Systematic Review and Meta-analysis of Prevalence of Hepatitis B in India

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Objective: *To evaluate the point prevalence of Hepatitis B in India.* ***Design:*** *Meta-analysis of data on point prevalence from different parts of the country.* ***Data sources:*** *Searches were made in Medline, Cochrane Library and Best bets and previous reviews. A limited hand search of cross references was also done. Finally a consultation with experts was held to enlarge the references base.* ***Review methods:*** *Studies reporting prevalence of HBsAg were selected. Data from high risk groups were excluded.* ***Main Results:*** *54 papers reporting data on 61 populations were identified. The true prevalence for each study was calculated from the reported prevalence using the specificity and sensitivity of the test employed. The true prevalence in non-tribal populations is 2.4% (95% CI: 2.2% - 2.7%). True prevalence among tribal populations is 15.9 % (CI: 11.4% - 20.4%).* ***Conclusion****: These figures may be useful in estimation of the burden of the disease in the country and for projecting the cost-benefits of immunization.*

Key words: *Hepatitis B, Meta-analysis, Prevalence.*

THE carrier rate of Hepatitis B in India is different in the different regions of the country. The overall carrier rate is often quoted as being 4.7%(1). This is the weighted mean of various studies and includes high risk populations(2). Lodha, *et al.*(3) did a systematic review of literature and concluded that the true prevalence of Hepatitis B in India was 1 to 2%. No statistical tool was used in the systematic review to synthesise the results of the different studies. There is therefore need to calculate the prevalence of Hepatitis B using appropriate meta-analytic tools. This study was undertaken under the auspices of the Indian Medical Association's 'Subcommittee on Immunization' to evaluate the true prevalence of Hepatitis B in India.

Material and Methods

Lodha, *et al.*(3) published a systematic review of Hepatitis B in India having accessed 128 papers. This analysis included 18 papers on prevalence(4-21). A limited hand search within these articles was performed to identify new references. We also used relevant papers that were referenced in the correspondence regarding the systematic review. This exercise identified 7 new papers(22-28). The 25 papers included data from 29 population studies.

To update the review, we did a search for papers published subsequently. Assuming publication delays of 18 to 24 months, we searched the literature from January 1999 onwards up to January 2006, and incorporated these studies into the analysis.

Search strategy and outcome

Search terms included "hepatitis b" [MeSH Terms] OR Hepatitis B [Text Word]) AND ("india" [MeSH Terms] OR India [Text Word])) AND ("1999"[PDAT] : "3000"[PDAT]. (Search date 19/1/06). Titles and abstracts identified by electronic searches were examined independently by 2 researchers on-screen, to select potentially relevant studies. All studies looking at the point prevalence of hepatitis B were considered prima facie relevant. Criteria for inclusion are given below. Differences were resolved by consensus. The full text paper was obtained wherever possible.

Inclusion & Exclusion criteria

We included studies of voluntary blood donors (VBD) (altruistic donations) and replacement donors (RBD) (blood donated to replace blood utilized in specific patients–often friends or blood relations of the donor) and studies involving antenatal women and community studies. We

excluded studies from the following special groups who were assumed to be at high risk for hepatitis B: patients from sexually-transmitted-disease clinics, thalassemia clinics, hospitalised patients, professional blood donors, sex workers, drug abusers, dialysis patients, and hospital staff.

Best bet

Best bet search (http;//www.bestbets.org/cgi-bin/browse.pl)

Search term: 'Hepatitis': All years.

Cochrane collaboration (http://www.cochrane.de/cc_bin/) Search term: 'Hepatitis B': All years.

Experts' consultation

A draft of this meta-analysis was sent to experts in the field who were invited to enlarge the review by contributing references which may have been missed using the search strategy adopted. Researchers in the field and stakeholder from various organizations namely; The India Advisory Expert Group, Indian Academy of Pediatrics, WHO, Ministry of Health, were invited to an experts consultation in Delhi. The draft paper was then modified using inputs from reviewers. Two new papers(16,22) were added and one study originally included in the non-tribal group(34), was identified as a study among tribals. These corrections were made and the meta-analysis was done again.

Overall this new systematic review includes data from a total 61 populations identified in 54 papers (*Table I*).

