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

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Abstract

Background.—Hepatitis B vaccination is recommended for persons with current or past sexually transmitted infections (STI). Our aim is to systematically assess the association of hepatitis B virus (HBV) sero-markers for current or past infection with syphilis, chlamydia, gonorrhea, or unspecified STIs.

Methods.—We conducted a systematic review and meta-analysis. PubMed, Embase, and Web of Science from 1982–2018 were searched using MeSH terms for HBV, STIs and epidemiology. We included studies conducted in Organization for Economic Cooperation and Development countries or Latin America that permit the calculation of prevalence ratios (PRs) for HBV and STIs and extracted PRs and counts by HBV and STI status.

Results.—Of 3,144 identified studies, 43 met inclusion requirements, yielding 72 PRs. We stratified outcomes by HBV sero-markers (surface antigen [HBsAg], core antigen [anti-HBc], combined), STI pathogen (syphilis, gonorrhea/chlamydia, unspecified), and STI history (current, past) resulting in 18 potential outcome groups, for which results were available for 14. For the four outcome groups related to HBsAg, PR point estimates ranged from 1.65 – 6.76. For the

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Compliance with Ethical Standards

Disclosure of potential conflicts of interest. The authors declare that they have no conflict of interest.

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five outcome groups related to anti-HBc, PRs ranged from 1.30 – 1.82; and for the five outcome groups related to combined HBV markers, PRs ranged from 1.15 – 1.89). The median HBsAg prevalence among people with a current or past STI was 4.17; not all studies reported HBsAg. Study settings and populations varied.

Conclusion.—This review found evidence of association between HBV infection and current or past STIs.

Summary:

Chronic hepatitis B virus (HBV) infection is a major source of morbidity and mortality in the United States and the most common source of HBV infection among adults is sexual contact. We conducted a comprehensive systematic review and meta-analysis of the association of hepatitis B prevalence among persons with current and past sexually transmitted infection and found the prevalence of hepatitis B significantly associated with sexually transmitted infection. These findings can inform potential recommendations for expanded hepatitis B testing.

Keywords

systematic review; meta-analysis; hepatitis B; sexually transmitted infections; gonorrhea; chlamydia; syphilis

Introduction

Chronic hepatitis B virus (HBV) infection is a major source of morbidity and mortality worldwide. An estimated 257 million persons worldwide are chronically infected with HBV, which results in approximately 887,000 deaths annually (1). In the United States, 847,000 persons were living with the disease in 2011–2012 (2) and 1,698 deaths were attributed to HBV in 2016 (3). About two-thirds of persons with chronic HBV infection were unaware of their infection, and an estimated 15% of treatment-eligible patients are receiving treatment (4, 5).

Chronic HBV infection is defined as the presence of hepatitis B surface antigen (HBsAg) for more than 6 months. Prevalence is highest among persons born in the Pacific Islands, Asia and Africa (2, 6). Other high-burden populations include men who have sex with men (MSM), persons who inject drugs (PWID), persons who have been incarcerated, and sexual and household contacts of persons with HBV infection (7). The Centers for Disease Control and Prevention (CDC) recommends screening for hepatitis B among person at risk; however current guidelines do not include testing persons with a history of STI (8).

Since both sexually transmitted infections (STI) and HBV infections can be transmitted through unprotected sexual contact, persons with current or past STI are at elevated risk for HBV infection. As a result, CDC recommends hepatitis B vaccination in adults seeking evaluation or treatment for STIs (9). While CDC does not recommend pre-vaccination testing for persons with current or past STI, the American Association for the Study of Liver Disease recommends hepatitis B testing for these persons (10), and the American College of Physicians recommends hepatitis B testing for persons with a history of STI as a best practice (7). Hepatitis B is commonly transmitted through sexual contact (11); however, the

hepatitis B prevalence among persons with current or past STI is unknown. We report the association of hepatitis B prevalence among persons with current and past STI through a comprehensive systematic review and meta-analysis.

Methods

Our methods are based on recommendations of the Cochrane Collaboration (12), and reporting is consistent with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and checklist; details available in Appendix A (13).

Data sources and searches.

We searched PubMed, Embase and Web of Science, employing terms from Medical Subject Headings (MeSH) relevant to HBV infection, STIs and epidemiology. We reviewed the literature between 1982, when the first HBV vaccine was approved, and our search date of March 18, 2018. Search terms and strategy are shown in Appendix B.

Study selection.

To be included, studies needed to report prevalence of hepatitis B and past or current syphilis, gonorrhoea/chlamydia or unspecified STIs, from any of the 36 high-income countries of the Organization for Economic Co-operation and Development (OECD) or a Latin American country. In addition, they either needed to provide measures of association such as odds ratios (ORs) or prevalence ratios (PRs) or provide data on HBV prevalence in both STI-exposed (past or current STI) and STI-unexposed (no past or current STI) sub-groups, from which PRs could be derived. Randomized controlled trials, prospective or retrospective observational cohorts, serial cross-sectional studies, and other longitudinal analyses published in any language were eligible for inclusion. Studies in peer-reviewed journals, reports from scientific conferences, and doctoral dissertations were eligible for inclusion. Studies in languages other than English were assessed by translating key passages into English using Google Translate. HBV infection could be defined as positive surface antigen (HBsAg) or as core antibody detection (anti-HBc), and we stratified results according to these two types of markers. We also included studies that combined HBV marker types without specifying which, surface antigen or core antibody, was used to define HBV infection. STI prevalence data could reflect current or past infections. Studies were excluded if they focused on persons with HIV or immigrant populations.

