

Supplementary Material

Hepatitis B prevalence association with sexually transmitted infections: a systematic review and meta-analysis

Elliot Marseille^A, Aaron M. Harris^B, Hacsí Horvath^C, Andrea Parriott^D, Mohsen Malekinejad^E, Noele P. Nelson^B, Michelle Van Handel^{ID B,F} and James G. Kahn^C

^AHealth Strategies International, Oakland CA, USA.

^BU.S. Centers for Disease Control and Prevention; National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, USA.

^CPhilip R. Lee Institute for Health Policy Studies, Global Health Sciences, and Global Health Economics Consortium, University of California, San Francisco CA, USA.

^DPhilip R. Lee Institute for Health Policy Studies and Consortium to Assess Prevention Economics, University of California, San Francisco CA, USA.

^EPhilip R. Lee Institute for Health Policy Studies, Global Health Sciences and Consortium to Assess Prevention Economics, University of California, San Francisco CA, USA.

^FCorresponding author. Email: mvanhandel@cdc.gov

Table S1. PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1, 2, 6, 13
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	See Abstract structured per journal guidelines on p. 3.
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5, 6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5, 6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6, 7, and Appendix B
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix B
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6, 7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. Specifically, after removing duplicate records, a research associate performed a broad first review of all downloaded material from the electronic searches to exclude citations that were plainly irrelevant (e.g., different disease), and then read the titles, abstracts and descriptor terms of the remaining downloaded citations to identify potentially eligible studies. The lead author sampled 50% of the	8, 9

		excluded studies in order to ensure no systematic exclusion of eligible studies. The research associate then obtained full text copies (PDFs) for all citations identified as potentially eligible. The lead author inspected these PDFs to establish the final relevance of the study according to the pre-specified inclusion criteria. Reasons for exclusion were recorded, such as no prevalence ratio reported or calculable from the available data, or the study pertained to a migrant population. The lead author extracted the prevalence ratios (PR) from the included studies when these were available. In cases in which the PR was not reported directly, the lead author used the “Open-EPI” 2x2 table function to construct PRs for all studies where data needed to populate a 2 x2 tables were reported. A senior statistician and study co-author checked each of these calculations, going back to the PDF to ensure that the numbers were extracted, interpreted and calculated properly. Finally, the calculations for the conversion of odds ratios to PRs was conducted by the lead author, and each such calculation was similarly reviewed by the senior statistician.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Tables 1 – 2, pages 7, 8.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Table 1, page 9, Appendix C
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3, 8; Tables 1 - 2
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7, 8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9, 14, Appendices C, E
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7, 8, 9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1, pages 9 - 10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tables 1 and 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12, Appendices

			C, E
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 2 – 3, pages 9 - 13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures 2 – 3, pages 9 - 13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Appendices C, D
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Table S2. Search methods