Data extraction and data analysis

(*a*) *Quality assessment*

Lodha, *et al.*(3) have pointed out that there is need to compensate for 'misclassification errors' caused by the false positives and false negatives (due to less than 100% specificity and sensitivity of the test used) where the estimated prevalence of a disease is low. The true prevalence can be calculated using the formula of Tu, *et al.* 1992(58). The

TABLE I–*Study Design and Sample Size of Studies Included in the Meta-Analysis*

Sl. No.	Author	Ref No.	Location	Sample population	Total samples	Positives	Method used
1	Abass Faud	29	Delhi	Mothers	6910	70	1
2	Ahmad B	30	Jodhpur	Volunteers (Community)	946	23	1
3	Benerjee A	31	Kolkata	Mothers	400	15	9
4	Bhagyalaxmi A	32	Ahemdabad	Community	702	10	1
5	Biswas SC	4	Chandigarh	Mothers	1000	23	4
6	Chakravarthi	33	Delhi	Mothers	400	17	1
7	Chakravarthi	33	Delhi	Child <5 yrs	400	9	1
8	Chandra M	33	AP	Tribal	890	46	1
9	Chandrasekharan S	35	Madurai	VBD	1819	75	1
10	Choudhury N	5	Lucknow	VBD	313	8	1
11	Chowdhury A	36	West Bengal	Community	7653	227	1
12	Elavia AJ	6	Bombay	Blood donor	10433	211	1
13	Ganju SA	37	Jodhpur	Community	200	7	1
14	Garg s	38	Jodhpur	Blood donor	46957	1615	1
15	Gupta I	7	Chandigarh	Mothers	2337	58	9
16	Gupta N	39	Ludhiana	VBD	44064	290	1
17	Irshad M	8	Delhi	VBD	20435	531	1
18	Joshi RM	40	Chandigarh	VBD	21180	426	9
19	Joshi SH	9	MP	Tribal pop	1314	206	4
20	Kaur H	41	Ludhiana	VBD	60780	1033	1
21	Kaur R	42	Delhi	Children	276	20	1

(*contd...*)

Sl. No.	Author	Ref No.	Location	Sample population	Total sample	Positives	Method used
22	Kaur U	22	Chandigarh	Community	818	24	9
23	Khatri JV	10	Bombay	Mothers	1276	8	4
24	Kurien T	43	Tamil nadu	Community	1981	113	1
25	MahaLakshmi B	44	Chennai	Community	483	17	9
26	Makroo RN	11	Srinagar	VBD	7900	88	4
27	Mohite JB	12	Navi Mumbai	VBD	1042	22	4
28	Mukherjee M	23	Rajastan	Tribal	536	55	4
29	Mukherjee M	23	Maharastra	Tribal	691	62	4
30	Mukherjee M	23	MP	Tribal	182	26	4
31	Murhekar MV	45	Andaman Nicobar	Community-tribal	887	197	1
32	Murhekar MV	49	Andaman Jarawas	Community-tribal	64	12	1
33	Murhekar MV	48	Andaman Nicobar	Children-tribal	1574	354	1
34	Murhekar MV	46	Andaman Nicobar	Community-tribal	1144	267	1
35	Murhekar MV	46	Andaman - Shompens	Community-tribal	37	14	1
36	Murhekar MV	46	Andaman Onges	Community-tribal	58	18	1
37	Murhekar MV	46	Andaman Andamanese	Community-tribal	27	1	1
38	Nandi J	13	Pune	VBD	94	6	1
39	Nanu A	24	Delhi	VBD + RBD	132093	2532	1
40	Nayak NC	14	Delhi	Others	8575	322	1
41	Nijhawan S	15	Jaipur	VBD + RBD	69330	1456	4
42	Panda SK	16	Delhi	Mothers	8431	191	1
43	Prakash C	25	Delhi	Mothers	1112	106	1
44	Prasad SR	17	Arunachal	Tribal	296	25	4
45	Qamer S	50	Aligarh	Children	460	20	4
46	Sahni Mohit	51	Delhi	Mothers	987	22	1
47	Satoskar	26	Bombay	VBD	3104	146	1
48	Sharma R	27	Aligrah	Mothers	157	16	4
49	Sharma R	27	Aligrah	Newborns	157	8	4
50	Sharma RR	52	Chandigarh	VBD+RBD	235461	2354	1
51	Singh B	53	Delhi	VBD+RBD	128589	2275	4
52	Singh H	54	Lucknow	Community	730	15	1
53	Singh J	55	Rajamundry	Community	737	24	4
54	Singh J	55	Bangalore	Community	816	34	4
55	Singhvi A	18	Vellore	VBD+RBD	35395	1006	1
56	Sumathy S	19	Chennai	VBD	530	37	2
57	Tandon BN	20	Delhi	Children <5	982	21	1
58	Thakur TJ	21	Himachal	VBD	1274	33	3
59	Varghese RM	57	Delhi	Mothers	6341	52	1
60	Vinod Kumar CS	56	Gulbarga	Community	267	19	9
61	Werner GT	28	Punjab	Community	385	13	4

VBD: Voluntary blood donor; RBD: Replacement blood donor; ELISA = 1; DIA = 2; RPHA = 3; TWO METHOD = 4; METHOD NOT KNOWN = 9.

