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Prevalence of Bovine Tuberculosis in a Dairy Cattle Farm

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Abstract:
Bovine tuberculosis (bTB) may be a chronic disease of cattle that impacts productivity and represents a serious public health threat. Despite the considerable economic costs and zoonotic risk consequences related to the disease, accurate estimates of bTB prevalence are lacking in many countries, including India, where national control programmes aren't yet implemented and therefore the disease is taken into account endemic. To deal with this critical knowledge gap, we performed a scientific review of the literature and a meta-analysis to estimate bTB prevalence in cattle in India and supply a foundation for the longer term formulation of rational disease control strategies and therefore the accurate assessment of economic and health impact risks. The literature search was performed in accordance with PRISMA guidelines and identified 100 cross-sectional studies on bTB in cattle in India across four electronic databases and handpicked publications. Of these, 20 articles were included, contributing a complete of 82,419 cows and buffaloes across 18 states and one union territory in India. The analyses further suggest that production system, species, breed, study location, diagnostic procedure, sample size and study period are likely moderators of bTB prevalence in India and wish to be considered when developing future disease surveillance and control programmes. Taken along side the projected increase in intensification of dairy production and therefore the subsequent increase within the likelihood of zoonotic transmission, the results of our study suggest that attempts to eliminate tuberculosis from humans would require simultaneous consideration of bTB control in cattle population in countries like India.

Keywords: *Bovine tuberculosis, chronic disease, meta-analysis, dairy production, cattle population.*

I. Introduction

Bovine tuberculosis (bTB) may be a chronic granulomatous disease that's predominantly caused by Mycobacterium bovis. While primarily affecting bovines, the pathogen features a broad host range that has humans. it's been estimated that M. bovis causes ~10% of the entire human TB cases in developing countries and subsequently poses a big threat to global health (Olea-Popelka et al., 2014) (Etchechoury et al., 2010) ("OIE, Bovine Tuberculosis: General Disease Information sheets,"). Before mandatory pasteurization of milk in many countries, M. bovis accounted for ~25% of all TB cases in children (Roswurm & Ranney, 1973). additionally to being a threat to public health, bTB is additionally a serious economic concern, costing an estimated USD 3 billion worldwide annually thanks to losses from reduced cattle productivity, culling and movement and trade restrictions (Waters, Palmer, Buddle, & Vordermeier, 2012).

In conjunction with possessing the most important population of cattle within the world (nearly 300 million cows and buffaloes) (Basic farming and Fisheries Statistics, Government of India 2017), India's lack of an impact programme poses a possible threat for bTB infection and transmission worldwide. Within the absence of a national surveillance programme, accurate prevalence data are lacking and, to our knowledge, there has so far not been a comprehensive review of the prevailing literature to work out an estimate of the general prevalence of bTB within the country. Such an estimate will prove crucial in future efforts to accurately assess risk and inform policy for the event of effective control strategies. during this systematic review and meta-analysis, we sought to deal with this critical gap and determine the general prevalence of bTB within the cattle of India. This systematic review conforms to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Liberati et al., 2009).

II. Method

A systematic look for published articles reporting prevalence data for bTB in cows and buffaloes in India was conducted on 30th August 2015. The four databases utilized in our search (CAB Direct, Web of Science, Web of Science Biological Abstracts and PubMed) were selected so as to comprehensively capture articles published in both international and native journals and minimize journal biases. After examining common MeSH terms for pre-identified and relevant publications, the subsequent search terms were used across all four databases: (("mycobacterium bovis" OR tuberculosis) AND (cows OR cattle OR bovine) AND (epidemiolog* OR prevalen* OR inciden* OR surve*) AND (India)). No restrictions were placed on the date of publication. The citation software program EndNote X8 (Clarivate Analytics, Philadelphia, PA) was wont to organize and take away duplicate articles between the databases. Additional articles were also identified manually from the reference lists of articles generated within the database search.