Data synthesis and analysis.

We used PRs as the measure of association between HBV infection and STIs. In addition to the few studies that provided PRs (or risk ratios) directly, studies were included if PRs could be constructed from the reported data. When adjusted measures were provided, typically as ORs, we used adjusted measures rather than crude measures. However, when adjusted measures were not reported, but data were available to construct unadjusted PRs from 2×2 data we did so, using Open-Epi's 2×2 table function (14). " 2×2 data" refers to the number of HBV negative and HBV positive cases for both STI negative and STI positive groups. We used 2×2 data even if unadjusted ORs were available in order to keep consistent and

precise methods. We converted both adjusted ORs and unadjusted ORs when 2×2 data were unavailable to PRs using the formula suggested by Zhang and Yu (15),

$$PR = OR / ((1 - P_0) + (P_0 \times OR))$$

where, P_0 is the prevalence of the outcome of interest (HBV-positivity) in the unexposed group (STI-negative).

We used Comprehensive Meta Analysis™ (Version 3.3, Englewood, New Jersey) software to perform the meta-analysis. We used a random effects model because included studies were diverse in design, setting, and population (16).

Hepatitis B screening should include HBsAg, antibody to HBsAg (anti-HBs), and anti-HBc so that patients can be categorized into clinical states for appropriate management (7). Our methods divided HBV serological markers because not all the studies included results of all 3 serologic markers. Therefore, we defined 18 meta-analyses strata, *a priori*, according to three variables that would likely affect the association of HBV infection and STI, as well as the clinical care for persons with HBV infection or STI, as follows: HBV markers (three groups: HBsAg, anti-HBc, combined), STI type (three groups: syphilis, gonorrhea or chlamydia [treated as one group], unspecified), and STI history (two groups: current or past). We used funnel plots to visually explore the relationship between the log of the pooled PR and their associated standard errors. To portray study heterogeneity, we reported the Iota-square statistic and its p-value for each pooled outcome (17, 18).

Data extraction and quality assessment.

We imported records resulting from our search into EndNote™ (Version X8, Pittsburgh, PA). One reviewer removed duplicate records. After removing duplicate records, a reviewer performed an initial review to exclude citations that were clearly irrelevant (e.g., different disease), and then screened citation titles, abstracts and keywords of the remaining citations to identify records for full-text review. The lead author conducted quality assessment by sampling 50% of the excluded records to ensure no systematic exclusion of eligible studies. The full text of each screened-in article was obtained and then reviewed by the lead author to establish 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 measures of association as described in the data synthesis and analysis section. Data were extracted into a database maintained in Microsoft Excel™ (Version Office 365, Redmond, Washington). A senior statistician and study co-author checked all calculations to ensure that the numbers were extracted, interpreted and calculated properly. For the risk of bias assessment, the Quality Assessment Tool for Observation Cohort and Cross-sectional Studies was used since only observational studies were identified (19). Two reviewers independently evaluated study quality and differences were resolved by a third reviewer to determine the adequacy of study population selection and recruitment, outcome and exposure measurement and assessment, and statistical analyses, relative to other observational studies, using (Appendix C).

Results

Search results.

Our searches yielded 3,144 unique citations, including 1,740 from PubMed, 235 from Embase and 1,169 from Web of Science, yielding 2,114 citations after removal of duplicates. (Figure 1). Screening of titles and abstracts identified 329 citations for full text review, of which 43 met inclusion criteria and were advanced to data extraction and inclusion in the meta-analysis. Key information on the 43 included studies is shown in Table 1.

Classifying studies by HBV marker type, we included nine studies reporting prevalence by surface antigen (HBsAg) positivity providing 13 PRs; 19 studies reporting core antibody (anti-HBc) prevalence providing 37 PRs; and 18 studies that did not identify which HBV marker was used providing 25 PRs. Thus, a total of 75 PRs were included in the meta-analysis from a total of 43 studies. Three studies (Carmo 2014, Hennessey 2009, and van Duynhoven 1997) provided data on both HBsAg and anti-HBc (20–22). Thus, the number of studies shown in Appendix D, 72, differs from the number of PRs, 75. Nearly half (47.9%) of the PRs reported associations with syphilis, 12.9% reported associations with chlamydia or gonorrhea, and 39.2% reported associations with unspecified STI. Of the 72 PRs, 38 (52.8%) were unadjusted and 34 were adjusted, typically by basic demographics such as age and sex. By geographical classification, PRs were divided between OECD countries excluding the U.S. (24.0%), the U.S. (37.5%), and Latin America (38.5%). (See Appendix D)

Hepatitis B prevalence among persons with STIs.

Among the 13 PRs that incorporated HBsAg, we derived 11 values for hepatitis B prevalence among persons with STIs finding that the median prevalence 4.17%, and ranged from 0.91% (95% CI: 0.60, 1.37%) among first-time blood donors in the U.S. for current syphilis (23) to 33.2% (95% CI: 27.4%, 39.0%) among MSM in the U.S. for current unspecified STIs (24). See Table 1.