What is Already Known

- The prevalence of hepatitis B in India is different in different regions; it is higher among tribal populations. It is often said that the chronic carrier rate in India is 4.7%.

What this Study Adds

- This meta-analysis reveals that the prevalence of Hepatitis B in tribal and non-tribal populations of India is 15.9 % (CI: 11.4% - 20.4%), and 2.4% (95% CI: 2.2 - 2.7%), respectively.

specificity and sensitivity of the test as described in the paper was used. If this was not mentioned, enzyme immunoelectrophoresis (ELISA) was considered 99.8% sensitive and 99.8% specific(59) reverse passive hemagglutinatin (RPHA) as 75% sensitive and 98% specific(60) and dipstick immunobinding enzyme-linked immunosorbent assay (DIA) 98% specific and sensitive(18). If two tests were done on one sample sequentially the test was considered true positive.

$$\text{True prevalence} = \frac{[\text{Estimated prevalence} - (1 - \text{specificity})]}{[\text{Sensitivity} - (1 - \text{specificity})]}$$

We disregarded studies where the test used was not specified and where the specificity and sensitivity of the test used was not known.

(*b*) *Sensitivity testing*

Sensitivity analysis was performed with all studies included, as if the specificity and sensitivity of all the tests used were 100% / 100%. This analysis included 12 papers which did not specify the specificity and sensitivity of the tests employed.

(*c*) *Forest plot and evidence of heterogeneity*

In the first stage, the prevalence with its 95% confidence intervals was calculated for each individual study. In the second stage of meta-analysis, an overall prevalence was calculated as a weighted average of individual summary statistics. The results were displayed as a forest plot (*Fig. 1*). The prevalence of Hepatitis B among tribal peoples was distinctly different from that of others. Meta-analysis has therefore to be done separately in the two groups.

Presentation of Graphs and Tables of the Meta analysis: Where a large number of studies are included in the forest plots, the weights and confidence intervals of individual studies are listed in a table separate form the graph, in order to reduce the clutter and to improve readability.

Meta analysis of data according to the population group studied: In the State of Delhi from where a large number of studies on prevalence have been published, we looked at the summary prevalence among voluntary blood donors, replacement donors and antenatal mothers separately. We did a similar analysis after pooling the studies from Punjab, Haryana and Chandigarh. All analyses were implemented on Stata 9.0. (Stata Corporation, 4905 Lakeway Drive, College Station, TX 77845, USA)

Results

The Medline search resulted in 272 hits, yielded 29 papers and 32 population studies after applying the inclusion criteria(29-57). Best Bet and the Cochrane collaboration yielded 2 and 96 papers respectively, but none were relevant.

Figure 2 shows the results of the meta-analysis of true prevalence data of hepatitis B among non tribal populations in India. The true prevalence in the non-tribal population is 2.4 (95% CI: 2.2%-2.7 %). True prevalence among tribal populations is 15.9%. (95% CI: 11.4 % -20.4 %) (*Fig.3*).

Sensitivity testing: Assuming 100% specificity and sensitivity the prevalence among non-tribal people was 2.7% (CI: 2.4% - 2.9%) The prevalence among tribal populations was 15.9% (CI: 11.4%-20.4%).