2.1 Study inclusion criteria

The inclusion/exclusion criteria for data extraction are detailed in Table 1. Included studies reported the prevalence of bTB in cows and/or buffaloes in India supported commonly accepted methods for the diagnosis of bTB. More specifically, studies whose main objectives weren't to work out bTB prevalence but required a preliminary prevalence study for determining initial disease status were included as long as data were reported and animals weren't pre-selected for bTB symptoms. Prevalence studies that examined the consequences of bTB control strategies were excluded so as to avoid the introduction of potential sampling bias, because the primary aims of those studies were to match the effectiveness of control strategies. as an example , Dhanda et al. have reported a rise in prevalence in herds at Puri, Orissa, from 9.1% in 1937 to 84.7% in 1942 (Dhanda & Lall, 1959). The cattle populations that were tested were a part of farms that didn't practice any bTB control strategies. We believe that inclusion of studies conducted on pre-selected herds as against randomly sampled prevalence studies wouldn't be truly representative of the prevailing prevalence within the region. Also, all other publications that didn't precisely fit the most exclusion categories were excluded within the “Other” category. Finally, all included studies were cross-sectional in nature.

Table 1 : Study inclusion/exclusion criteria

Cross-sectional prevalence study	Wrong type of study: not a cross-sectional study or animals chosen for bTB symptoms
Study conducted in India	Study conducted elsewhere
Tested for *Mycobacterium bovis* using standard diagnostic tests	Study not addressing bTB
Any breed of cow or buffalo	Study neither performed on cow nor on buffalo
Reported the prevalence of bTB and the number of total animals screened	No statistics reported
In English	Language limitation: Not in English
Full text of publication obtained	Full text unavailable
	Other

2.3 Data extraction

Before beginning data extraction, a template was created supported population demographics and other conditions common to bTB prevalence studies. The info set recording general study characteristics included author, publication year, study period, location of study, diagnostic assay used, criteria for positivity, sample size, prevalence by different production system, overall prevalence for cow and buffalo combined, overall prevalence for specific cattle breeds, and overall prevalence for male and feminine animals. Headings for prevalence data weakened by more specific characteristics were production system (organized farm, rural, Gaushala and other), cow breed (exotic, indigenous and cross-bred), sex, age (younger or older than 6 months) and species (cow versus buffalo). Data extracted from studies’ individual farm-level data by each of the three of the authors (SS, LE and BR) were assigned to different strata targeted during this study. The determination of bTB infection status was accepted as reported by the studies.

A pilot test on 10 randomly selected papers was performed so as to check the inclusion and exclusion criteria and finalize the info extraction form. For the formal review of all articles generated, an initial screening for inclusion was made supported the titles and abstracts, and publications that were clearly supported different species, countries or diseases were immediately excluded. Otherwise, full texts were read for any prevalence data that would be extracted. Three of the authors (SS, LE and BR) independently reviewed all publications before comparing their respective data forms. When discrepancies were found amongst the forms, the authors (SS, LE and BR) collectively discussed their reasoning before reaching a final consensus.

2.4 Statistical analysis

All quantitative analyses were performed in RStudio (version 1.0.143) (“R core team, R: A language and environment for statistical computing.” R core team 2015) where the “meta” package was wont to estimate models (Schwarzer, 2007) (Viechtbauer, 2010). The prevalence estimates from individual studies were logit-transformed, and therefore the pooled prevalence was estimated using meta-analytic models. Cochran's Q statistic (Cochran, 1954) was computed to check for heterogeneity, and Higgin's statistic (Higgins, Thompson, Deeks, & Altman, 2003) (I2 > 50% represents a minimum of moderate heterogeneity) helped describe the variability within the pooled prevalence estimate thanks to heterogeneity between studies.

To visualize the prevalence of bTB within the different states of India, we generated a map utilizing an open-source library called D3.js (Data-Drive Documents) (Bostock, Ogievetsky, & Heer, 2011). This allowed us to plot data positions via the centroids of given shapefile locations represented within the map and control graphical elements supported their values (Cleveland & McGill, 1984). We utilized endless log scale for circle size to represent bTB prevalence and an influence function for circle lightness to represent the arrogance within the prevalence estimates of every state, ratifying values to visual variables on a linear scale (Bertin, 1983).