All searches 1 January 1981 – 18 March 2018

PubMed (k=1740)		
"mh" = MeSH term		
"sh" = subject heading		
"tw" = term can appear in my field except author name and affiliation, etc..		
Search	Query	Result
5	Dates 1981 - 2018	1740
4	#1 and #2 and #3	1778
3	"Hepatitis B"[mh] OR "hepatitis B"[tw] OR "hep B" [tw] OR HBV[tw] OR "serum hepatitis"[tw] OR "hippie hepatitis"[tw] OR "hepatitis type B"[tw] OR CHB[tw] OR "acute HB"[tw] OR AHB[tw]	95121
2	Epidemiology[mh] OR "epidemiology"[sh] OR "Incidence"[mh] OR "Prevalence"[mh] OR "Coinfection"[mh] OR incidence[tw OR incident[tw] OR cases[tw] OR prevalence[tw] OR seroprevalence OR "seroprevalence"[tw] OR seroincidence[tw] OR "sero-incidence"[tw] OR coinfection[tw] OR "co-infection"[tw]	3957463
1	Sexually Transmitted Diseases, Bacterial[mh] OR "Syphilis"[mh] OR "Gonorrhea"[mh] OR "Chlamydia infections"[mh] OR venereal[tw] OR "sexually transmitted"[tw] OR "sexually transmissible"[tw] OR VD[tw] OR STD[tw] OR STI[tw] OR syphilis[tw] OR syphilitic[tw] OR treponema[tw] OR pallidum[tw] OR gonorrhea[tw] OR gonorrhoea[tw] OR chlamydia[tw] OR "Lymphogranuloma Venereum"[tw]	128484
Web of Science 9k=1,169)		
Index: SCI-EXPANDED		
1	Topic: (venereal OR "sexually transmitted" OR "Sexually transmissible" OR VD OR STD OR STI OR syphilis OR spgilitic OR treponema OR pallidum OR gonorrhea OR chlamydia OR "Lymphogranuloma Venereum") AND	
2	Topic: (incidence OR incident OR cases OR prevalence OR seroprevalence OR sero-prevalence OR sesroincidence OR sero-incidence Orcoinfectuin OR co-infection) AND	
3	Topic: ("hepatitis B" OR "hepatitis-B" OR "hep B" OR HBV OR "serum hepatitis" OR "hippie hepatitis" OR "hepatitis type B" OR "chronic HB" OR CHB OR "acute HB" OR AHB)	

Embase (k=235)	
	'exp' = explode4 to include descending heirarchires of subterms in 'Emtree' (analogoius to MeSH)
	'mj' = indexed in articlres as major focus
	'mixed infection' is the Emtree term for coinfection
1	mixed infection'/exp/mj OR 'seroepidemiology'/exp/mj OR 'disease surveillance'/exp/mj OR 'incidence'/exp/mj OR 'seroprevalence'/exp/mj OR 'incidence'/mj OR incident OR cases OR 'prevalence'/mj OR 'seroprevalence'/mj OR 'sero prevalence' OR seroincidence OR 'seroincidence' OR 'coinfection'/mj OR 'co infection'/mj) AND
2	hepatitis b'/exp/mj OR 'hepatitis b'/mj OR 'hepatitis-b'/mj OR 'hep b' OR 'hbv'/mj OR 'serum hepatitis'/mj OR 'hippie hepatitis'/mj OR 'hepatitis type b' OR 'chronic hb' OR chb OR 'acute hb' hb' OR chb OR 'acute hb' AND
3	('sexually transmitted disease'/exp/mj OR venereal OR 'sexually transmitted' OR 'sexually transmissible' OR 'vd'/mj OR 'std'/mj OR sti OR 'syphilis'/mj OR syphilitic OR 'treponema'/mj OR 'pallidum'/mj OR 'gonorrhoea'/mj OR gonorrhoea OR 'chlamydia'/mj OR 'lymphogranuloma venereum'/mj)

Table S3. Risk of Bias Assessment Summary*

Criteria	Baddour, Sex Transm Dis, 1988	Barrett, Sex Transm Dis, 1992	Bratos, Sex Transm Dis, 1993	Carmo, Gen Hosp Psychiatry, 2014	Carvalho, Cad Saude Publica, 2017	Corona, Epidemiol Infect, 1991	Corona, J Med Virol, 1996	Deininger, Klin Wochenschr, 1990
Research question clearly stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Study population clearly specified and defined	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Participation rate of eligible persons ≥50%	Yes	No	No	Yes	Yes	Yes	Yes	Cannot determine
Subjects selected / recruited from same or similar populations? Were inclusion and exclusion criteria prespecified and applied uniformly to all participants	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sample size justification, power description or variance and effect estimates provided	No	No	No	No	Yes	No	Cannot determine	Cannot determine
Exposure(s) of interest (STI infection) measured prior to the outcome(s) (HBV infection) being measured	No	Yes	No	No	No	No	No	No
Timeframe sufficient so that one could reasonably expect to see a temporal association between exposure and outcome	No	No	No	No	No	No	No	No
Independent variables clearly defined, valid, reliable, and implemented consistently across all study participants	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Independent variable(s) assessed more than once over time	No	No	No	No	No	No	No	No
Dependent variables clearly defined, valid, reliable and implemented consistently across all study participants	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcome assessors blinded to the exposure status of participants	Cannot determine	Cannot determine	Cannot determine	Cannot determine	Cannot determine	Yes	Yes	Cannot determine
Potential confounding variables adjusted statistically for impact on exposure and outcome	Yes	Yes	No	Yes	Yes	No	Yes	No
Overall quality rating	Fair	Fair	Fair	Fair	Fair	Fair	Good	Fair

