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Review Article

Horizontal Modes of Transmission of Hepatitis B Virus (HBV): A Systematic Review and Meta-Analysis

Sasidharanpillai Sabeena [1], Nagaraja Ravishankar [2]

1. *Clinical Virology, Allure Residency, Near the British School, Kathmandu, Nepal*
2. *Department of Biostatistics, Vallabhbhai Patel Chest Institute, University of Delhi, New Delhi, India*

***Corresponding Author:** Email: sabeenauthradam@gmail.com

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Abstract

Background: Horizontal transmission of hepatitis B virus (HBV) is a significant transmission route in households, among contact sport athletes and institutionalized individuals. Children often are infected by non-sexual close contacts with an increased tendency to become chronic carriers. Hence, the awareness about various high-risk behaviours leading to horizontal transmission in the community is essential. A systematic review and meta-analysis was carried out to assess quantitatively the pooled prevalence of horizontally transmitted HBV infection globally.

Methods: The study was started after ruling out registered or ongoing systematic reviews related to this topic in the PROSPERO database. The study protocol was documented in PROSPERO with a registration number CRD42021235165. We searched electronic databases for published articles in English between 1981 and April 2021 reporting horizontal modes of hepatitis B transmission among unvaccinated contacts. Meta-analysis was carried out in STATA version 13.0 (College Station, Texas 77,845 USA). The forest plots were constructed using metaprop package in STATA.

Results: Forty-one studies were systematically reviewed and 15 studies were qualified for the meta-analysis, including 1619 hepatitis B cases and 4869 contacts. The overall pooled prevalence of horizontally transmitted HBV infection among the contacts was 38% (95% CI 30%-46%). The pooled prevalence among 3,912 household contacts from nine qualified studies was estimated as 44% (95% CI 35%-54%). The pooled prevalence rates among institutionalized individuals and contact sport athletes were 30% (95% CI 23%-37%) and 18% (95% CI 5%-32%), respectively.

Conclusion: The likelihood of horizontal transmission of HBV is greater among household contacts of chronic carriers of HBV and institutionalized individuals.

Keywords: Contacts; Hepatitis B; Horizontal; Household; Prevalence

Introduction

Hepatitis B virus (HBV) infection results in acute and chronic liver infection, leading to liver cirrhosis and hepatocellular carcinoma after many decades. The highest prevalence rates of HBV infection were reported from the WHO Western Pacific and African regions (1). Chronic HBV infection varies between 3.5% and 5.6% among adults and 1.3% to 3.4% in children below five

years (2). The prevalence rate is highly heterogeneous, and the highest rate reported from sub-Saharan Africa and East Asia is 5-10% despite the availability of effective vaccines (3). India is home to more than 40 million chronic HBV carriers with an estimated 3-4.2% prevalence of Hepatitis B surface antigen (HBsAg) (4).

The main modes of transmission of HBV are vertical transmission, sexual transmission, and parenteral contact with blood or blood products. This hepatotropic virus is highly stable at 37 ℃ on environmental surfaces for more than 22 days (5). HBV is detected in blood and body fluids such as saliva, tears, sweat, semen, and vaginal secretions of infected individuals (6). Most hepatitis B cases in low prevalence areas are attributed to injection drug use and high-risk sexual exposures (7). A recent study from China which is part of the Western-Pacific region, estimated an overall pooled prevalence of 6.9% (95% confidence interval (CI) 5.84%-7.95%)(8). Ethiopia, located in East Africa, stated an overall HBV pooled prevalence of 6% and a prevalence estimate of 5% each among pregnant women and health care workers (HCWs)(9). The pooled risk of transmission from mother to child in Sub-Saharan Africa is 4.8% (95% CI 1.3-13%) (10). Meanwhile, the estimated pooled data among pregnant women from the Middle East was 1.2%, with a 95% CI of 0.9%-1.6% (11).

Transmission from mother to child happening perinatally is the predominant mode of spread in high prevalent areas (12,13). Horizontal transmission is defined as the transmission of the virus in the absence of sexual, perinatal or parenteral modes of spread (14). This less efficient transmission mode happens when there is contact with saliva, tears or minute quantities of blood during needle stick injuries, tattooing, piercing, community shaving, sharing sharps at home, or workplaces.