III. Results

3.1 Characteristics of included studies

From the 285 publications screened, 44 articles were included within the systematic review. Within the instance that a publication reported prevalence data for multiple states, years, cattle breeds, species or production systems, they were considered as separate strata level data. The study by Iyer (1944) has been extracted into three strata level data, the strata being the three locations during which the study was performed. An equivalent was finished other studies that included data on different production system, breed, species, etc. These studies included within the quantitative analyses spanned from 1942 to 2015 and provided bTB prevalence data for a complete sample size of 82,419 of which 29,037 were buffaloes and 53,382 were cows (Table 2).

Table 2 : Reported bTB prevalence for included studies

Lall et al. (1969)	Haryana	DIT	1567	2.7
Lall et al. (1969)	Bihar	DIT	169	4.7
Lall et al. (1969)	Uttar Pradesh	DIT	1418	4.9
Lall et al. (1969)	Rajasthan	DIT	727	2.6
Lall et al. (1969)	Telangana	DIT	426	1.9
Lall et al. (1969)	Maharashtra	DIT	194	1.0
Lall et al. (1969)	West Bengal	DIT	65	0.0
Lall et al. (1969)	Himachal Pradesh	DIT	177	0.6
Purohit and Mehrotra (1969)	Rajasthan	SICT	1010	1.8
Rawat and Kataria (1971)	Madhya Pradesh	DIT	1830	2.4
Nagaraja, Krishnaswamy, Adinarayanaiah, Murthy, and Nanjiah (1973)	Karnataka	DIT	3250	5.2
Joshi, Sharma, Dhillon, and Sodhi (1976)	Punjab	DIT	1081	10.5
Bali and Khanna (1979)	Haryana	SIT	663	1.4
Bali and Khanna (1979)	Haryana	SIT	624	4.6
Paily, Georgekutty, and Venugopal (1979)	Kerala	SIT	608	0.8
Appuswamy, Batish, Parkash, and Ranganathan (1980)	Haryana	Culture	308	4.6
Kulshreshtha, Jagjit, and Chandiramani (1980)	Haryana	SIT	13089	2.5
Bali and Singh (1980)	Haryana	SIT	628	2.4
Bala and Sidhu (1981)	West Bengal	NR	475	41.5
Bala and Sidhu (1981)	Haryana	NR	712	1.1
Bala and Sidhu (1981)	Uttar Pradesh	NR	732	13.1

Murti and Hazarika (1982)	Meghalaya	SICT	302	8.9
Sharma et al. (1985)	Uttar Pradesh	PM, ZN staining	1268	13.3
Bapat and Bangi (1985)	Maharashtra	SICT	2043	1.2
Maity, Deb and Pramanik (1992)	West Bengal	PM, ZN staining	1571	0.4
Sharma, Kwatra, Joshi, and Saharma (1994)	Punjab	SIT	2623	4.0
Rakesh Sisodia, Shuykla and Sisodia (1995)	Madhya Pradesh	SIT	465	9.0
Rajaram, Rao and Manickam (1996)	Tamil Nadu	SIT	1339	14.6
Mishra, Panda, and Panda (1997)	Orissa	SIT	670	3.4
Dev, Purohit, and Joshi (1998)	Rajasthan	SICT	75	10.7
Kumar, Sharma, Iyer, and Prasad (1998)	Uttar Pradesh	PM, ZN staining	1435	9.8
Aswathanarayana et al. (1998)	Karnataka	SIT	1189	25.7
Kumar and Parihar (1998)	Uttar Pradesh	PM Exam	2028	0.8
Chowdhury, Sarkar, Pal, Roy, and Chakraborty (2001)	West Bengal	PM, ZN staining	1050	3.9
Mukhopadhyay, Antony, and Pillai (2001)	Pondicherry	SICT	41	51.2
Shringi (2004)	Rajasthan	SIT	353	4.8
Singh, Gumber, Randhawa, Aradhana and Dhand (2004)	Punjab	SIT	627	9.1
Dali et al. (2004)	Maharashtra	NR**	340	6.2
Raval, Sunil, Belsare, Kanani and Patel (2006)	Gujarat	SIT	164	1.8
Raval et al. (2006)	Gujarat	SIT	167	0.0
Raval et al. (2006)	Gujarat	SIT	172	0.0
Raval et al. (2006)	Gujarat	SIT	152	3.3
Raval et al. (2006)	Gujarat	SIT	161	1.9
Ganesan (2006)	Tamil Nadu	SIT	63	65.1
Nishath and Ganesan (2006)	Tamil Nadu	SIT	63	49.2
Taggar and Bhadwal (2008)	Jammu and Kashmir	SIT	40	37.5
Phaniraja, Jayaramu, Jagadeesh and Kumar (2010)	Karnataka	SIT	2668	2.4
Aneesh, Mandeep, Katoch, Prasenjit, and Katoch (2010)	Himachal Pradesh	SIT	440	14.3
Trangadia, Rana and Srinivasan (2013)	Gujarat	SIT	2310	2.3
Trangadia et al. (2013)	Uttar Pradesh	SIT	338	0.6
Bhanu Rekha, Gunaseelan, Pawar, and Giri (2014)	Tamil Nadu	ELISA	357	4.5
Neeraja et al. (2014)	Karnataka	SIE	45	26.7
Ashish, Amit, and Deepak (2014)	Uttar Pradesh	SIT	245	14.3