Table S3. Risk of Bias Assessment Summary (Cont)

Criteria	El Maerrawi, International J STD AIDS, 2015	Fiscus, Sex Transm Dis., 1994	Gilson, Sex Transm Infect, 1998	Hakre, Sex Transm Infect, 2013	Hart, Sex Transm Dis, 1993	Hawkins, J Infect Dis., 1992	Hennessey, J Urban Health, 2009	Hwang, Clin Infect Dis, 2000
Research question clearly stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Study population clearly specified and defined	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Participation rate of eligible persons ≥50%	Yes	Yes	Yes	Yes	Cannot determine	Yes	Yes	Yes
Subjects selected / recruited from same or similar populations? Were inclusion and exclusion criteria prespecified and applied uniformly to all participants	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sample size justification, power description or variance and effect estimates provided	No	No	No	Yes	No	No	No	No
Exposure(s) of interest (STI infection) measured prior to the outcome(s) (HBV infection) being measured	No	No	No	No	No	Yes	No	No
Timeframe sufficient so that one could reasonably expect to see a temporal association between exposure and outcome	No	No	No	No	No	Yes	No	No
Independent variables clearly defined, valid, reliable, and implemented consistently across all study participants	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Independent variable(s) assessed more than once over time	No	No	No	No	Yes	Yes	No	No
Dependent variables clearly defined, valid, reliable and implemented consistently across all study participants	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcome assessors blinded to the exposure status of participants	Cannot determine	Cannot determine	Cannot determine	Cannot determine	Cannot determine	Cannot determine	Cannot determine	Yes
Potential confounding variables adjusted statistically for impact on exposure and outcome	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Overall quality rating	Fair	Fair	Fair	Good	Fair	Good	Fair	Good

Table S3. Risk of Bias Assessment Summary (Cont)

Criteria	Juarez-Figueroa, Sex Transm Infect, 1998	Lama, Am J Trop Med Hyg, 2010	Levine, Am J Epi, 1995	Matos, Sex Transm Infect, 2008	Mele, Eur J Epidemiol, 1988	Miranda, Sex Transm Dis, 2001	Moura, International J Inf Dis, 2015	Oliveira, PLOS One, 2016
Research question clearly stated	Yes	yes	Yes	Yes	Yes	Yes	Yes	Yes
Study population clearly specified and defined	Yes	yes	Yes	Yes	Yes	Yes	Yes	Yes
Participation rate of eligible persons ≥50%	Cannot determine	yes	Yes	Yes	Yes	Yes	Yes	No
Subjects selected / recruited from same or similar populations? Were inclusion and exclusion criteria prespecified and applied uniformly to all participants	Yes	yes	Yes	Yes	Yes	Yes	Yes	Yes
Sample size justification, power description or variance and effect estimates provided	No	No	No	Yes	No	No	No	Yes
Exposure(s) of interest (STI infection) measured prior to the outcome(s) (HBV infection) being measured	No	No	No	No	No	No	No	Yes
Timeframe sufficient so that one could reasonably expect to see a temporal association between exposure and outcome	No	No	No	No	No	No	No	Yes
Independent variables clearly defined, valid, reliable, and implemented consistently across all study participants	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Independent variable(s) assessed more than once over time	No	No	No	No	No	No	No	No
Dependent variables clearly defined, valid, reliable and implemented consistently across all study participants	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcome assessors blinded to the exposure status of participants	Cannot determine	Cannot determine	Cannot determine	Cannot determine	Cannot determine	Not reported	Cannot determine	Cannot determine
Potential confounding variables adjusted statistically for impact on exposure and outcome	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Overall quality rating	Fair	Fair	Fair	Good	Fair	Fair	Fair	Fair