The rationale of the study

Awareness about various high-risk behaviours leading to horizontal transmission in the community and preventive measures other than immunization is essential. There are non-responders to vaccines, highly susceptible immunocompromised individuals, cases infected with HBV mutants, and individuals with limited response to antiviral agents. Children often are infected by non-sexual close contacts with an increased tendency to become chronic carriers. They are more likely to be HBVe antigen-positive with a higher viral load. Population migration for livelihood from high to low prevalence areas has led to increased horizontal infection rates in childhood, increasing the global burden of the chronic carrier state.

The main aim of the present systematic review and meta-analysis was to quantitatively assess the global prevalence of HBV infection among individuals who were infected horizontally. The secondary objective was to evaluate the prevalence of horizontally transmitted HBV infection among family members, contactsports athletes and institutionalized individuals.

Methods

The protocol was documented in PROSPERO: International prospective register of systematic reviews database (http: // www. crd. york.ac.uk/prospero/) with registration number CRD42021235165 (https://www.crd.york.ac.uk/prospero/#recordDetails).

We searched electronic databases for published articles in English between January 1981 and April 2021 based on standard systematic review guidelines recommended by Cochrane collaboration (https://www.cochrane.org) and Campbell Collaboration (htps://www.campbellcollaboration.org). The protocol was designed based on Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (15). The meta-analysis component was modified appropriately to synthesize the pooled prevalence rate of horizontally acquired hepatitis B infection with 95% CI.

Description of the condition

Horizontal transmission

HBV transmission happening without apparent sexual, perinatal or parenteral transmission is known as horizontal transmission (14).

Chronic Hepatitis B cases (Hepatitis B carriers)

Hepatitis B carriers are individuals who are positive for hepatitis B surface antigen (HBsAg), Hepatitis B e antigen (HBeAg) or Hepatitis B DNA at least twice, six months apart (16). These persons are asymptomatic with no evidence of liver disease or may be showing clinical manifestations of chronic hepatitis, cirrhosis or hepatocellular carcinoma.

Study protocol

A detailed electronic literature search of all the published articles between January 1981 and April 2021 on horizontal modes of transmission of HBV infection was carried out. The electronic databases explored were MEDLINE/PubMed, Scopus, and Google Scholar. The relevant articles in English involving human subjects were identified using search terms such as "hepatitis B" OR "HBV" AND "horizontal transmission" NOT "vertical transmission" NOT "perinatal transmission" NOT "sexual transmission" NOT "Human Immunodeficiency Virus" OR "HIV" NOT "Hepatitis C virus".

Inclusion process and criteria

Cross-sectional, case-control, cohort studies and case series reporting horizontal modes of hepatitis B transmission among unvaccinated humans by serology or molecular assays were included. Studies concerning horizontal transmission among pre-school children were included if the perinatal infection was ruled out.

Exclusion criteria

Duplicate articles, a replica of original studies, irrelevant studies, policy papers, comments, animal studies and studies in languages other than English were eliminated. Articles with no information on exposure to various risk factors such as sexual exposure, operative procedures, transfusion of blood/blood products or intravenous drug use were excluded and study considering sexual transmission as the horizontal mode of transmission were excluded (17). Studies not ruling out the possibility of perinatal transmission in families, prevalence data among spouses and vaccinated individuals were also not included (18-20). Studies reporting horizontal transmission among soldiers and prisoners were not incorporated as the study participants were observed to be having high-risk sexual activities and intravenous drug use.

Data extraction

A validated proforma focusing on the first author, year of publication, region, the period during which samples were archived, study design, study setting, number of cases, number of chronic patients, number of contacts tested positive for Hepatitis B infection (HBsAg/HBeAg/HBV DNA positivity), and HBsAg positivity was developed.

We adopted a three-stage selection process for the final inclusion of the studies. One reviewer assessed the titles of articles for relevance (n=322). After excluding duplicates and irrelevant topics (n =235), the reviewer moved the articles to the second stage. In the second stage, the abstracts of the studies (n=87) were independently analyzed. After reviewing abstracts, full texts version of the most relevant studies (n=64) were retrieved and scrutinized by two reviewers independently and collated based on consensus. A manual library search for articles in peer-reviewed journals was carried out, and references of retrieved articles were reviewed to increase the search sensitivity. When there was incomplete or inadequate information, authors were contacted electronically. The study selection process was depicted in the PRISMA chart (Fig.1). The search concluded on Apr 30, 2021.

