination, followed by sputum smear examination and culture
Rao *et al*.[16]	2013	Jabalpur, Madhya Pradesh	Mixed	2009-2010	95.1	Screening with tuberculosis symptoms, followed by sputum smear examination and culture
Chadha *et al*.[17]	2012	Nelamangala, Karnataka	Rural	2008-2010	88.2	Screening with tuberculosis symptoms, followed by sputum smear examination and culture
Rao *et al*.[18]	2010	Chhindwara, Madhya Pradesh	Rural	2008-2008	96.3	Screening with tuberculosis symptoms, followed by sputum smear examination and culture
Rao *et al*.[19]	2010	Sheopur district, Madhya Pradesh	Rural	2007-2008	96.9	Screening with tuberculosis symptoms, followed by sputum smear examination and culture
Yadav *et al*.[20]	2010	Dindori, Madhya Pradesh	Rural	2008-2008	97.4	Screening with tuberculosis symptoms, followed by sputum smear examination
Bhat *et al*.[21]	2009	Madhya Pradesh	Rural	2007-2008	95.1	Screening with tuberculosis symptoms, followed by sputum smear examination and culture
Murhekar *et al*.[22]	2004	Nicobars, Andaman and Nicobar Islands	Rural	2001-2002	95.8	Screening with tuberculosis symptoms and/or radiographic examination, followed by sputum smear examination
Gopi *et al*.[23]	2003	Tiruvallur, Tamil Nadu	Mixed	1999-2001	91.0	Screening with tuberculosis symptoms and/or radiographic examination, followed by sputum smear examination and culture

NR: Not reported

Table 2: Prevalence of smear-positive, culture-positive, and bacteriological-positive pulmonary tuberculosis

Author	Years	Sample size	Pulmonary tuberculosis						
			Prevalence of smear positive	Prevalence of culture positive	Prevalence of bacteriological positive				
					Overall	Male	Female	Urban	Rural
Dhanaraj *et al*.[12]	2015	59,957	228	259	349	571	140	349	NR
Aggarwal *et al*.[13]	2015	91,030	4.7	23.1	24.5	34.5	14.2	11.7	32.9
Sharma *et al*.[14]	2015	105,202	77	77.9	117.9	163.2	67.9	83.1	166.5
Narang *et al*.[15]	2015	50,332	121.1	149.4	188.7	242.6	99.2	135.4	184.6
Kolappan *et al*.[9]	2013	92,255	168	360	NR	NR	NR	NR	NR
Kolappan *et al*.[9]	2013	89,413	152	283	NR	NR	NR	NR	NR
Kolappan *et al*.[9]	2013	85,474	229	402	NR	NR	NR	NR	NR
Kolappan *et al*.[9]	2013	83,425	294	548	NR	NR	NR	NR	NR
Rao *et al*.[16]	2012	99,918	171.9	207.1	255.3	355.8	109	153.9	348.9
Chadha *et al*.[17]	2012	71,874	83	152	196	315.9	50.9	NR	196
Rao *et al*.[18]	2010	2586	NR	NR	432	NR	NR	NR	NR
Rao *et al*.[19]	2010	11,116	NR	NR	1518	2156	933	NR	NR
Yadav *et al*.[20]	2010	2359	146	NR	NR	NR	NR	NR	NR
Bhat *et al*.[21]	2009	22,270	NR	NR	387	554	233	NR	NR
Murhekar *et al*.[22]	2004	11,032	728.5	NR	NR	NR	NR	NR	NR
Gopi *et al*.[23]	2003	83,390	323	605	NR	NR	NR	NR	NR

Prevalence figures are in per 100,000 population. NR: Not reported

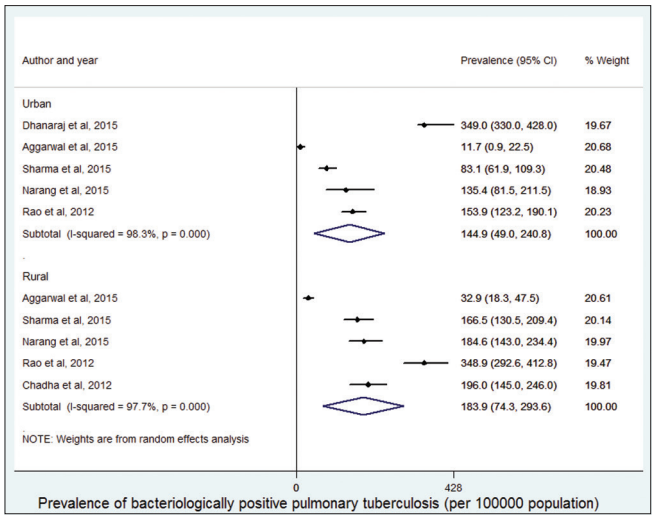

Figure 3: Forest plot of the meta-analysis for the prevalence of bacteriologically positive pulmonary tuberculosis in the urban and rural areas