Included studies used common diagnostic procedure s for bTB testing including the only subcutaneous test (SIT), single intradermal comparative tuberculin skin test (SICT), double subcutaneous test (DIT), enzyme-linked immunosorbent assay (ELISA), interferon-gamma release assay (IGRA), Ziehl–Neelsen (ZN) staining and detailed post-mortem (PM) examinations; some studies performed multiple tests that included SIT, IGRA and ELISA (SIE). While most studies followed OIE recommended guidelines for diagnostic test positivity at =4 mm after 72 hr ("International Office of Epizootics (OIE)," OIE, 2006) (the cut-off for both SIT and SICT tests), some studies defined their cut-off point as =5 mm; however, alittle number of publications didn't report criteria for test positivity (NR). A couple of studies classified animals as "doubtful" if the rise in skin thickness was between 3 and 4 mm. We didn't use any cut-off values on the amount of animals for classification of the varied production systems. Most included publications explicitly mentioned the sort of production system that was utilized in their studies. Within the instance that a study didn't specify the assembly system, we didn't include that study under any production system strata. To look at any effect of your time on the prevalence of bTB, the study periods were separated into four time intervals: 1941–1960; 1961–1980; 1981–2000; and, 2001–2015.

3.2 Meta-analysis

To assess for potential publication bias, a funnel plot was constructed of the logit prevalence against standard error. The shortage of symmetry within the funnel plot illustrates potential publication bias towards smaller studies with lower prevalence. Egger's asymmetry test was significant and showed presence of bias (p-value < 0.001), while Begg's rank correlation test didn't (p-value > 0.05).

Given the evidence for publication bias and improved qualitative fit of the RE model, we specialise in this model, which accounts for heterogeneity between individual studies, to estimate the prevalence of bTB in India from these data. The RE model was estimated from logit-transformed prevalence rates from individual publications, and therefore the pooled prevalence estimate of bTB in India decided to be 7.3% (95% CI: 5.6, 9.5). Cochran's (Q) value (Q = 3939.85, df = 105 and p < 0.0001) and Higgins statistic (I2 = 98.9%) were computed to check for heterogeneity. The meta-analysis, and comparison to the RE model, is graphically summarized during a forest plot.

3.3 Meta-regression

3.3.1 Univariable meta-regression

Due to the presence of statistical heterogeneity, we conducted univariable meta-regression so as to work out the effect of study-level covariates on the estimates of cumulative prevalence. The moderators considered for the analyses were study period, study location, sample size, production system, species, cattle breed and diagnostic procedure used. As seen in Table 3, the proportion of every predictor variable's effect on heterogeneity (R2) ranged from 0% to 16.5% within the RE model. Further, under the RE model, the very best value of R2 was observed for study location while, diagnostic technique, and sample size exhibited no effect on heterogeneity (R2 = 0%).