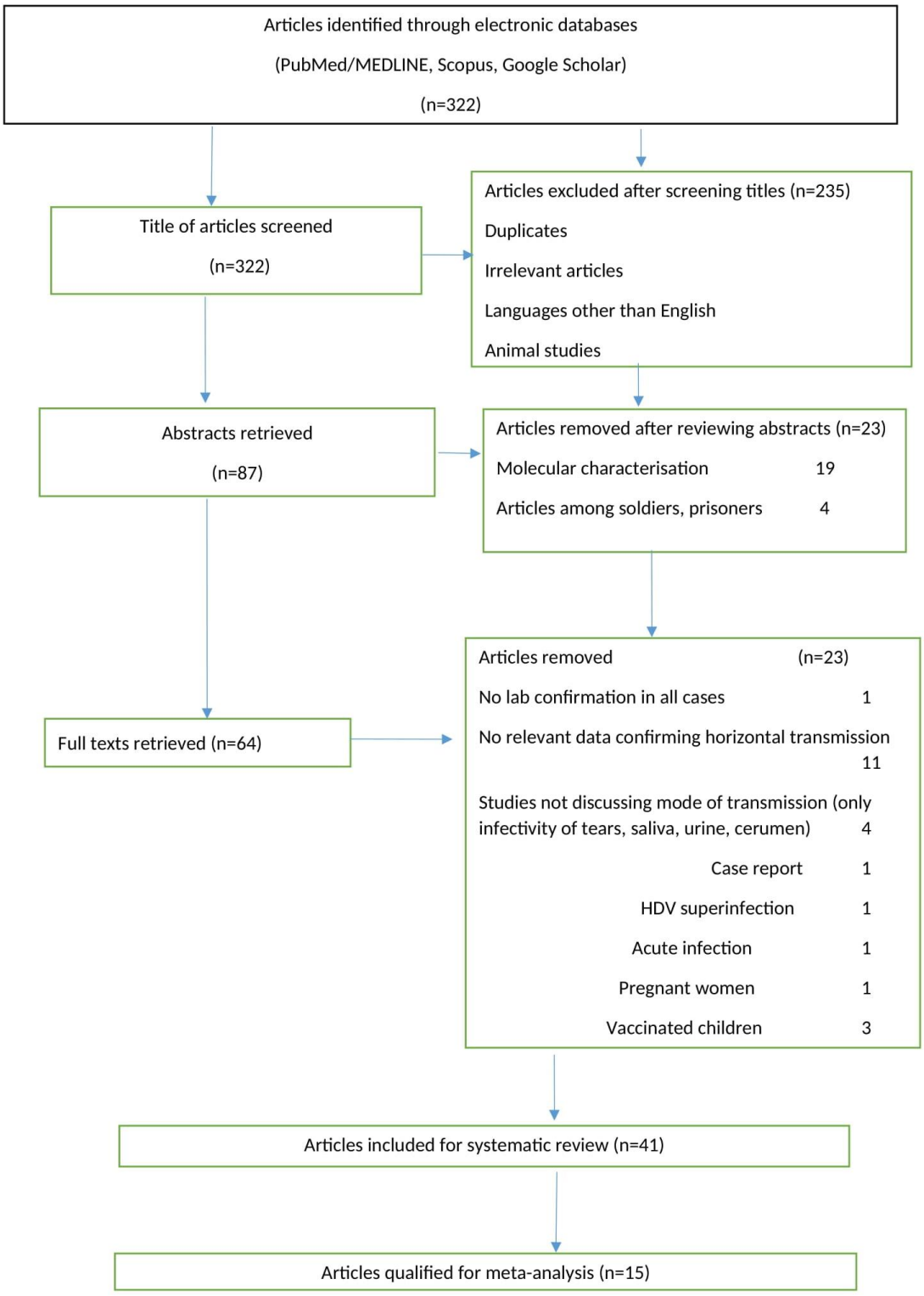

Fig. 1: PRISMA chart Depicting the Study Selection for Systematic Review and Meta-Analysis. The flow diagram describes the number of studies identified, screened, full-text articles retrieved, and reviewed

Quality assessment (Risk of bias in individual studies)

We employed the National Institutes of Health checklist for observational, cohort and cross-sectional studies to assess the risk of bias in individual studies chosen after the abstract and content review (21). All the 14 questions were applied to cohort studies. The studies with a minimum score of eight or above, seven, or five or less than five "Yes responses" were considered good, fair, and poor quality, respectively. For cross-sectional and case-control studies, question numbers 1, 2, 3, 4, 5 and 11 were applicable. The responses to the remaining eight questions [6-10,12,13,14] were marked as not applicable (NA). Each question was categorized as Yes, No, others-CD (can-not determine), NA (not applicable), NR (not reported). The studies with six "Yes" responses were considered good, and those with four /five were taken as fair. The studies with less than four "Yes responses" were considered of poor quality.