Meta-analysis results.

Overall, we found positive and statistically significant associations between HBV infection and STI prevalence in 12 of the 14 strata for which we were able to calculate pooled PRs. None of the pooled results showed negative associations between HBV infection and STIs. Specific results grouped by HBV marker are presented below:

Surface antigen (HBsAg) as the marker for HBV-positivity—We reported four data points (two pooled and two based on a single study) for the association of STI and HBV infection for studies using HBsAg as the marker for HBV-positivity. Of these, three showed statistically significant associations: past syphilis (k=1, PR 2.36, 95% CI: 1.36, 4.08), current syphilis (k=6, PR 6.76, 95% CI: 2.10, 21.76), (Figure 2) and past unspecified STIs (k=5, PR 1.65, 95% CI: 1.08, 2.52), (See Figure 3 in web appendix). The result for current chlamydia / gonorrhea showed a positive but statistically insignificant association (k=1, PR 2.00, 95% CI: 0.93, 4.32). (See Figure 4 in web appendix). (Note that these figures do not always match the results shown in Appendix E, as the latter displays unadjusted

outcomes only). We observed high heterogeneity (I^2 73.6% and 91.4%) in the two analyses for which heterogeneity could be assessed.

Core antibody (anti-HBc) as the marker for HBV-positivity—We reported five pooled data outcomes for the association of STI and HBV infection for studies using anti-HBc as the marker for HBV-positivity. All showed statistically significant associations: past syphilis (k=6, PR 1.48, 95% CI: 1.10, 1.99), current syphilis (k=7, PR 1.82, 95% CI: 1.60, 2.06), past chlamydia / gonorrhea, (k=8, PR 1.30, 95% CI: 1.02, 1.66), and past and current unspecified STIs, (k=12, PR 1.62, 95% CI: 1.31, 1.99) and (k=4, PR 1.42, 95% CI: 1.23, 1.63), respectively. The result for current unspecified STIs showed moderate heterogeneity, (I^2 42.4%). The other four outcomes had high heterogeneity with I^2 ranging from 83.8% - 97.6%

Combined surface antigen (HBsAg) or core antibody (anti-HBc) as the marker for HBV-positivity—We reported five pooled outcomes for the association of STI and HBV infection for studies that combined HBV marker types. Three of these showed statistically significant associations: current syphilis (k=7, PR 1.69, 95% CI: 1.39, 2.07), past chlamydia / gonorrhea, (k=2, PR 1.73, 95% CI: 1.48, 2.01), and past and unspecified STIs (k=8, PR 1.89, 95% CI: 1.52, 2.37). The pooled outcomes for past syphilis and current chlamydia / gonorrhea were not statistically significant (k=3, PR 1.51, 95% CI: 0.89, 1.52) and (k=2, PR 1.15, 95% CI: 0.77, 1.62), respectively. The result showed high heterogeneity for current and past syphilis (I^2 95 – 96%), moderate heterogeneity for unspecified STI (I^2 45%), and low heterogeneity for current and past chlamydia / gonorrhea (I^2 0% - 15%). See Table 2 below.

Sensitivity analysis.

Gilson 1998 used a different measure of STI prevalence than the other studies, namely <2 versus ≥ 2 lifetime episodes (25). If this study is removed, the pooled PR for the association between anti-HBc and past unspecified STIs is 1.43 (CI 1.23– 1.67) versus 1.62 (CI 1.31– 1.99) when Gilson 1998 is included.

The majority (88%) of studies had an overall study quality rating of fair relative to other observational studies (Appendix C). No studies had an overall quality rating of poor, and thus no sensitivity analyses were conducted to assess impact of excluding studies with a poor quality rating. However, there was noted variability identified for statistical adjustment for potential confounding variables. In order to understand the effect that a mix of adjusted and unadjusted measures may have had on our results, we ran the analysis using unadjusted measures only. Of the 11 pooled PRs that were statistically significant in the full data set, two lost their statistical significance (the association between HBsAg and unspecified past STIs, and between anti-HBc and unspecified current STIs). See Appendix E.

Discussion

We undertook a systematic review and meta-analysis of the relationship between HBV infection and current or past STIs. We found a substantial body of evidence suggesting that there are positive and statistically significant associations between the prevalence of

hepatitis B and STIs in the mix of countries, settings, and subpopulations for which we found usable studies. HBsAg prevalence among persons with STIs were derived from 11 of the 13 outcomes available for studies specifically reporting HBsAg prevalence with a median value of 4.17% and a range of 0.91% to 33.20% depending on the population, setting, and infection pathogen.

Among adults in the United States, the most common route of transmission for hepatitis B virus is sexual contact. Among the 26% of persons with case-reports of acute HBV infection with information about risk behaviors or exposures, 22.9% reported having two or more sexual partners, 6.5% reported sexual contact with an HBV-infected person, and 12.2% of males reported having sex with another male (26). As many as 10%–40% of adults seeking treatment in STI clinics have evidence of current or past HBV infection, and 39% were screened or sought care for an STI prior to becoming infected with HBV (27). As a result, CDC recommends vaccination of adults at risk for HBV infection including persons at risk for infection by sexual exposure (28).