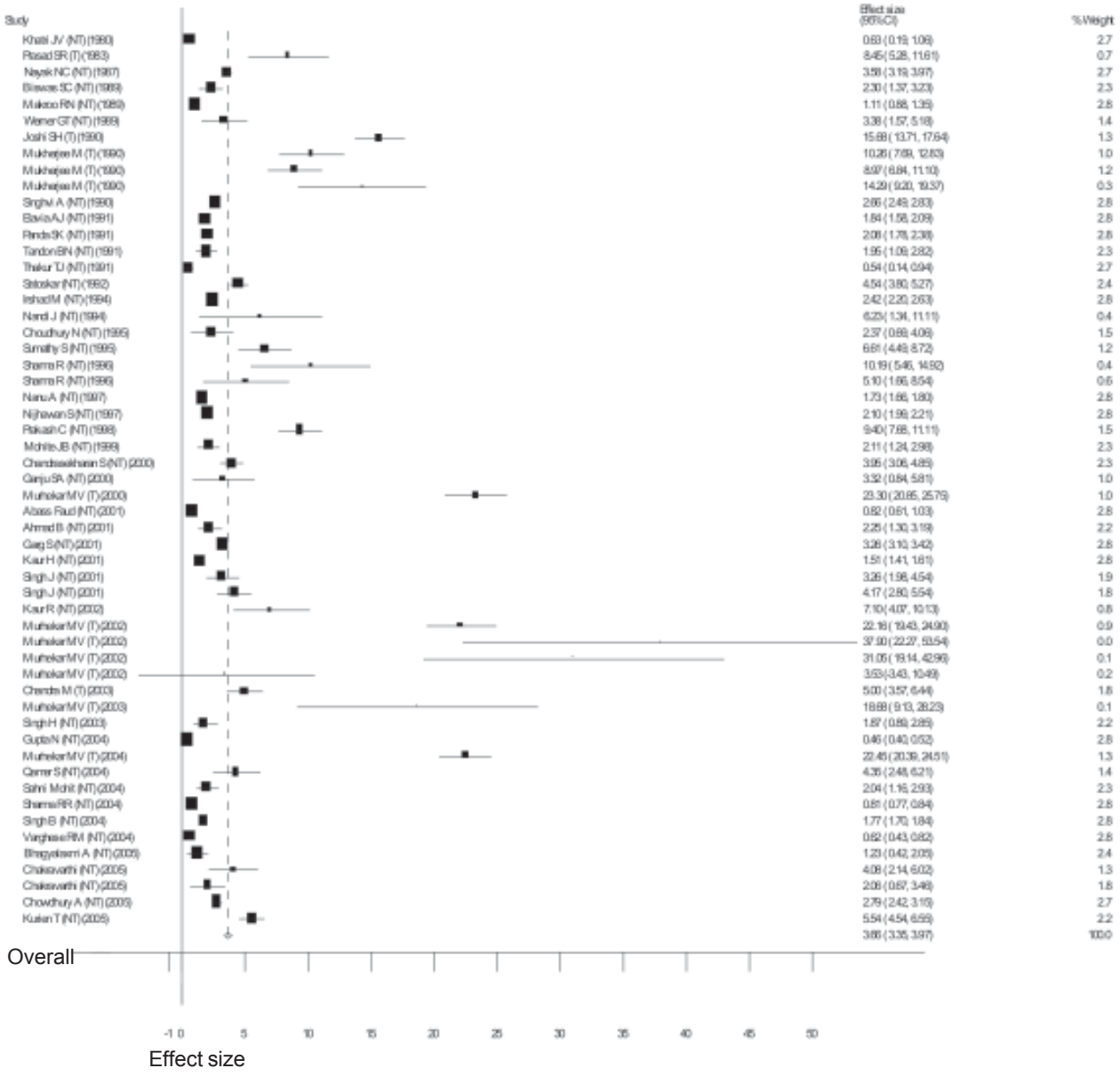


Fig.1. Forest plot of studies on prevalence of Hepatitis B showing two types of population.

Prevalence in the sub-groups

Figure 4 shows the table and graph of the meta-analysis of studies from Delhi classified according to the population group studied. It appears that voluntary blood donors have a higher prevalence than replacement donors. A similar pattern was seen in Punjab, Haryana and Chandigarh (*Fig.5*). Here replacement donors had prevalence even lower than the overall mean.

Discussion

This is the first meta-analysis of hepatitis B prevalence studies in India.

In our analysis, the results showed significant heterogeneity and we had to study the tribal populations separately from that of non-tribal populations(61). Even after analyzing the non-tribal and tribal populations separately, there was significant heterogeneity among the studies.