Data analysis

Meta-analysis was accomplished in STATA version 13.0 (College Station, Texas 77,845 USA). The forest plots were constructed using metaprop package in STATA. A considerable amount of heterogeneity across the studies was anticipated because most of the studies were mainly observational. The pooled prevalence with 95% CI was reported along with Chi^2 statistic (Q statistic) and I^2 index to quantify the heterogeneity between the qualified studies. I^2 value ranging from 0% to 24% indicates the study results are very consistent. I^2 values of 25%-49% imply low heterogeneity, and I^2 values of 50-74% indicate moderate heterogeneity. High heterogeneity between the studies was reported based on the I^2 value ranging between 75%-100% (22).

Publication bias

We employed Eggers's test to assess the publication bias (23). Weighted linear regression with standardized effect estimate and precision was considered the dependent and independent variables, respectively. In the present study, $\log_e$ prevalence rate was considered the effect estimate and the precision was given as 1/standard error of $\log_e$ prevalence rate. Using the inverse variance approach (1/variance of the effect estimate), weights were assigned. A statistically significant bias coefficient provides evidence for publication bias.

Ethics approval

The systematic review and meta-analysis used published data in indexed journals. We performed secondary data analysis that requires no ethical approval.

Results

Included studies for meta-analysis of the global prevalence of HPV infection

In the present study, 41 studies were systematically reviewed and 15 studies were qualified for the quantitative synthesis (meta-analysis), including 1,619 chronic hepatitis B cases and 4,869 non-sexual close contacts. Horizontal transmission often happens among family members, friends, contact sport athletes, and institutionalized individuals with an infected person's blood or other body fluids.

Meta-analysis of horizontally transmitted HBV infection

The pooled prevalence of overall hepatitis B infection among 4,869 contacts from 15 qualified studies was 38% (95% CI 30%-46%). The I^2 value was 96.10%, implying high heterogeneity and the random-effects model was used for pooling (Fig.2).