CDC does not currently recommend pre-vaccination serologic testing for HBV among persons with current or a history of STI (9), although the American Association for the Study of Liver Disease has recommended testing this group since 2009 (10). HBV infection and STI share common modes of transmission, and hepatitis B can be transmitted by sexual exposure. Transmission also occurs by close person-to-person contact by open cuts and sores, in hyperendemic areas (28). Therefore, persons with STI are likely at increased risk of HBV infection and should be vaccinated, and considered for pre-vaccination serologic testing (29). Screening, linkage to care, and vaccination programs for adults at risk for hepatitis B are a best practice (6). Our review suggests high hepatitis B prevalence among persons with current or past STI. As a result of this higher hepatitis B prevalence, person with a history of STI could benefit by receiving hepatitis B vaccination if they are negative or be linked to life saving care and treatment if they are found to be positive. In addition, those who are identified as positive can be counseled and is an opportunity to disrupt transmission of the virus to others.

While there was a large range of values for HBV infection and STI prevalence in the populations included in this review, the range of prevalence ratios is much more constrained. The pooled estimates vary from 1.65 to 6.76 for HBsAg, from 1.30 to 1.82 for anti-HBc and 1.15 to 1.89 unspecified HBsAg / anti-HBc. This suggests that, given a known prevalence of STIs within a potential target population, one might make reasonably precise estimates of the yield of HBV-positive persons.

We observed an overall clustering of effect sizes around the top of all three funnels reflecting the preponderance of large studies. This observation suggests that smaller studies could have been excluded. However, there is no reason to think that this exclusion was due to the magnitude or direction of their association. In addition, any potential exclusion of such studies is unlikely to affect the pooled effect sizes. For one of the three plots, we observed a few effect sizes on the right side of the plot but not on the left side at the bottom of the funnel; in addition to risk of publication bias, data heterogeneity chance, and other reasons may explain this asymmetry (17). (See Appendix F).

Among the strengths of this paper are its comprehensive look at the range of relevant HBV markers and STIs combined with a sufficiently large number of outcomes to test for statistical significance within each stratum. Thus, we were able to group 'like with like' and still obtain, for most pooled estimates, a fairly narrow confidence interval. The results were robust to sensitivity analyses in which a study with a different approach to portraying STI outcomes was omitted, and to confining the analyses to unadjusted outcomes only.

However, there are limitations to the methods employed in this study. We confined our literature search to PubMed, Embase and the Web of Science data bases, and did not exhaustively review the grey literature. It is thus possible that we excluded relevant information that may have affected findings. Because there are no other published systematic reviews pertaining to our research question, it is not possible to compare our results against those of other investigators who might have used different methods. As in all systematic reviews, we evaluated only studies that met inclusion criteria. Broader criteria, such as acceptance of earlier studies, or a different geographic or economic specification of included countries, might have yielded a different result, although the inclusion / exclusion criteria used are appropriate to the research question we addressed.

Given the existence of contextual heterogeneity (i.e., variation in population, study design, outcome reporting metrics) and statistical heterogeneity, we used random effects. Thus, the pooled point estimates provide an overall average effect size that may not be accurate for specific target populations and settings. Therefore, in addition to point estimates, confidence intervals should be taken into considerations for decision-making pertaining to disease screening programs or modeling. Given the cross-sectional nature of most of studies and the fact that both types of infections share common risk factors, we only assessed their association, not causal relationships. Related, during the quality assessment, we did not reduce the overall quality rating for studies that did not measure exposures prior to the outcome of interest since it would not be ethical in most instances to delay an effective vaccination in order to monitor outcomes overtime.

We derived PRs from adjusted measures of association when available and thus have a mix of adjusted and unadjusted PRs. Sensitivity analyses suggests this is not a major issue. Not all studies included HBsAg, which may have limited our estimations of the association between STI and infectious HBV. Including studies that reported on HBsAg or anti-HBc markers but did not specify which was used to determine hepatitis B status introduces an element of ambiguity in the interpretation of that sub-set of findings. However, these findings are consistent with findings pertaining to the known HBV marker types. Removing these results does not affect our overall findings. Even if we stratified data by HBV markers and STI pathogens, there is still a high degree of heterogeneity in some of the pooled analyses. This suggests that factors other than those for which we stratified may explain the heterogeneity.

Conclusion

This systematic review and meta-analysis found a substantial body of evidence suggesting robust and statistically significant associations between the prevalence of HBV infection and