Table S3. Risk of Bias Assessment Summary (Cont)

Criteria	Weinstock, JAMA, 1993	Zocratto, Sub Use Misuse, 2010	Zou, Transfusion, 2009	% of studies with “yes” response
Research question clearly stated	Yes	Yes	Yes	100%
Study population clearly specified and defined	Yes	Yes	Yes	100%
Participation rate of eligible persons ≥50%	Yes	Cannot determine	Yes	67%
Subjects selected / recruited from same or similar populations? Were inclusion and exclusion criteria prespecified and applied uniformly to all participants	Yes	No	Yes	98%
Sample size justification, power description or variance and effect estimates provided	No	Yes	No	12%
Exposure(s) of interest (STI infection) measured prior to the outcome(s) (HBV infection) being measured	No	No	No	7%
Timeframe sufficient so that one could reasonably expect to see a temporal association between exposure and outcome	No	No	No	5%
Independent variables clearly defined, valid, reliable, and implemented consistently across all study participants	Yes	Yes	Yes	100%
Independent variable(s) assessed more than once over time	No	No	Yes	9%
Dependent variables clearly defined, valid, reliable and implemented consistently across all study participants	Yes	Yes	Yes	100%
Outcome assessors blinded to the exposure status of participants	Cannot determine	Yes	Yes	14%
Potential confounding variables adjusted statistically for impact on exposure and outcome	No	Yes	No	77%
Overall quality rating	Fair	Fair	Fair	88%

* [Quality Assessment Tool for Observation Cohort and Cross-sectional Studies](#) was used since only observational studies were identified. Questions were excluded from the assessment if deemed not applicable; specifically, questions related to exposures that can vary in amount or level and loss to follow-up after baseline.

Table S4. Classification of studies and prevalence ratios (PRs) by HBV marker type, STI category and geography

HBV markers	Studies ¹	Measures of association	Distribution of PRs by STI category			Distribution of PRs by geography		
			Syphilis	Chlamydia or Gonorrhea	Unspecified STI	OECD excl USA	USA	Latin America
Surface antigens only (HBsAg)	9	13	53.8%	7.7%	38.5%	30.8%	30.8%	38.5%
Core antibodies only	19	37	35.1%	18.9%	45.9%	29.7%	43.2%	27.0%
Either type of markers	18	22	45.5%	18.2%	36.4%	9.1%	45.5%	45.5%
All HBV marker categories	43	72	47.9%	12.9%	39.2%	24.0%	37.5%	38.5%

1. Sum by HBV marker exam-and exceeds total. Three studies (Carmo 2014, Hennessey 2008, and van Duynhoven 1997) contributed outcomes to two HBV marker type

Table S5. Summary of evidence for the association of HBV infection with STIs – unadjusted outcomes only