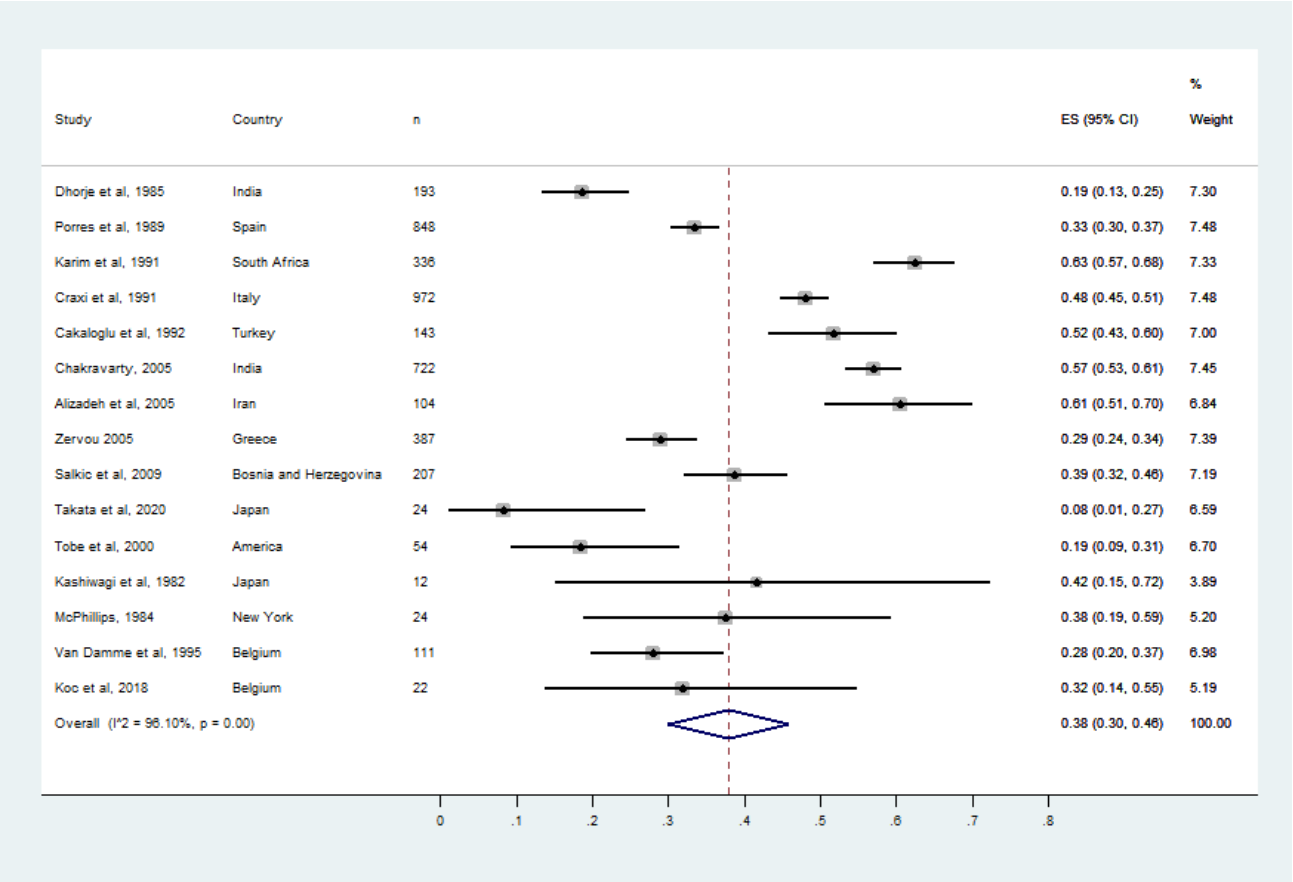

Fig 2: The Forest Plot of the summary effect size (Prevalence of HBV) using random effects model among horizontal contacts of hepatitis B cases. Squares indicate the effect size of individual studies and the extended lines denote 95% confidence intervals (CI). Sizes of squares imply the weight of studies based on sample size using a random effects analysis. The diamond data indicates pooled prevalence. Test of heterogeneity: I^2=96.10 %, p=0.00

Horizontal transmission in families

Nine studies comprising six cross-sectional studies, two cohort studies, and one case-control study were incorporated for the meta-analysis (Table 1). These studies were carried out in India, Spain, South Africa, Italy, Turkey, Iran, Greece, and Bosnia by enrolling 1403 index cases of chronic hepatitis B and 3,912 household contacts between 1980 and 2006 (24-32). Out of the nine studies, three were community-based, including asymptomatic hepatitis B carriers as index cases (26,28,30). Hospital-based studies enrolled acute hepatitis cases (24), chronic hepatitis cases, hepatocellular carcinomas (25,27,32), cases with advanced liver diseases (27) as well as healthy carriers. The study by Zervou et al. included HBsAg positive blood donors from the blood bank (31). None of the index cases and contacts were vaccinated. The prevalence of hepatitis B infection among contacts varied between 18.7% and 62.5% (24,26). Except for one study in children by Karim et al., all the studies enrolled adults and children above one year of age (26). The prevalence rate among spouses or sexual partners was not considered for the quantitative synthesis. All the studies were qualified as good, and the prevalence of HBsAg varied between 10.6% and 29.4% (25,27).

Table 1: Qualified studies reporting horizontal transmission of HBV among family members