Table 3 : Univariable meta-regression

Predictors	Proportion (R^2) (%)	*p* value (RE)
Study period	7.0	0.04
Study location	16.5	0.01
Diagnostic technique	0.0	0.70
Species	0.7	0.22
Breed	0.7	0.40
Production system	2.5	0.16
Sample Size	0.0	0.95

Note : Proportion of effect of predictors on heterogeneity. All variables had a p < 0.01 within the FE model.

3.3.2 Multivariable meta-regression

All moderators from the univariable meta-regression were subjected to multivariable meta-regression (Table 4), which showed that these moderators accounted for 31.4% of the observed heterogeneity. Hence, the many variables included in our regression model explain only a fraction of the variability observed.

Table 4: Multivariable meta-regression

Predictors	Categories	No. of studies	Odds ratio (95% CI)	*p*-value (RE)
Study period	1941–1960	7	Reference	
	1961–1980	36	0.15 (0.04, 0.65)	0.01
	1981–2000	29	0.21 (0.05, 1.01)	0.05
	2001–2016	34	0.14 (0.03, 0.65)	0.01
Production systems	Gaushala	6	Reference	
	Organized	71	0.34 (0.09, 1.20)	0.09
	Rural	4	0.24 (0.04, 1.52)	0.13
	Semen station	1	1.05 (0.03, 34.89)	0.98
	Slaughterhouse	9	0.57 (0.06, 5.51)	0.61
Species	Buffalo	23	Reference	
	Cow	83	0.60 (0.28, 1.27)	0.16
Study location	Andhra Pradesh	2	Reference	
	Bihar	1	2.57 (0.13, 52.46)	0.54
	Gujarat	10	0.33 (0.03, 3.59)	0.36
	Haryana	15	0.51 (0.06, 4.48)	0.54
	Himachal Pradesh	3	3.88 (0.30, 49.20)	0.29
	Jammu and Kashmir	1	7.74 (0.27, 218.94)	0.22
	Karnataka	7	1.82 (0.19, 17.33)	0.60
	Kerala	2	0.22 (0.01, 5.80)	0.36
	Madhya Pradesh	5	1.56 (0.14, 17.54)	0.72
	Maharashtra	7	0.81 (0.08, 8.70)	0.86
	Meghalaya	2	1.22 (0.06, 24.31)	0.89
	Orissa	2	0.73 (0.03, 17.07)	0.84
	Pondicherry	1	58.57 (2.16, 1595.91)	0.01
	Punjab	12	2.12 (0.26, 17.49)	0.48
	Rajasthan	6	1.89 (0.18, 19.82)	0.58
	Tamil Nadu	5	8.17 (0.55, 121.89)	0.12
	Uttar Pradesh	16	1.32 (0.15, 11.50)	0.80
	Uttarakhand	2	0.13 (0.01, 3.21)	0.21
	West Bengal	7	2.39 (0.23, 24.87)	0.46
Diagnostic test	SIT	46	Reference	
	Culture	2	3.99 (0.53, 30.28)	0.18
	DIT	25	0.69 (0.23, 2.10)	0.52
	ELISA	2	0.71 (0.09, 5.52)	0.75
	PM Exam	6	0.08 (0.01, 0.77)	0.03
	SICT	11	0.69 (0.18, 2.65)	0.59

	SIE	1	0.07 (0.00, 1.03)	0.05
Breed	Cross-bred	19	Reference	
	Exotic	10	1.08 (0.37, 3.18)	0.88
	Indigenous	15	0.97 (0.39, 2.37)	0.94
Sample size			1.00	< 0.0001

Note : Multivariable meta-regression of the chosen predictors on the prevalence of bTB in India. (R2 = 31.4%, n = 106).

Analysis of variance (ANOVA) tests indicated that five (study period, study location, species, diagnostic assay and breed) of the seven moderators were significant ($p < 0.25$) when the opposite variables were included (Table 5).