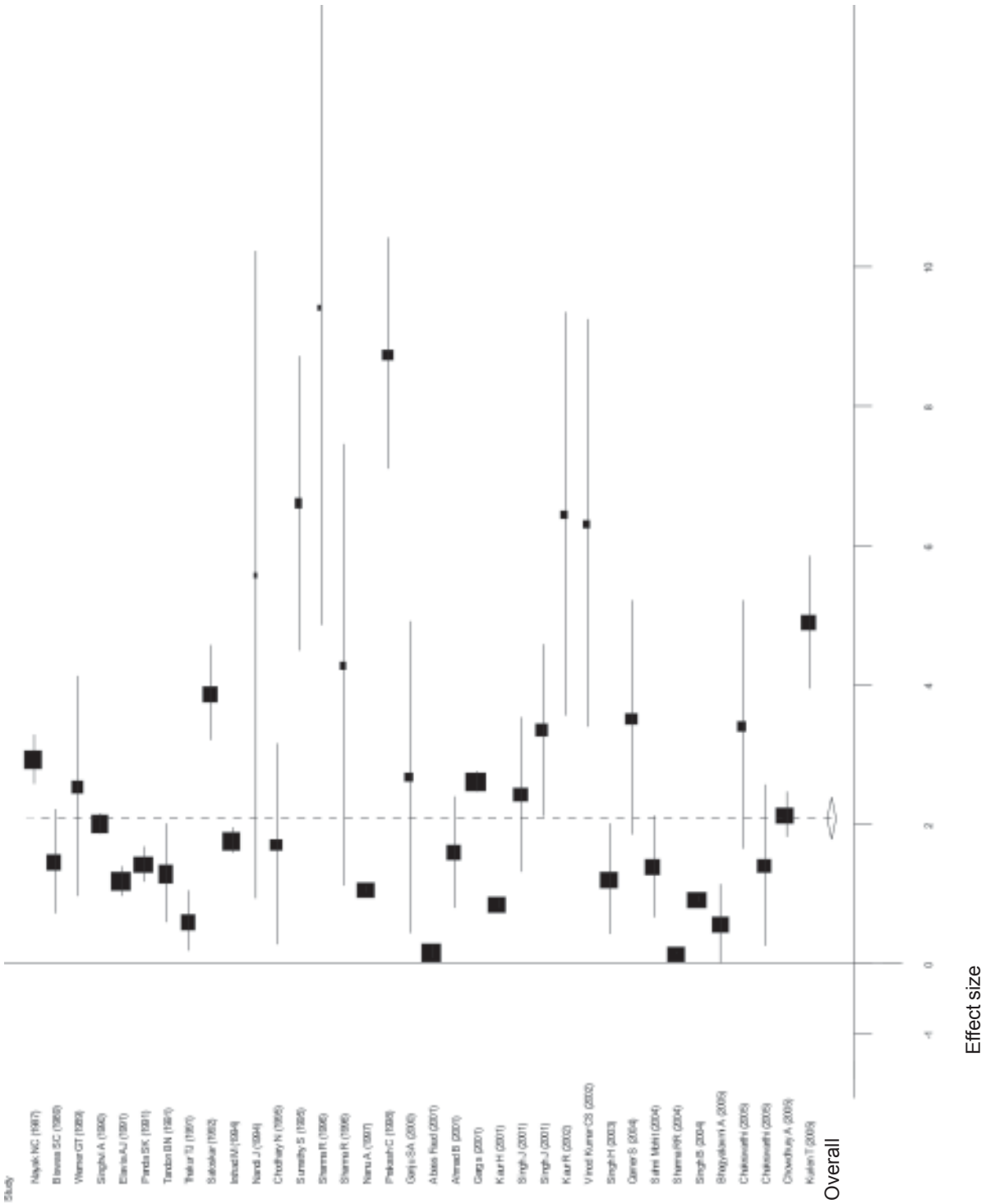


Fig.2. True Prévalence of Hepatitis B in Non Tribal Populations of India

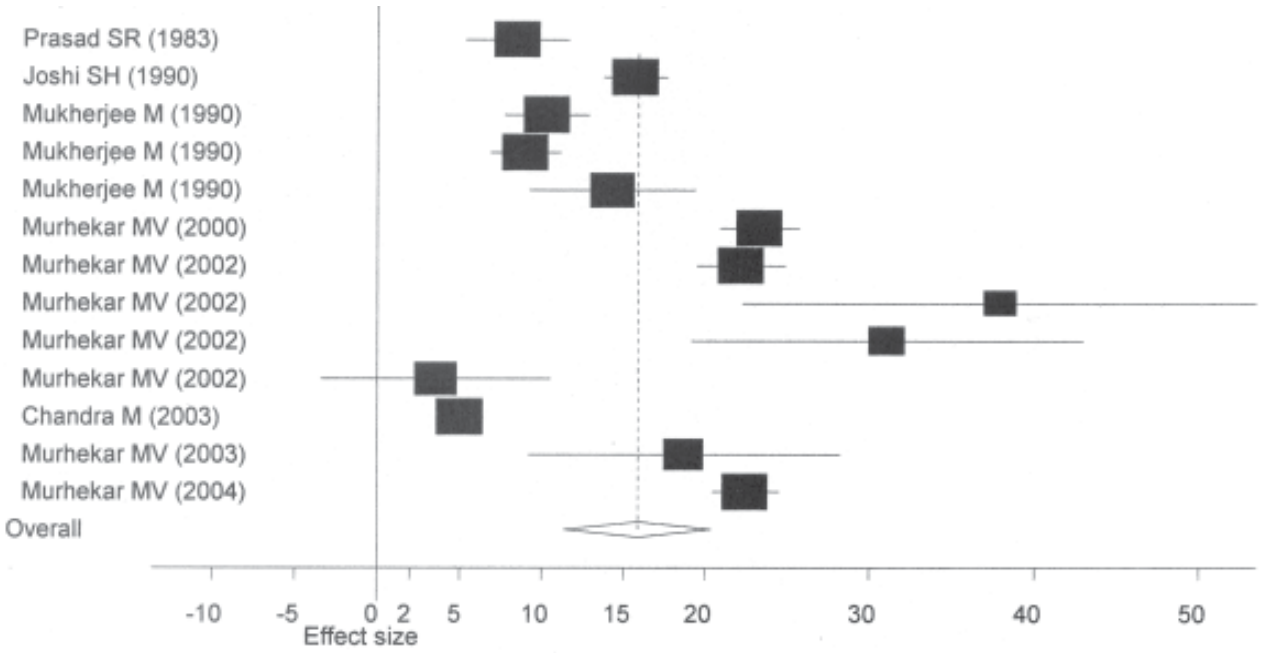


Fig.3. True prevalence of Hepatitis B among Tribal populations of India

(Heterogeneity Chi-square significant (P <0.01) in both groups and the I^2 being 85% in tribal populations and >90% in non-tribal populations). This is not unexpected in view of the different populations studied and the nature of variations associated with the different methods, kits, antigens etc used in estimating the prevalence. However, a meta-analysis of such studies might still be useful in providing an idea of the overall prevalence.

Nearly all the studies we have analysed are cross-sectional studies and are therefore indicative of the point prevalence of the disease. A chronic carrier is one with persistence of infection for more than 6 months(62). Studies that have followed up initial HBsAg positive cases for 6 months have found 75% to 80% chronic carriers. Assuming that the chronic carrier rate is 80% of the point prevalence, the chronic carrier rate in the country among non-tribal populations is 1.9%.

John and Abraham(63) have questioned the inclusion of voluntary blood donors in the systematic review by Lodha, *et al.*(2). They refer to a study among voluntary donors at Vellore where the carrier rate was 0.7%. This, they suggest, is artificially low because voluntary donors are a self-selected group and persons who are found hepatitis B positive, do not come for repeat blood donation. They suggest using data from replacement donors. Lodha et al. in their rejoinder have justified the use of voluntary donors and suggested that replacement donors on the other hand, are likely contaminated by professional donors masquerading as replacement donors. To test these contrary viewpoints, we conducted subgroups analysis of patients tested in Delhi. The carrier rate among voluntary donors was in fact higher than that of replacement donors and if we had taken the suggestion of John *et al* to exclude voluntary donors, the true prevalence would come out to be lower than 2.4%. On examining at the forest plots from the Delhi studies; voluntary donors, replacement donors and ante-natal mothers have prevalence close to the overall mean and it seems appropriate that all these groups are included in the systematic review and meta-analysis. The analysis of data from Haryana and Punjab also support this conclusion.