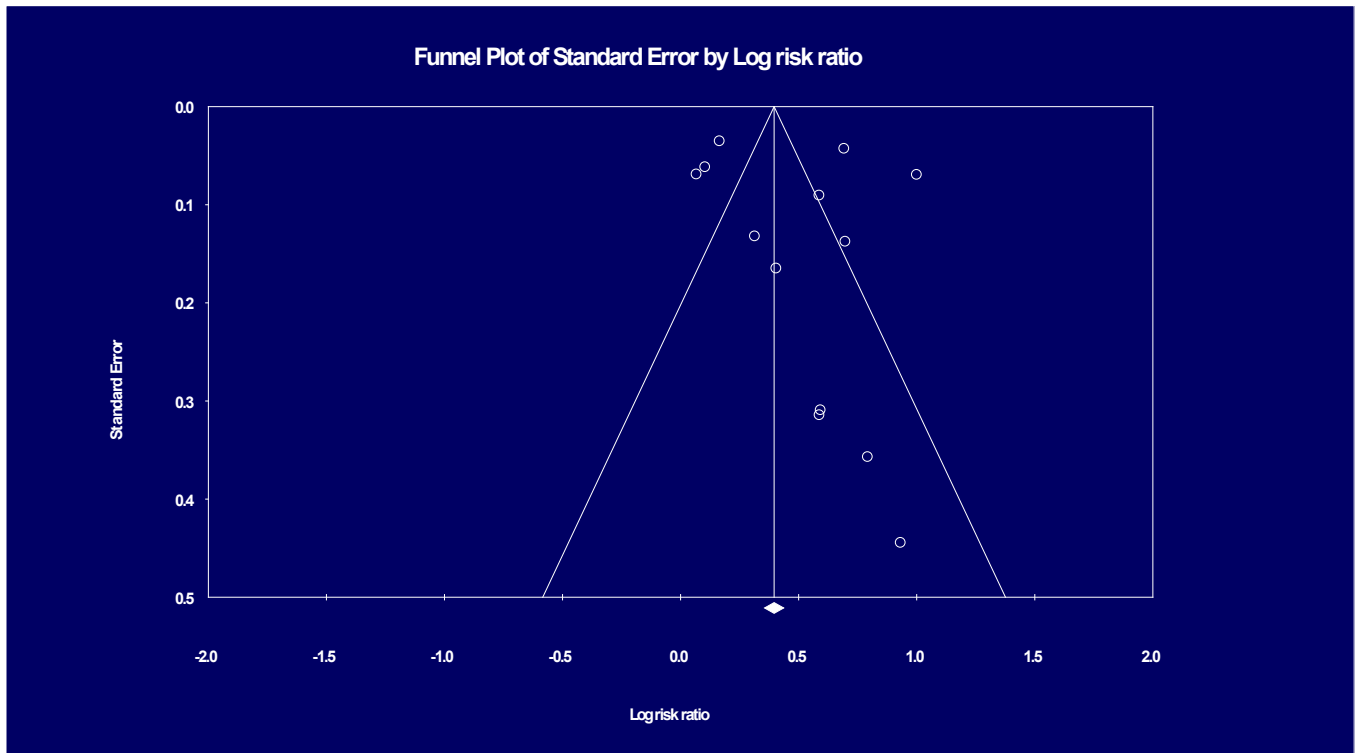
Outcome	Number of data points	Prevalence Ratio (95% CI) Pooled if ≥2 studies	I² (Q test p-value)	References (distinguishing characteristic for studies with >1 outcome)
HBV surface antigen (HBsAg)				
Syphilis – Current	1	12.5 (4.64-33.67)	N/A	Miranda 2001
Syphilis – Past	1	2.36 (1.36-4.08)	N/A	Carmo 2014
Chlamydia / gonorrhoea – Current	1	2.0 (0.93-4.32)	N/A	Hart 1992
Unspecified STIs – Past	2	0.93 (0.67 – 1.30)	N/A	Carmo 2014; Miranda 2001
HBV core antibodies (anti-HBc)				
Syphilis – Current	4	1.70 (1.32- 2.19)	0.00%; (0.58)	Bratos 1993; Fiscus 1994; Hakre 2013; Oliviera 2001
Syphilis – Past	2	2.32 (1.72-3.14)	92.9%; (0.00)	Deininger 1990; Weinstock 1993
Chlamydia / gonorrhoea – Past	7	1.35 (1.03-1.77)	93.2%; (0.00)	Tien 2004 No Drug; Tien 2004 (Chlamydia, IDUs); Tien 2004 (Chlamydia, No illicit drug); Tien 2004 (Chlamydia, Non-IDUs); Tien 2004 (Gonorrhoea, IDUs); Tien 2004 (Gonorrhoea, Non-IDUs); Weinstock 1993
Unspecified STIs – Current	2	1.27 (0.86-1.86)	0.00% (0.46)	Oliviera 2001; Oliviera 2001 clinic
Unspecified STIs – Past	12	1.73 (1.22-2.46)	83.8% (0.00)	Carvalho 2017; Gilson 1998 (MSM); Gilson 1998 (MSW); Gilson 1998 (Women); Mele 1988; Ribeiro 2017 (Coag pts); Ribeiro 2017