Table 5 : ANOVA results

Predictors	***p*-value (RE)**
Study period	0.04*
Study location	0.001*
Production system	0.55
Species	0.16*
Diagnostic test	0.12*
Breed	0.13*
Sample size	0.93

Note : ANOVA results of individual predictors subjected to multivariable meta-regression. All variables had a p < 0.01 within the FE model. *represents significance.

3.4 Effect of moderators on prevalence of bTB

Prevalence estimates using both the RE and FE models are reported in Table 6. As noted above, the values reported from RE model are likely more appropriate given the observed heterogeneity within the studies because the FE model is biased by studies with larger sample size. supported the RE model, the prevalence of bTB in cows, 6.3% (95% CI: 4.9, 8.0), was marginally above the prevalence in buffaloes, 4.3% (95% CI: 2.7, 6.7). Amongst cows, prevalence by breed didn't vary greatly as cross-bred cows were found to possess the very best prevalence with 8.1% (95% CI: 4.6, 13.8), followed by indigenous cows with 7.4% (95% CI: 4.0, 13.1), and exotic cows with 7.0% (95% CI: 3.7, 12.9). Unlike cattle breed, larger differences were seen amongst production systems as cattle housed in Gaushalas (protective shelters for unproductive or destitute cows in India) had a better prevalence, 19.1% (95% CI: 13.0, 27.1) than those kept in organized farms, 5.1% (95% CI: 3.8, 6.7) and rural conditions, 4.4% (95% CI: 1.0, 16.5). The period of time, 1941–1960, was found to possess the very best prevalence, 13.8% (95% CI: 10.5, 17.9), while 1961–1980 was found to possess rock bottom , 3.6% (95% CI: 2.6, 4.9). a complete of 28,073 animals had been tested during 1961–1980. The period of time between 1981 and 2000 showed a prevalence of seven .0% (95% CI: 4.8, 10.2), and therefore the prevalence of the foremost recent period of time between 2001 and 2015 decided to be 6.8% (95% CI: 4.3, 10.7) (Table 6).

Table 6 : Pooled prevalence estimates (derived from both RE and FE models) of the varied predictors namely, cattle species, breed, production system and study period

Predictors		**Sample size**	**Prevalence (95% CI) (RE model)**	**Prevalence (95% CI) (FE model)**
Species	Buffalo	29,037	4.3% (2.7, 6.7)	16.0% (15.5, 16.4)
	Cow	53,382	6.3% (4.9, 8.0)	10.2% (9.8, 10.5)
Cattle breed	Exotic	2,011	7.0% (3.7, 12.9)	16% (14.1, 18.2)
	Cross-bred	9,548	8.1% (4.6, 13.8)	13.5% (12.7, 14.5)

Production systems	Indigenous	4,169	7.4% (4.0, 13.1)	15.5% (14.0, 17.1)
	Gaushala	576	19.1% (13.0, 27.1)	18.7% (15.7, 22.3)
	Organized farm	43,847	5.1% (3.8, 6.7)	8.4% (8.1, 8.7)
	Rural farm	1,607	4.4% (1.0, 16.5)	3.3% (2.2, 4.7)
Study period	1941–1960	26,961	13.8% (10.5, 17.9)	17.0% (16.6, 17.5)
	1961–1980	28,073	3.6% (2.6, 4.9)	3.9% (3.6, 4.2)
	1981–2000	16,927	7.0% (4.8, 10.2)	13.9% (13.2, 14.6)
	2001–2016	10,458	6.8% (4.3, 10.7)	9.2% (8.5, 10.0)

3.5 Geographical distribution of included studies in India

Study reports from included publications encompassed 18 states and one union territory in India. No reports were found for Arunachal Pradesh, Assam, Chhattisgarh, Goa, Jharkhand, Manipur, Mizoram, Nagaland, Sikkim, Telangana, Tripura, Andaman and Nicobar Islands, Chandigarh, Dadra and Nagar Haveli, Daman and Diu, Delhi, and Lakshadweep, comprising a complete of 11 states and 6 union territories. It are often observed from the map that the prevalence of bTB varied highly between states (Table 7).