STIs for multiple infections and using various serologic tests. These findings may be useful in better understanding the potential benefits of pre-vaccination serologic testing for HBV among persons with or at risk for STIs and framing potential recommendations for expanded hepatitis B testing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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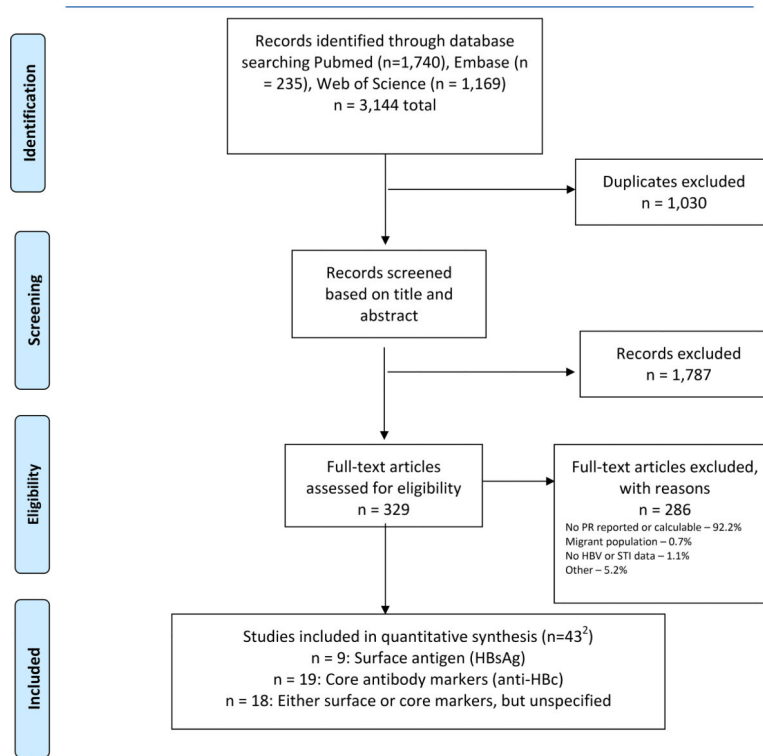


Figure 1:
Flowchart for systematic review¹

¹From: 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](https://doi.org/10.1371/journal.pmed1000097)

2. Three studies contributed outcomes to two HBV marker types

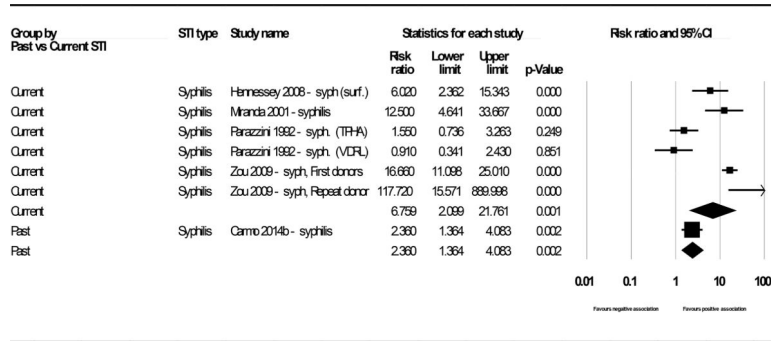


Figure 2.
Forest plot - Association between HBsAg and past and current syphilis.

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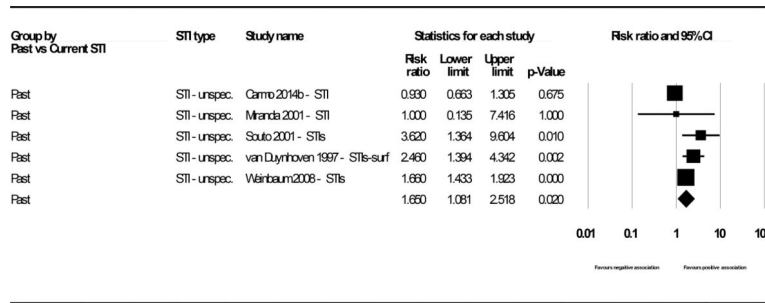


Figure 3.
Forest plot - Association between HBsAg and past unspecified STIs.

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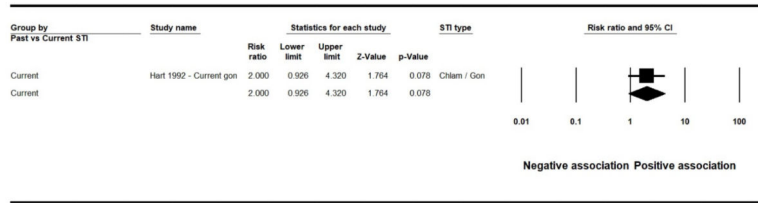


Figure 4.
Forest plot - Association between HBsAg and current gonorrhea

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Table 1. Characteristics of 43 studies included in calculation of association between HBV infections and STIs