Prevalence of bacteriologically positive pulmonary tuberculosis after removing studies with high prevalence

Of the nine studies which reported the prevalence of bacteriologically positive pulmonary tuberculosis, three reported a high prevalence.[18,19,21] Sensitivity analysis was undertaken by estimating the pooled prevalence for the six studies after excluding these three studies.[12-17] The prevalence in these six studies ranged from 24.5 to 349/100,000 population. The pooled prevalence was 186.6/100,000 population (95% CI: 93.9–279.4) [Figure 5]. However, significant heterogeneity remained (I^2 = 98.4%, $P < 0.001$) as was observed with inclusion of the three studies. The prevalence among males ranged from 34.5 to 571/100,000 population. The prevalence among females ranged from 14.2 to 140/100,000 population. The pooled prevalence of bacteriologically positive pulmonary tuberculosis was higher among males (277.7/100,000 population, 95% CI: 135.8–419.6) compared to the pooled prevalence among females (77.5/100,000 population, 95% CI: 39.6–115.4). The heterogeneity remained for the pooled estimates of both male (I^2 = 98.6%, $P < 0.001$) and female (I^2 = 93.5%, $P < 0.001$) population.

Quality assessment

Across the nine quality domains evaluated, majority of the studies met five or more of the quality criteria [Table 3]. Eight studies met all the quality criteria assessed.[12-17,19,21] Two studies did not mention CIs in their main results. The response rate of four studies could not be commented upon. The sample size of seven studies was not based on prestudy considerations of statistical power. Five studies had measurements that were unlikely to be valid and reliable. Two studies had samples of participants that could not be representative of the population to which the findings were referred.

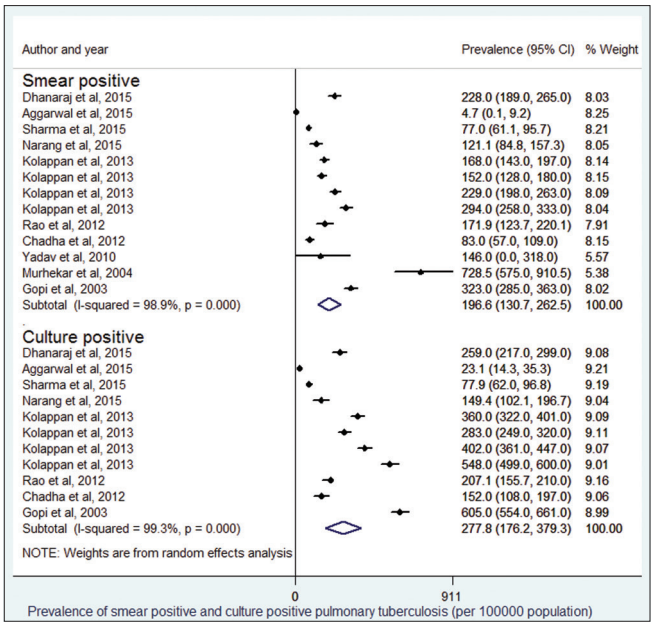

Figure 4: Forest plot for the meta-analysis for the prevalence of smear-positive and culture-positive pulmonary tuberculosis

Publication bias

We used funnel plots to assess publication bias. In Figure 6a-c, the vertical line represents the summary of the prevalence of pulmonary tuberculosis. The diagonal lines represent the 95% confidence limits around the summary prevalence estimate. These show the expected distribution of studies in the absence of heterogeneity or selection biases. Funnel plots were constructed for the overall prevalence of bacteriologically positive pulmonary tuberculosis (A), prevalence of smear-positive pulmonary tuberculosis (B), and prevalence of culture-positive pulmonary tuberculosis (C). The funnel plot asymmetry was assessed by Egger's linear regression test. It showed significant publication bias for overall bacteriologically positive pulmonary tuberculosis, smear-positive pulmonary tuberculosis, and culture-positive pulmonary tuberculosis.