Table 7 : Pooled prevalence estimates (RE model) of bTB prevalence in India by state

STATE	Sample size	Prevalence (95% CI) (RE model)
Andhra Pradesh	426	2% (1.0, 3.9)
Bihar	169	4.7% (2.4, 9.2)
Gujarat	28,268	3.6% (2.2, 5.8)
Haryana	17,693	3.3% (1.9, 5.4)
Himachal Pradesh	617	15.4% (4.2, 43.4)
Jammu and Kashmir	40	37.5% (24.0, 53.2)
Karnataka	7,152	7.9% (3.0, 19.2)
Kerala	608	1.0% (0.3, 3.6)
Madhya Pradesh	2,295	6.3% (2.7, 14.00)
Maharashtra	2,697	2.7% (1.0, 6.9)
Meghalaya	302	8.7% (5.1, 14.3)
Orissa	670	4.5% (1.5, 12.5)
Pondicherry	41	51.2% (36.3, 66.0)
Punjab	5,780	8.9% (5.5, 14.2)
Rajasthan	2,165	5.0% (2.1, 11.5)
Tamil Nadu	1,822	19.6% (6.6, 45.9)
Uttar Pradesh	8,156	6.5% (4.3, 9.8)
Uttarakhand	227	0.4% (0.1, 3.1)
West Bengal	3,291	7.8% (2.1, 25.7)
Grand Total	82,419	

IV. Discussion

After screening of 285 publications, we extracted data from 44 cross-sectional studies published in peer-reviewed journals that report the prevalence of bTB in India and conducted meta-analysis. The pooled prevalence estimate (RE model) for all of India was found to be 7.3% (95% CI: 5.6, 9.5). Despite being a disease of antiquity with significant animal and public health costs that are controlled in most developed countries over a half-century ago, bTB features a high and widespread prevalence in India as no national control strategies are implemented within the country. These data suggest that India, because the world's largest producer of milk (~156 MMT), accounting for ~18.5% of the world's total milk production and therefore the world's largest meat exporter (~1.9 MMT), has an urgent and so far unmet need for control of bTB for both economic and public health reasons (DADF, 2015).

Overall, the ordering of prevalence estimates determined using the FE model for various production systems follows an equivalent trend as within the RE model (i.e., prevalence in Gaushala > Organized farms > Rural farms) (Table 6). However, given the observed heterogeneity within the studies, it's difficult to assess the validity of the FE model, and hence, further study is important to clarify the precise influence that every production system has on bTB prevalence before definitive conclusions are often made. We note that accurate estimates of prevalence rates for every production system are particularly important within the Indian context where the magnitude of animals housed in Gaushalas and therefore the increasing population of cattle being reared under intensive conditions have the potential to considerably impact overall prevalence and influence assessment of bTB transmission rates and targeted interventions.

Regarding animal species (cow versus buffalo), the meta-analysis (RE model) shows prevalence to be higher in cows [6.3% (95% CI: 4.9, 8.0)] than in buffaloes [4.3% (95% CI: 2.7, 6.7)]. However, we note that the prevalence in buffaloes determined using the FE model was 16.0% (95% CI: 15.5, 16.4) which in cows was 10.2% (95% CI: 9.8, 10.5). The high prevalence observed in buffaloes using the FE model is presumably driven by one study that sampled 21,592 buffaloes (of a complete buffalo sample size of 29,037 included during this meta-analysis) and recorded a prevalence of 17.4% (Dhanda & Lall, 1959). As per the govt of India's Department of Animal, Dairy and Fisheries (DADF) 2015–2017 Annual report, the share of milk contribution from buffaloes is 49% which of cows is 48% (DADF, 2015). Assuming a conservative 10% loss in milk productivity thanks to bTB (Thoen, 2008) and therefore the overall estimated bTB prevalence rates supported the RE model, the annual costs to farmers only from loss in milk production in cows and buffaloes in India are estimated to range from 375 to 544 million USD (Supporting information Table S1). We note that the necessity for intensification of dairy production to satisfy increased milk demand and national priorities for nutritional improvement and rural development is probably going to significantly increase bTB disease prevalence because the disease is understood to more easily spread amongst intensively reared cattle. With the inevitable increase in bTB prevalence, this already large economic cost will only still grow if no intervention measures are implemented.