<i>A. Studies using surface antigen (HbsAg) as HBV marker</i>									
Author, Pub., Year	Country	Setting	Quality rating	Population	STI measure	Hepatitis B prevalence (%)		Prevalence ratios ¹	
						STI-negatives	STI-positives		
Carmo, Gen Hosp Psychiatry, 2014	Brazil	26 public mental health services	Fair	Randomly selected adults with mental illness under care	Past STIs Past syphilis	2.00	1.92, (NR) 4.17, (NR)	2176, 0.93, (0.66–1.36) 2140, 2.36, (1.36–4.07)	
Hart, Sex Transm Dis, 1993	Australia	STI clinic, Adelaide	Fair	All attendees during study period - Females	Current gonorrhoea	7.10	NR	3998, 2.00, (0.90–4.20)	
Hennessey, Urban Health, 2009	USA	Jail - Chicago, Detroit, S.F.	Fair	Incoming jail inmates (M + F)	Current syphilis	0.90	2.00, (0.40–3.70)	11165, 6.02, (2.30–14.94)	
Miranda, Sex Transm Dis., 2001	Brazil	Antenatal clinics in Vitória Municipality	Fair	Pregnant women	Past STIs Current syphilis	0.80	NR 10.42 (4.09–22.61)	1608, 1.00, (0.13–7.15) 1608, 12.50, (4.64–33.66)	
Parazzini, Genitourin Med., 1992	Italy	Two STI clinics	Fair	Patients who referred themselves to clinic for suspected STD or STD treatment	Current syphilis - TPFA Current syphilis - VDRL	7.80 6.90	15.06 (8.45–25.18) 9.09 (3.91–18.78)	588, 1.55, (0.81–3.59) 588, 0.91, (0.31–2.21)	
Souto, Mem Inst Oswaldo Cruz., 2001	Brazil	Area comprising 16 gold mine camps in Apiacas county	Fair	Malaria-exposed gold Miners	Past STIs	2.70	8.92 (6.20–12.62)	472, 3.62, (1.29–9.08)	
van Duynhoven, Genitourin Med., 1997	Netherlands	STI clinic at University Hospital of Rotterdam	Fair	STD clinic clients	Past STIs	1.10	2.72 (1.95–3.80)	2876, 2.46, (1.39–4.35)	
Weinbaum, Am J Public Health, 2008	USA	MSM-identified venues: Balt, Dallas, L.A., Miami, NYC, S.F., Seattle	Good	MSM	Current STIs	16.00	33.20 (27.40–39)	2824, 1.66, (1.46–1.96)	
Zou, Transfusion, 2009	USA	Blood donation sites	Fair	First time blood donors Repeat blood donors	Current syphilis	0.05 0.01	0.91 (0.6–1.37) 1.17 (0.78–1.75)	1203, 16.66, (11.08–24.97) 155, 117.72, (16.57–947)	

<i>B. Studies using core antibody (anti-Hbc) as HBV marker</i>							
Author, Pub., Year	Country	Setting	Quality rating	Population	STI measure	Hepatitis B prevalence in STI-negatives	Prevalence ratios ¹ N, point est., (Low-High 95% CI)
Bratos, Sex Transm Dis., 1993	Spain	Public health clinic	Fair	Female prostitutes	Current syphilis	9.70	127, 2.54, (1.06–6.08)
Carmo, Gen Hosp Psychiatry, 2014	Brazil	26 public mental health services	Fair	Randomly selected adults with mental illness under care	Past STIs	15.70	2176, 1.20, (1.07–1.33)
					Past syphilis	16.20	2140, 1.29, (1.05–1.58)
Carvalho, Cad Saude Publica, 2017	Brazil	Public shelter in city of Goiânia	Fair	Persons experiencing homelessness	Past STIs	15.50	271, 1.13, (0.83–1.60)
Corona, Epidemiol Infect., 1991	Italy	STI clinic in Rome	Fair	Consecutive outpatients - non-PWID heterosexuals	Past STIs	21.10	1136, 1.56, (1.28–1.86)
				Consecutive outpatients - non-PWID homosexuals	50.00	196, 1.25, (0.92–1.54)	
Corona, J Med Virol., 1996	Italy	STI clinic in Rome	Good	Non-PWID heterosexuals	Past chlamydia / gonorrhea	18.10	1497, 0.98, (0.73–1.27)
Deininger, Klin Wochenschr., 1990	Germany	HIV Clinic	Fair	Gay and bisexual men	Past syphilis	52.30	1961, 2.00, (1.80–2.13)
					Current syphilis	5.60	139, 1.50, (1.10–2.10)
Fiscus, Sex Transm Dis., 1994	USA	STI clinics; three counties in N. Carolina	Fair	STD clinic clients tested for syphilis	Current syphilis	28.90	441, 5.19, (3.38–7.65)
Gilson, Sex Transm Infect., 1998	United Kingdom	Open access GUM clinic in central London	Fair	HIV-neg homosexual men	Past STIs >2 vs <2 lifetime episodes	6.30	527, 0.94, (0.38–2.27)
				HIV-neg heterosexual men	4.60	821, 1.00, (0.03–2.66)	
				HIV-neg women	8.00	38, 2.21, (1.10–4.46)	
Hakre, Sex Transm Infect., 2013	Panama	Venues for registered and unregistered FSWs in 8 Provinces	Good	FSWs	Current syphilis	3.70	2071, 1.84, (1.10–4.21)
Hawkins, J Infect Dis., 1992	USA (see "Setting")	Six US Navy ships on deployment to S. America, W. Africa & Mediterranean	Good	Crew members and Marine Corp personnel	Past STIs	16.00	11166, 1.80, (1.50–2.14)
Hennessey, J Urban Health, 2009	USA	Jail - Chicago, Detroit, San Francisco	Fair	Incoming jail inmates (M + F)	Current syphilis		