				(CRF pts); Trepka 2003 (Females); Trepka 2003 (Males)
HBsAg or anti-HBc; unspecified				
Syphilis – Current	4	2.01 (1.35-3.27)	71.99% (0.13)	Moura 2015; Pando 2006; Segura 2010; Zocratto 2010
Syphilis – Past	2	1.51 (0.89-1.52)	85.8% (0.01)	Levine 1995; Rosenblum 1990
Chlamydia / gonorrhea – Current	2	1.15 (0.77-1.62)	15.3% (0.28)	Barrett 1992 (More STIs); Barrett 1992 (Fewer STIs)
Chlamydia / gonorrhea – Past	1	1.65 (1.32-2.06)	N/A	Rosenblum 1990
Unspecified STIs – Past	1	2.83 (1.12-7.13)	45.1% (0.08)	Baddour 1988

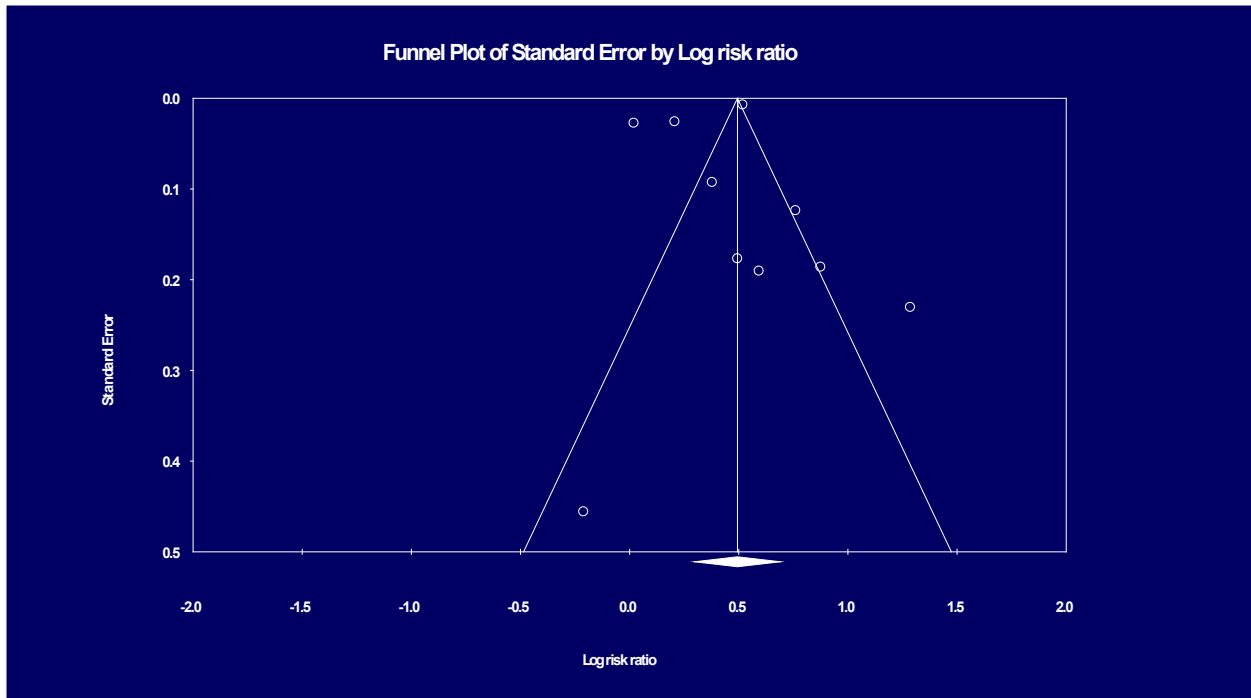
Fig. S1. Funnel plots 1–3.