Published studies on the influence of breed on genetic susceptibility to bTB showed that the native breed of cattle is more immune to the disease than exotic breed (Vordermeier et al., 2012) (Soparkar, 1925) (Liston & Soparkar, 1917) (Sharma, Vanamayya, & Parihar, 1985), affirming a generally held and commonly disseminated dogma. In contrast, our results note no significant differences in bTB prevalence between cow breeds in either the RE or the FE models (Table 3). However, given the heterogeneity observed within the studies, rigorous investigations of truth differences in susceptibility amongst different cattle breeds to bTB are going to be essential for evidence-based formulation of a rational approach to regulate this disease in India.

Our analysis also indicated the presence of temporal heterogeneity (R2 = 7.04%) over the 74-year time-frame (1942–2015) represented by the included studies (Table 3). While the precise source(s) of this heterogeneity is unclear, contributors may include differences in environmental conditions over time (Humblet et al., 2010) (Bekara, Azizi, Bénet, & Durand, 2015), the amount of studies within whenever interval, animals tested, test operators' skills/methods and therefore the diagnostic tests themselves. Recent studies have also shown that the standard , origin and source of tuberculin used are variable within tuberculin-based tests, highlighting a scarcity of standardization (Bakker et al., 2005). Additionally to such variation within individual tests, the performance, sensitivity and specificity vary across tuberculin-based tests making comparisons difficult and imprecise (Hartnack & Torgerson, 2012) (Varello et al., 2008) (Cousins & Florisson, 2005) (Ameni, Miörner, Roger, & Tibbo, 2000). While most tests are tuberculin-based, there are potential causes for heterogeneity that remain to be explored. Thus, combined with the prevailing limitations of non-standardized and ranging performance characteristics of current diagnostic tests, we underscore the necessity for a national surveillance programme employing a single, well-standardized diagnostic test performed by independent, well trained operators using OIE approved protocols and well-standardized tuberculin antigen to enable accurate monitoring of bTB prevalence over time and therefore the impacts of any potential intervention or control programme.

Mycobacterium bovis has also been isolated from milk samples of tuberculous cattle (Aswathanarayana, Rao, Krishnappa, Ramanatha, & Raghavan, 1998) (Veerasami et al., 2012). Given the very fact that over 70% of the milk in India is sold unpasteurized (FAO/OIE/WHO, 1993), this raises concerns regarding the potential for zoonotic transmission of bTB and continued spread of human tuberculosis (India has the world's largest burden of human TB) (Thoen, LoBue, & de Kantor, 2006). In May 2014, the planet Health Assembly adopted a replacement strategy to achieve an ambitious goal of ending the worldwide TB epidemic by 2035: the top TB strategy (Uplekar et al., 2015). Given the prevalence of bTB and therefore the potential for zoonotic transmission, particularly to children et al. who consume unpasteurized or unprocessed milk from infected cows, there's a critical need for a national bTB control programme in India and other developing countries as attempts to eradicate the disease from humans without eradicating it from cattle are likely to prove futile. Importantly, implementation of a national control programme wouldn't only enable accurate temporal trends and estimates of bTB prevalence, risk and economic costs, but would equally importantly improve the health and productivity of cattle in India.

V. Conclusion

Overall, the results of our systematic review and meta-analysis conducted on 44 publications indicate high and widespread bTB prevalence in India of seven .3% (95% CI: 5.6, 9.5). Further study is important to get more robust state-by-state prevalence estimates and explore other moderators of risk (including herd size, animal sex, and age, amongst others) that are likely to impact development and implementation of a rational and effective bTB control strategy. Taken along side the expected dairy intensification, growing demands for increased milk production and therefore the zoonotic nature of M. bovis, the results of our current studies highlight the importance of developing and implementing a national bTB control programme which will got to include a national surveillance plan using (a) well-standardized method(s) and evidence-based intervention(s) that are likely to figure in India and other developing country settings.

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