DISCUSSION

This meta-analysis and systematic review were conducted to estimate the pooled national prevalence of tuberculosis in India. The prevalence of tuberculosis varied based on sex and distribution of population in urban and rural areas. The pooled prevalence of bacteriologically positive pulmonary tuberculosis was 295.9/10,000 population. Males had a higher pooled prevalence of bacteriologically positive pulmonary tuberculosis than females. Rural areas had a higher pooled prevalence of bacteriologically positive pulmonary tuberculosis than urban areas. The pooled prevalence of culture-positive pulmonary tuberculosis was higher compared to the pooled prevalence of smear-positive pulmonary tuberculosis.

In a longitudinal analysis of the national tuberculosis survey data of China from 1990 to 2010 by Wang *et al.*,

Table 3: Risk of bias assessment of the studies included in the meta-analysis

Questions	Dhanaraj *et al.*	Aggarwal *et al.*	Sharma *et al.*	Narang *et al.*	Kolappan *et al.*	Kolappan *et al.*	Kolappan *et al.*	Rao *et al.*	Chadha *et al.*	Rao *et al.*	Rao *et al.*	Yadav *et al.*	Bhat *et al.*	Murhekar *et al.*	Gopi *et al.*
Did the study address a clearly focused question/issue?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Is the research method (study design) appropriate for answering the research question?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Is the method of selection of the participants (employees, teams, divisions, organizations) clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
Could the way, the sample was obtained introduce (selection) bias?	N	N	N	N	N	N	N	N	N	CS	N	CS	N	N	N
Was the sample of participants representative with regard to the population to which the findings will be referred?	Y	Y	Y	Y	Y	Y	Y	Y	Y	CS	Y	CS	Y	Y	Y
Was the sample size based on prestudy considerations of statistical power?	Y	Y	Y	Y	N	N	N	Y	Y	N	Y	N	Y	N	Y
Was a satisfactory response rate achieved?	Y	Y	Y	Y	CS	CS	CS	Y	Y	Y	Y	Y	Y	Y	Y
Are the measurements (questionnaires) likely to be valid and reliable?	Y	Y	Y	Y	CS	CS	CS	Y	Y	CS	Y	Y	Y	Y	Y
Are confidence intervals given for the main results?	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	N	N

Y: Yes, N: No, CS: Cannot say

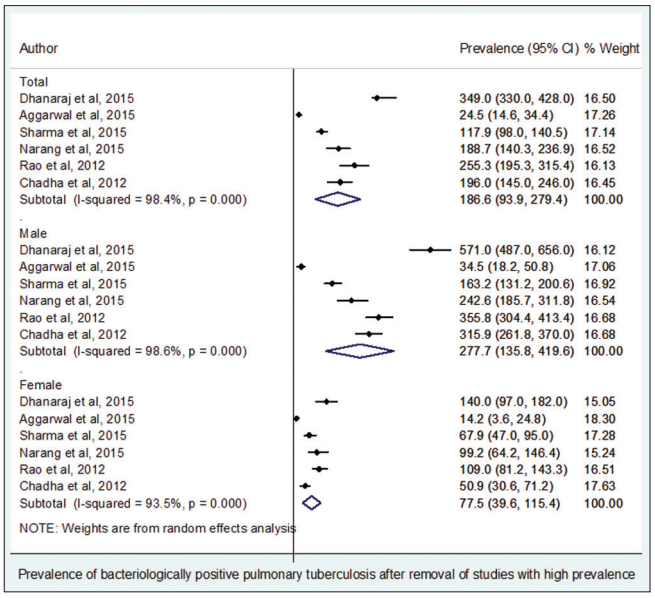

Figure 5: Forest plot of the meta-analysis for the prevalence of total bacteriologically positive pulmonary tuberculosis after removal of three studies with high prevalence

it was found that the prevalence of smear-positive pulmonary tuberculosis decreased from 170/100,000 population to 59/100,000 population.[24] The prevalence was higher among male population and in rural areas than among female population and urban areas. In this period of 20 years, China managed to halve its tuberculosis prevalence. Wang *et al*. attributed this success to the implementation of DOTS strategy and major shift of treatment from hospitals to primary health centers.[25]