<i>C. Studies using core antibody (anti-Hbc) as HBV marker</i>							
Author, Pub., Year	Country	Setting	Quality rating	Population	STI measure	Hepatitis B prevalence in STI-negatives	Prevalence ratios N, point est., (Low- High 95% CI)
Juarez-Figueroa, Sex Transm Infect., 1998	Mexico	Centre for HIV/STI detection in FSWs	Fair	FSWs	Current syphilis	5.80	1498, 1.81, (0.91–3.06)
Mele, Eur J Epidemiol., 1988	Italy	STI clinic	Fair	STD clinic clients, male; heterosexual & gay/bisexual	Past STIs	46.40	913, 1.32, (1.15–1.58)
Oliveira, Mem Inst Oswaldo Cruz, 2001	Brazil	STI Clinic, Universidade Federal Fluminense, State of Rio de Janeiro	Fair	STD clinic clients	Current syphilis	11.60	440, 1.80, (1.03–3.54)
					Past STIs	12.60	433, 1.12, (0.68–1.85)
					Clinic STI history	9.50	440, 1.50, (0.82–2.75)
Ribeiro, Int J Environ Res Public Health, 2017	Brazil	Private hemodialysis clinic & public hematology center, Fortaleza, Brazil	Fair	Male & female pts with chronic renal failure	Past STIs	54.90	141, 1.07, (0.78–1.47)
				Male and female pts with coagulopathy		20.00	50, 4.00, (2.00–8.00)
Tien, Clin Infect Dis., 2004	USA	At home or work	Fair	Females at risk of HIV - PWID	Past gonorrhea Past chlamydia	76.00	581, 1.06, (0.97–1.16)
				Females at risk of HIV - non-PWID		581, 1.03, (0.89–1.13)	
						30.00	512, 1.46, (1.15–1.85)
							512, 1.67, (1.23–2.26)
				Females at risk of HIV - no illicit drug use		17.00	850, 1.25, (0.84–1.87)
							850, 0.88, (0.42–1.83)
				Females at risk of HIV - PWID	Past syphilis	76.00	581, 1.07, (0.90–1.18)
				Females at risk of HIV - non-PWID			512, 1.18, (1.08–1.24)
				Females at risk of HIV - no illicit drug use			850, 1.11, (0.95–1.21)
Trepka, Sex Transm Dis., 2003	USA	Large public STI clinic	Fair	Male clinic clients 18+ yo	Past STIs	20.00	376, 2.32, (1.63–3.30)

Authors	Country	Setting	Quality rating	Population	STI measure	Hepatitis B prevalence in STI-negatives	Prevalence ratios ¹ N, point est., (Low-High 95% CI)
van Duynhoven, Genitourin Med., 1997	Netherlands	STI clinic at University Hospital of Rotterdam	Fair	Female clinic clients 18+ yo	Past STIs	16.00	242, 1.59, (1.00–2.63)
Weinstock, JAMA., 1993	USA	Public STI Clinic; San Francisco	Fair	STD clinic clients	Past STIs	12.90	2848, 1.33, (1.09–1.56)
				Patients with new problem and routine screening for syphilis	Past gonorrhea	18.80	1159, 2.30, (1.95–2.68)
					Past syphilis	24.40	1155, 2.72, (2.33–3.06)
D. Studies using either surface (HBsAg) or core (anti-HBc) HBV markers							
Baddour, Sex Transm Dis, 1988	USA	STI clinic	Fair	African American females	Past STIs	8.60	136, 2.83, (1.12–7.12)
Barrett, Sex Transm Dis, 1992	USA	STI Clinic Jefferson City Dept. of Health; Birmingham, Ala.	Fair	Women 19 y.o.+; not pregnant and planning to use contraception for trial period	Current gon./ chlamydia 0.01 – 0.23 STIs	14.00	557, 0.91, (0.54–1.48)
					Current gon./ chlamydia 0.24 – 1.00 STIs		557, 1.33, (0.82–2.07)
El Maerawi, International J STD AIDS, 2015	Brazil	Sao Paulo prison for men	Fair	Sao Paulo prison for men; all inmates were included	Past STIs	21.00	21, 1.81, (1.15–2.57)
Hwang, Clin Infect Dis, 2000	USA	Two drug treatment clinics in Houston & drug treatment clinic in Lubbock, Texas	Good	Indigent residents addicted to drugs and alcohol	Past STIs	22.40	407, 1.41, (0.84–2.07)
Lama, Am J Trop Med Hyg, 2010	Peru	Sentinel surveillance survey in 6 HBV-endemic cities	Fair	Men 18+ y.o. and had sexual intercourse with 1+ men during previous year	Current syphilis	25.50	354, 1.46, (1.21–1.74)
Levine, Am J Epi, 1995	USA	Baltimore; extensive community outreach	Fair	Former and current IV drug users who were subjects of ALIVE HIV longitudinal study	Past syphilis	83.50	2193, 1.02, (0.97–1.08)
Matos, Sex Transm Infect, 2008	Brazil	Highway through Goiania City	Good	Truck drivers	Past STIs	14.60	615, 1.78, (1.05–3.00)
Moura, International J Inf Dis, 2015	Brazil	Maceio, capital of State of Alagoas, Municipal Health Office	Fair	Pregnant women	Current syphilis	0.40	54729, 0.81, (0.33–1.97)
Oliveira, PLOS One, 2016	Brazil	MSM in City of Goiania	Fair	MSM recruited using Respondent-Driven Sampling	Past STIs	15.40	522, 3.33, (1.83–4.80)