S No	*Reference*	*Region*	*Study design*	*Study Period*	*Index cases (N)*	*Household contacts (N)*	*HBsAg+/Anti-HBc+ along with Ani HBs +*				
							HBV+ N(%)	HBsAg+ N(%)	siblings N	Children N	Parents N
1	Dhorje et al 1985[24]	Pune, India, South Asia	Case-control	1984	40	193	36 (18.7)	22 (11.4)	6/35	13/81	15/26
2	Porres et al[25] 1989	Spain South west Europe	Cohort	1980-1985	285	848	284 (33.5)	249 (29.4)	58 /136 (43)	57 /359 (16)	89/150 (59)
3	Karim et al[26] 1991	South Africa	Cross-sectional	1985-1986	60	336	210 (62.5)	50 (14.9)	52/108	NA	46/60
4	Craxi et al 1991[27]	Italy South Europe	Cross-sectional	1984-1985	226	972	466 (47.9)	103 (10.6)	59	95	77
5	Cakaloglu et al 1992[28]	Turkey West Asia Southeast Europe	Cross-sectional	1984-1985	215	143	74 (51.7)	29 (20.3)	18/25	18/ 55	10/14
6	Chakravarty 2005[29]	India South Asia	Cross-sectional	1998-2000	215	722	412 (57.0)	140 (19.4)	38/133	66/165 (40)	17/59
7	Alizadeh et al 2005[30]	Iran West Asia	Cross sectional	2003	115	104	63 (60.6)	12 (11.5)	2 /15	7/64	1 /16
8	Zervou 2005[31]	Greece South Europe	cohort	1991-1999	166	387	112 (28.9)	54 (13.9)	39/43	28/179	45/54
9	Salkic et al 2009 [32]	Bosnia and Herzegovina South Europe	Cross sectional	2004-2006	81	207	80 (38.6)	25/207 (12.1)	6/7	22/122	24/29

HBsAg, hepatitis B surface antigen; Anti-HBc hepatitis B core antibody; Anti-HBs, hepatitis B surface antibody; NA, not applicable.

Meta-analysis of horizontal transmission in families

As depicted in Fig. 3, the pooled prevalence of overall hepatitis B infection among 3,912 household contacts from nine qualified studies was 44% (95% CI 35%-54%). The pooled prevalence of HBsAg was 16% (95% CI 11%-21%), which specifies active infection. The I^2 values were 97.23% and 93.34% respectively, when the estimated prevalence rates of horizontally transmitted HBV infection and HBsAg among contacts were pooled, implying high heterogeneity. Hence, the random-effects model was used for pooling.