Assessment of publication bias is germane to systematic reviews investigating the effect of risk factors or interventions on health outcomes where the concern is that small studies with findings perceived as unfavorable, (i.e., no effect for assessed risk factors or interventions) might have been systematically excluded. Although this review assesses the association between HBV infection and STI, we did not anticipate finding many eligible studies that intended specifically to assess this association *a priori*. By virtue of the nature of the literature we evaluated, predominantly large cross-sectional studies concurrently assessing hepatitis B and STI, we believe that it is less likely that journals rejected studies that would have been eligible for this review. Given that this scenario cannot be disregarded, to explore our hypothesis, we plotted the log of PRs against their standard errors on three meta-analyzed pooled PRs with more than 10 data points.

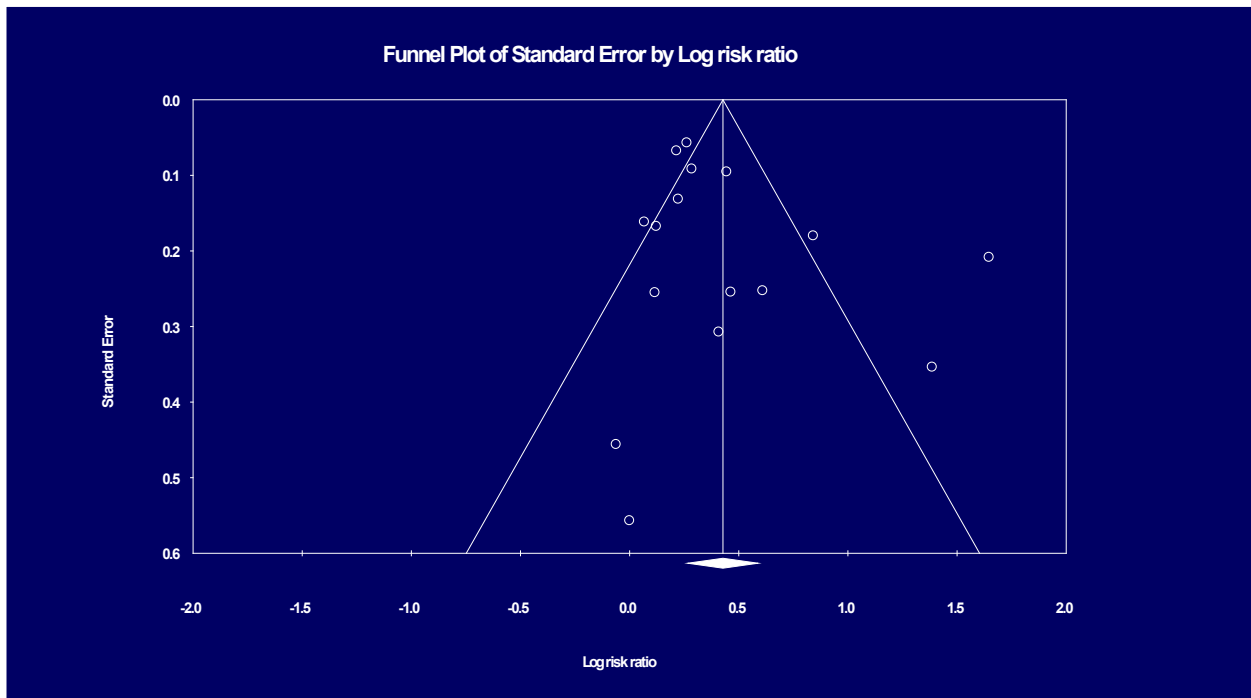
We explored the extent of publication bias via the CMA program’s “Funnel Plot command. Using 10 outcomes as the threshold for meaningful results from this test, only one pooled result, anti-HBc versus unspecified STIs was admissible. We therefore combined results for past and present STIs, which added two more pool results that exceeded 10 outcomes. The resulting funnel plots are shown below.



Funnel Plot 1: Association of HBV core antibody (anti-HBC); with combined past and current syphilis. (N = 13).



Funnel Plot 2: Association of HBV antibody or surface antigen (HBsAg / anti-HBC); with combined past and current syphilis, (N = 10).



Funnel Plot 3: Association of HBV antibody or surface antigen (HBsAg / anti-HBC); with combined past and current unspecified STIs, (N = 16)