Pando, Sex Transm Dis, 2006	Argentina	Recruitment from gay nightclubs, porn cinemas, gyms, and streets	Fair	MSM	Past STIs	32.40	694, 1.47, (1.18–1.77)
Pando, Am J Trop Med Hyg, 2006	Argentina	FSWs in 6 cities contacted through an NGO	Fair	FSWs	Current syphilis	14.40	625, 1.80, (1.25–2.64)
Pando, J Med Micro, 2008	Argentina	Three public hospitals in Buenos Aires	Fair	TB patients > 18 years old	Past STIs	11.6%	181, 2.3 (1.2–4.7)
Remis, Am J Pub Health, 2000	Canada	Clinic and community settings	Fair	HIV-neg MSM	Past STIs	40.9%	328, 2.14 (1.57–2.39)
Rosenblum, J Infect Dis, 1990	USA	Belle Glade, Florida	Fair	Adults from randomly selected households	Past gonorrhea or chlamydia		328, 1.80 (1.38–2.11)
Rosenblum, JAMA, 1992	USA	Detention centers in Miami and L.A., brothels in NV, STI clinics in CO, drug Tx programs in NJ, street / social network outreach in Atlanta, NJ, and S.F.	Fair	Women 18 years old+ who had exchanged sexual services for money or drugs at least once since 1978	Current syphilis	21.0%	723, 2.05 (2.00–4.80)
Seage, Pub Health Rep, 1997	USA	Student participants recruited via outreach at colleges. Other participants recruited from Fenway Community Health Center, and gay nightclubs	Fair	MSM enrolled in college in Boston area and younger than 30 or, if not students, 18 to 24 years old.	Past syphilis	29.0%	714, 1.64 (1.16–2.32)
Segura, AIDS Care, 2010	Argentina	NGO clinic	Fair	MSM	Past gonorrhea	26.0%	712, 1.65 (1.32–2.06)
Zocrato, Sub Use Misuse, 2010	Argentina and Uruguay	Outreached clients recruited by civil associations. Hospitalized or outpatients recruited from 2 public and 1 nonpublic hospital for drug user and psychiatric diseases	Fair	Out-of-treatment and in-treatment Non-Injecting Cocaine Users from low-income neighborhoods in Montevideo and Buenos Aires.	Past syphilis	70.0%	646, 2.7 (1.9–4.0)
					Past STIs	11.7%	317, 3.11 (1.11–8.76)
					Current syphilis	25.0%	811, 2.40 (1.50–3.11)
					Current syphilis	10.8%	89, 3.62 (2.16–5.33)

Table 2.

Summary of evidence for the association of HBV infection with STIs

Outcome	Number of data points	Prevalence Ratio (95% CI); pooled if 2 studies	I ² (Q test p-value)	References (distinguishing characteristic for studies with >1 outcome)
HBV surface antigen (HBsAg)				
Syphilis – Current	6	6.76 (2.10–21.76)	91.4% (0.00)	Hennessey 2009; Miranda 2001; Parazzini 1992 (TPHA); Parazzini 1992 (VDRL); Zou 2009 (First-time donors); Zou 2009 (Repeat donors)
Syphilis – Past	1	2.36 (1.36–4.08)	N/A	Carmo 2014
Chlamydia / gonorrhea – Current	1	2.0 (0.93–4.32)	N/A	Hart 1992
Unspecified STIs – Past	5	1.65 (1.08–2.52)	73.6% (0.004)	Carmo 2014; Miranda 2001; Souto 2001; van Duynhoven 1997; Weinbaum 2008
HBV core antibodies (anti-HBc)				
Syphilis – Current	7	1.82 (1.60–2.06)	84.0%; (0.00)	Bratos 1993; Corona 1993; Fiscus 1994; Hakre 2013; Hennessey 2009; Juarez-Figueroa 1998; Oliveira 2001
Syphilis – Past	6	1.48 (1.10–1.99)	97.6%; (0.00)	Carmo 2014; Deiminger 1990; Tien 2004 (PWID); Tien 2004 (No illicit drugs); Tien 2004 (Non- PWID); Weinstock 1993
Chlamydia / gonorrhea – Past	8	1.30 (1.02–1.66)	92.3%; (0.00)	Corona 1996; Tien 2004 (No illicit drug); Tien 2004 (Chlamydia, PWID); Tien 2004 (Chlamydia, No illicit drug); Tien 2004 (Chlamydia, non-PWID); Tien 2004 (Gonorrhea, PWID); Tien 2004 (Gonorrhea, non-PWID); Weinstock 1993
Unspecified STIs – Current	4	1.42 (1.23–1.63)	42.4% (0.00)	Corona 1991 (non-IDU heterosexual); Corona 1991 (non-IDU homosexual); Oliveira 2001; Oliveira 2001 clinic
HBsAg or anti-HBc; combined				
Syphilis – Current	7	1.69 (1.39–2.07)	96.1% (0.00)	Lama 2010; Moura 2015; Pando 2006; Rosenblum 1990; Rosenblum 1992; Segura 2010; Zoccratto 2010
Syphilis – Past	3	1.51 (0.89–1.52)	95.0% (0.00)	Levine 1995; Remis 2000; 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	2	1.73 (1.48–2.01)	0.0% (0.58)	Remis 2000; Rosenblum 1990
Unspecified STIs – Past	8	1.89 (1.52–2.37)	45.1% (0.08)	Baddour 1988; El Maerawi 2005; Hwang 2000; Matos 2008; Oliveira 2015; Pando 2006; Pando 2008; Seage 1997