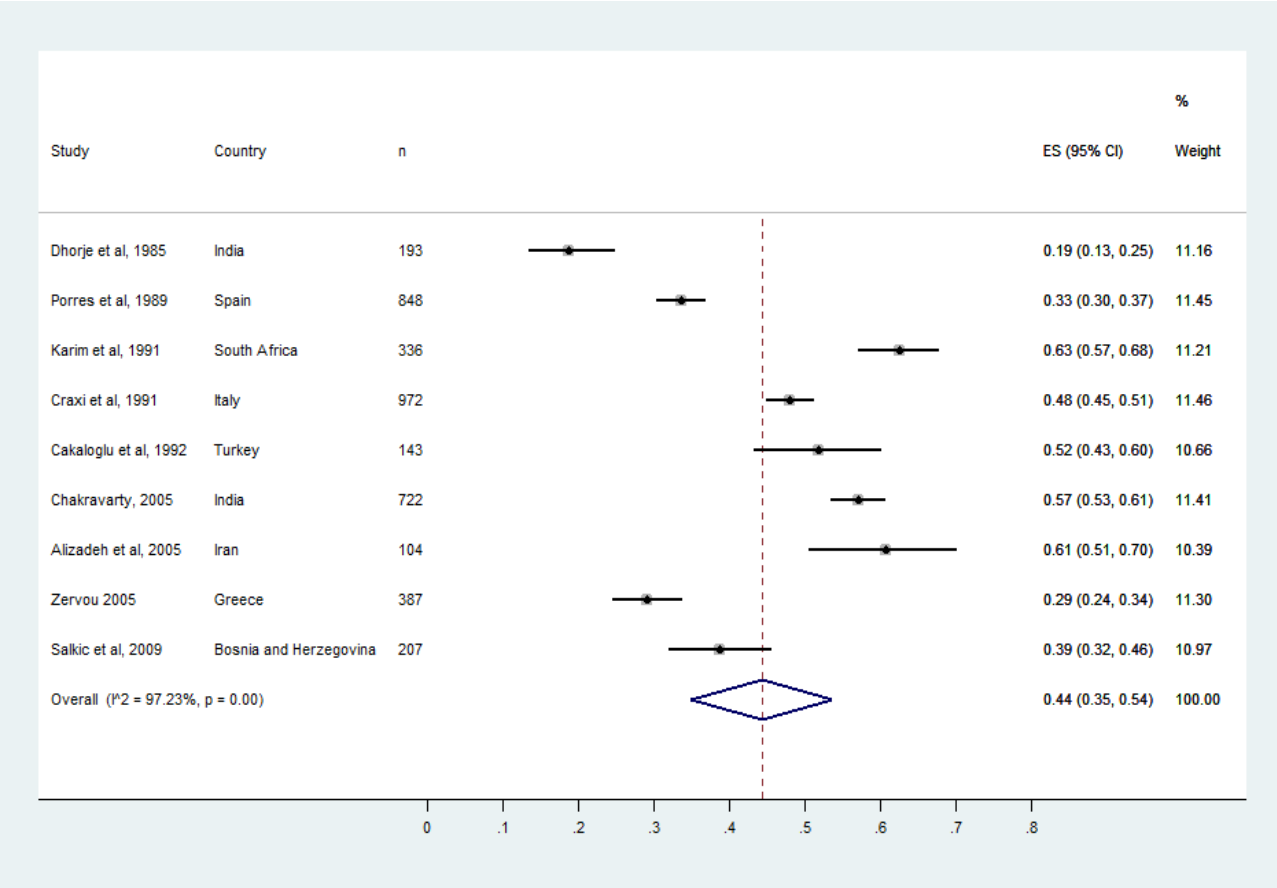

Fig. 3: The Forest Plot of the summary effect size (Prevalence of horizontally transmitted HBV) using random effects model among household contacts of hepatitis B cases. Squares indicate the effect size of individual studies and the extended lines denote 95% confidence intervals (CI). Sizes of squares imply the weight of studies based on sample size using a random effects analysis. The diamond data indicates pooled prevalence. Test of heterogeneity: I^2=97.23%, p=0.00

Horizontal transmission among contact sport athletes

According to the literature, there are sparse reports of horizontal transmission among contact sport athletes. As shown in Table 2, three studies conducted among young adult men engaged in wrestling, sumo wrestling and football were qualified for the quantitative synthesis (33-35). All the 19 cases as well as 90 contacts were not vaccinated. Amongst the contacts, infectivity varied between 8.3% to 41.7% (33,35). One case each in the included studies was found to develop chronic carrier state on further follow up (33-35).

Meta-analysis of horizontal transmission among contact sport athletes

The pooled prevalence of hepatitis B infection among athletes engaged in collision and contact sports was 18% (95% CI 5%-32%). I^2 value was 62.39, indicating moderate heterogeneity. The random-effects model was used for pooling due to the methodological heterogeneity of observational studies.

Horizontal transmission among institutionalized individuals

Two studies carried out among institutionalized intellectually disabled individuals and one survey among Turkish migrants were qualified for the

present meta-analysis (36-38). Two studies were carried out during the final decades of the twentieth century in New York and Belgium (36,37). The third study was carried out between 2009 and 2014 (38). One study was qualified as fair as the age group of the cases and contacts were not specified (37). The study from the United States carried out among migrant children was excluded as the horizontal mode of transmission was not confirmed (18). Collectively, 151 cases and 157 contacts were included with overall HBV positivity among contacts varying between 27.9% and 37.5%, as in Table 2.

Table 2: Studies reporting transmission of HBV among contact sport athletes and institutionalized individuals

S No	*Reference*	*Region*	*Exposure*	*Time Interval (months)*	*Cases (N)*	*Contacts (N)*	*Age (years)*	*HBV + Acute/ subclinical infection N (%)*
1	Takata et al 2020[33]	Japan	Wrestling	5	3	24	19-21	2 (8.3)
2	Tobe et al 2000[34]	America	Football	19	11	54	mean 20.5±1.5	10 (18.5)
3	Kashiwagi et al 1982[35]	Japan	Wrestling	12	5	12	15-17	5 (41.7)
4	McPhillips 1984[36]	New York	institutionalized	12	5	24	9-69	9 (37.5)
5	Van Damme et al 1995[37]	Belgium	institutionalized	12	123	111	---	31 (27.9)
6	Koc et al 2018[38]	Belgium	institutionalized	60	23	22	44±13.7	7 (32.5)

Meta-analysis of horizontal transmission among institutionalized individuals

The pooled prevalence of horizontal transmission of hepatitis B infection among institutionalized individuals was 30% (95% CI 23%-37%), with I^2 value of 0.00 indicating the absence of heterogeneity. Taking into consideration the methodological heterogeneity of observational studies, the random-effects model was used for pooling.

Publication bias

The *P*-value for the bias coefficient is more than 0.05, which is statistically non-significant (Table 3). Hence, there is no evidence of publication bias.