It is possible that despite the extensive search done by the authors, the specific search terms used, they may not have captured all good quality papers published in peer-reviewed indexed journals. The electronic search was therefore supplemented by a

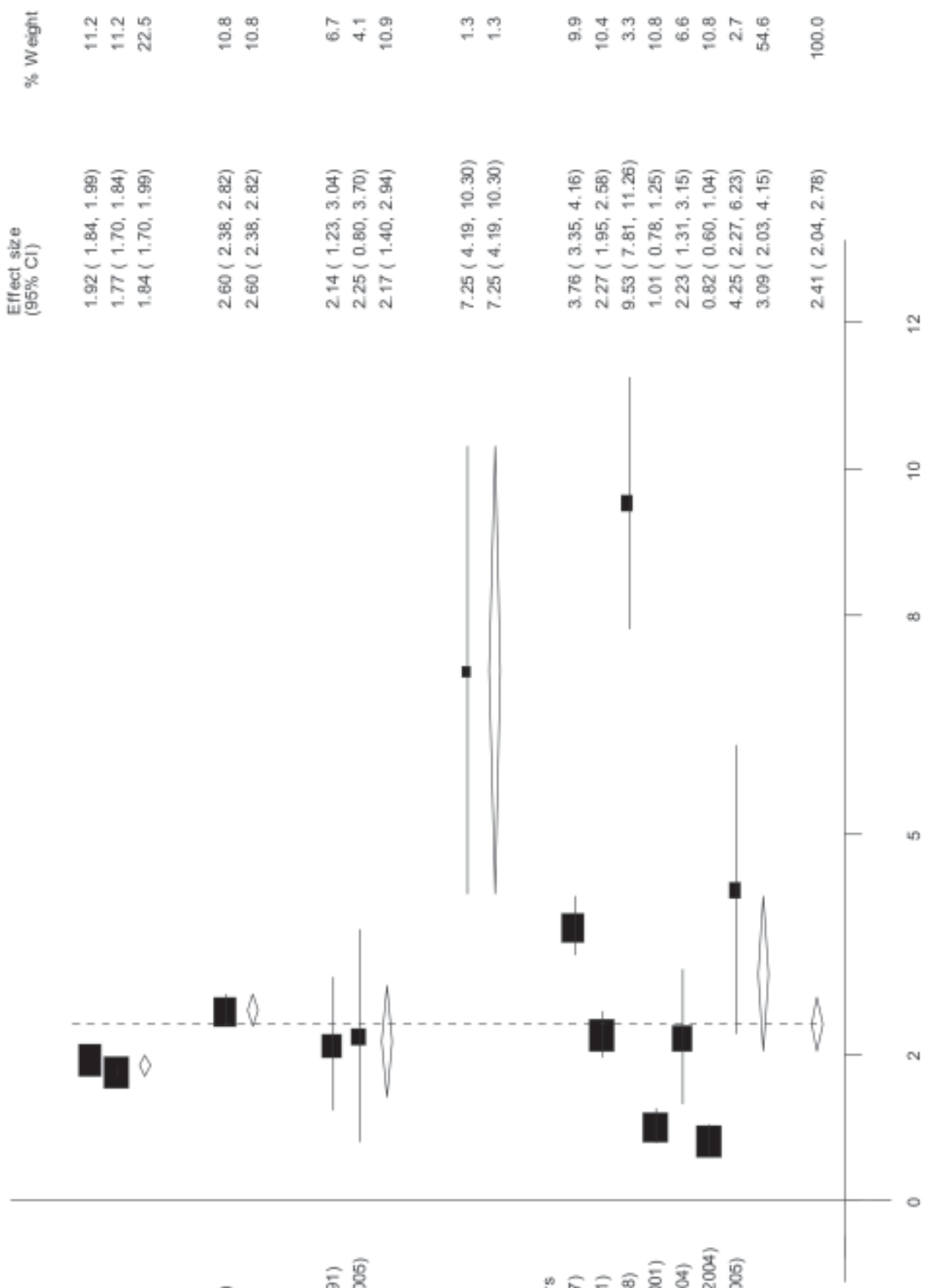
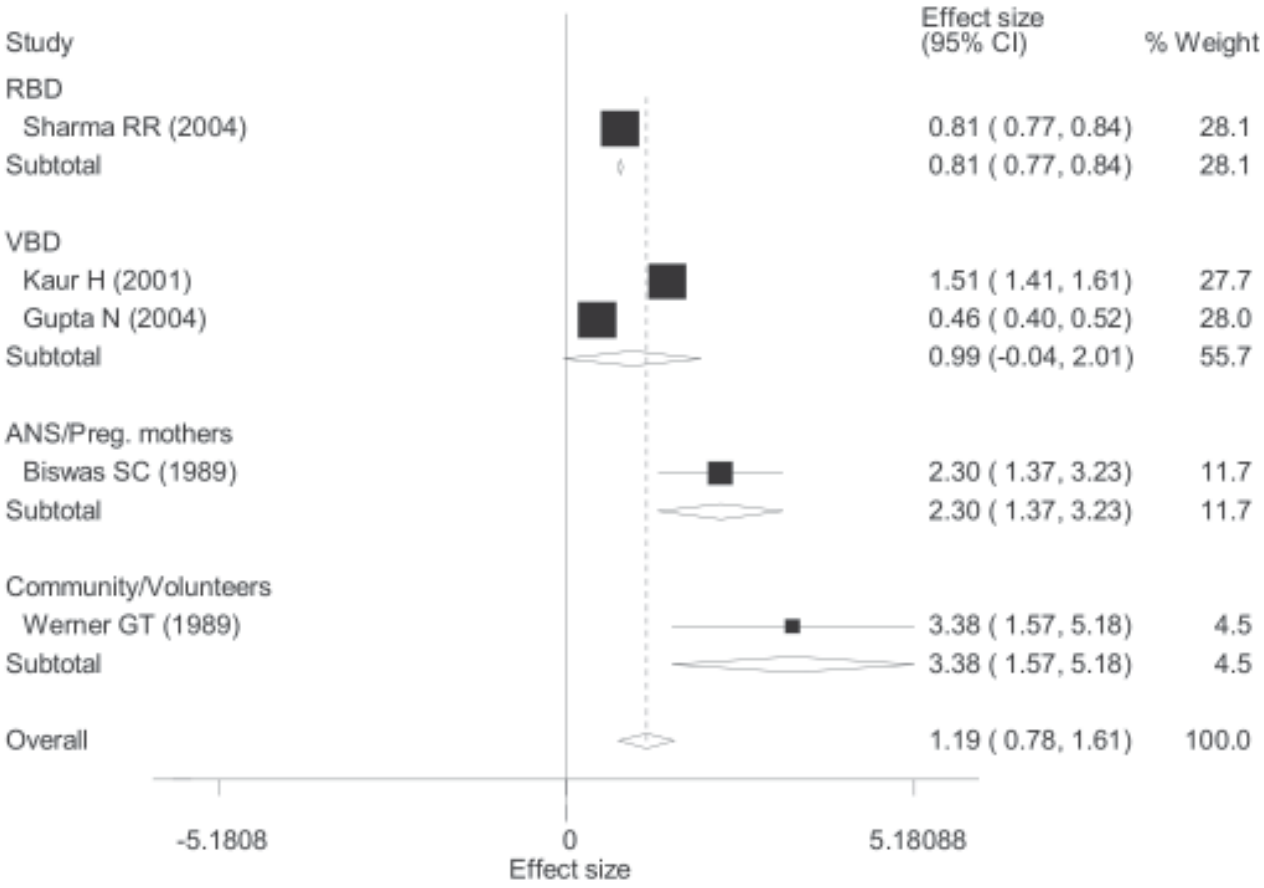