Senkoro *et al*. conducted a national survey in 2012 on tuberculosis prevalence in Tanzania.[26] The United Republic of Tanzania is one of the top 20 countries of the 30 high tuberculosis burden countries.[27] The prevalence of bacteriologically positive pulmonary tuberculosis was 293/100,000 population. The prevalence was higher among male population and in rural areas. The estimated incidence of tuberculosis was much less than that of the survey-reported prevalence.[27] A population-based national tuberculosis prevalence survey among adults aged 15 years and above by Qadeer *et al*. in Pakistan found that the prevalence of bacteriologically positive pulmonary tuberculosis was 398/100,000 population.[28] The tuberculosis prevalence increased with age and was 1.8 times higher among men.

In the first population-based national tuberculosis prevalence survey in Ethiopia from 2010 to 2011, reported in 2014, it was found that the prevalence of bacteriologically positive pulmonary tuberculosis was 277/100,000 population,[29] which was lower than the estimated incidence of tuberculosis reported in the Global Tuberculosis Reports of 2011 and 2012.[30,31]

To our knowledge, this is the first meta-analysis of community-based cross-sectional studies on the

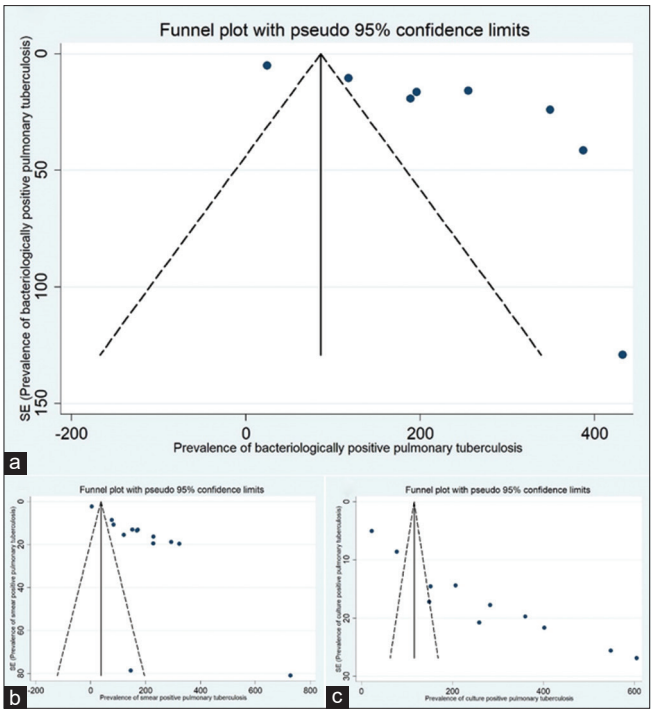

Figure 6: Funnel plot for assessing publication bias for (a) Bacteriologically positive pulmonary tuberculosis, (b) Smear positive pulmonary tuberculosis and (c) Culture positive pulmonary tuberculosis

prevalence of tuberculosis in India. In total, we identified 16 studies, which allowed us to pool results from 961,633 participants. These 16 studies were distributed in the major states of India. The results of this meta-analysis may help in comparing the prevalence from future meta-analysis or surveys. The findings of this systematic review and meta-analysis should be interpreted with the follow limitations. Even though we followed a comprehensive search strategy, there is a possibility of noninclusion of some studies. The pooled estimate for the prevalence of tuberculosis in India may not fully represent the magnitude because many areas of the country were not yet investigated. Significant heterogeneity exists among the included studies. Even though we used a random effects model, the findings are to be interpreted with consideration of sampling error. Limitations associated with publication bias should be considered.

Even though the RNTCP with incorporation of DOTS strategy started in 1997, the burden of tuberculosis continues to deserve priority attention.[32] India is one of the top 20 high tuberculosis burden countries with increasing burden of multidrug resistance and coinfection with HIV and diabetes mellitus.[2]

CONCLUSIONS

Our findings suggest a large variation in the prevalence of pulmonary tuberculosis in India. This highlights the need for a nationwide population-based survey using uniform methodology to provide reliable estimates of the burden of tuberculosis. This would be useful for planning and implementation of control measures and also for their monitoring and evaluation.

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Conflicts of interest
There are no conflicts of interest.

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