Table 3: Table depicts the results of Egger's test for publication bias

Coefficient	*Estimate (95%CI)*	*P-value*
Publications related to horizontally transmitted HBV Positivity in families		
Slope	0.4091 (0. 0646, 0. 7537)	0.026
Bias	1.0707 (-13.9551, 16.0965)	0.871
Publications related to horizontally transmitted HBsAg Positivity in families		
Slope	0.1325 (-0. 0244, 0.2894)	0.086
Bias	1.4714 (-7.6791, 10.6220)	0.715
Publications related to horizontally transmitted HBsAg Positivity in contact sport athletes		
Slope	-0. 0243 (-2.0265, 1.9779)	0.902
Bias	2.9901 (-28.0587, 34.0391)	0.436
Publications related to horizontally transmitted HBsAg Positivity in institutionalized individuals		
Slope	0. 2286 (-0. 2476, 0. 7048)	0.103
Bias	1.1913 (-6.3639, 8.7466)	0.295

Discussion

We observed that most of the published studies on intrafamilial transmission do not differentiate between vertical, horizontal and sexual modes of transmission. The confirmation of the acquisition of infection within the families, sports clubs or institutions is often made by the clustering effect, which indicates the simultaneous occurrence of a significant number of positive cases (26). If the mother is HBV positive, a higher likelihood of horizontal transmission to children was found in many studies (25,39). Horizontal transmission happening in families was observed to be the major route of transmission at the community level. Sports necessitating physical contact between the players, such as boxing, wrestling, soccer and basketball, are known as collision or contact sports (40). A limited number of studies report horizontal transmission of hepatitis B among collision and contact sports athletes (33-35). In our meta-analysis, horizontal transmission among institutionalized individuals was observed in only three studies. The studies including infants of HBsAg positive mothers at birth or within six months of age were not included in this systematic review due to the placental transfer of HBsAg and HBV DNA, which increased the false positivity rate. These babies have to be tested at 6-12 months of age to rule out HBV infection and retested after 6-7 months to confirm chronicity if detected to be positive (41,42).

Even though HBV DNA levels are the highest in serum samples of carriers, body fluids such as sweat, tears, saliva, and urine are also potential sources of transmission(6,43). Horizontal transmission can happen non-iatrogenically in daycare centres (44), institutions of intellectually disabled (45,46), tattoo parlours (47,48), slaughterhouses (49), and barbershops(50). Multiple needle pricks and cuts by scissors have resulted in Hepatitis B outbreaks among barbers, butchers (49-51), receivers of acupuncture treatment(52) and during skin piercing. Minor cuts or small abrasions occurring in day care centres, schools, homes, closed institutions or high-risk contact/collision sports can result in HBV transmission. Persons with chronic HBV infection shed the virus from open wounds into environmental surfaces resulting in infection of contacts with open lesions (53). Meanwhile, there was no increased risk of horizontally transmitted HBV infection among soccer players from Australia and wrestlers in Tehran (54,55). The study from Tehran pointed out the greater prevalence rates of high-risk sexual activity and intravenous drug use among wrestlers than football and volleyball players.

Very high HBV DNA titres were detected in salivary and tear samples of young children resulting in an increased transmission rate amongst children at home and schools (6). Hepatitis B surface antigen was also detected on tables, walls, and bottles in schools and daycare centres (56). Transmission from chronic hepatitis B carriers at homes, gyms, schools or closed institutions can be interrupted by covering minor wounds or cuts by gauzes or bandages. Sharing of sharp objects such as razors, nail cutters, kitchen knives, bath towels, dental cleaning objects and partially eaten food items has to be avoided between asymptomatic carriers and contacts (57). Current research mainly focuses on the genetic variation of hepatotropic viruses aiming to develop vaccines and drugs (58-61). This is the first systematic review and meta-analysis of horizontal transmission of HBV to the best of our knowledge.

The main limitation of our meta-analysis is the dearth of community-based studies concerning horizontal transmission in families. Another factor resulting in overestimation was the underreporting of high-risk sexual behaviour and intravenous drug use by study participants.

Conclusion

Familial clustering of HBV infection is mainly attributed to horizontal transmission. Routine screening and immunization of household contacts and institutionalized individuals are essential as they are at a higher risk of hepatitis B infection

by non-sexual close contacts. Athletes engaged in collision and contact sports should take necessary precautions, as there is greater likelihood of horizontal transmission through minor abrasions and cuts.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

Authors have no conflicts of interest to declare for this study.

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