Fig. 4. Prevalence of Hepatitis B in Delhi

VBD: Voluntary blood donor, RBD: Replacement blood donor, ANC: Ante-natal case



VBD: Voluntary blood donor, RBD: Replacement blood donor, ANC: Ante-natal case

Fig. 5. Prevalence of Hepatitis B in Punjab and Haryana

limited hand search of references. Further, a consultation with experts was conducted specifically to enlarge the systematic review by including additional references.

In these studies that we have retrieved and analysed, there was little attempt to get a sample representative of population in India. Most studies published data from 'convenience samples'– women coming for antenatal check-up or people coming to make blood donations and mostly from urban areas. This constitutes a further limitation to the inference drawn.

It is understood that only a large national epidemiological study can give the final answer as to the overall prevalence of Hepatitis B in India. In the absence of such a national sample survey, a meta-analysis of all the studies from India provides the best evidence.

Blood donors constituted 85% of the total sample and blood donors are frequently male. Pregnant women constituted 4.2% of the sample and children 0.25%. Internationally males have a higher prevalence of hepatitis B(64) and the large representation of males in this analysis may overestimate the true prevalence in a society made up of equal numbers of males and females.

Conclusion

We found that the point prevalence among non-tribal populations is 2.4% (corresponding to a chronic carrier rate of 1.9%) and the point prevalence among tribal populations is 15.8%. These figures may be useful in estimation of the burden of the disease in the country and for projecting the cost-benefits of immunization.

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Contributors: The project was conceived by JP as member of the 'IMA Sub committee on Immunization'. AB, DN, TT did the systematic review. AB and VS did the meta-analysis. AB, DN, TT and JP did the write up. All authors have approved of the manuscript. JP stands guarantor for the study.

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