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Review Article

Hepatitis Delta Prevalence in South America: A Systematic Review and Meta-Analysis

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Abstract

Hepatitis delta virus (HDV) has been associated with acute or chronic hepatitis in Latin America, but there is no prevalence study covering South American countries. This meta-analysis aimed to estimate anti-HDV prevalence through a systematic review of published articles in English, Portuguese and Spanish until December 2017. Searches were conducted in Health Virtual Library, Capes, Lilacs, PubMed, and SciELO, according to defined criteria regarding participant selection and geographical setting. Study quality was assessed using the GRADE guidelines. Pooled anti-HDV prevalence was calculated using the DerSimonian-Laird random-effects model with Freeman-Tukey double arcsine transformation. Out of the 405 identified articles, only 31 met the eligibility criteria for inclusion in the meta-analysis. In South America, pooled anti-HDV prevalence among hepatitis B virus carriers was 22.37% (95% confidence interval: 13.72–32.26), though it appeared less frequently in some countries and populations, according to the data collection date. The findings indicated significant successive reductions in anti-HDV prevalence over thirty years. However, there was a scarcity of HDV epidemiological studies outside the Amazon Basin, notably in the Southwest continent and absence of target population standardization. There was a high HDV prevalence in South American countries, despite differences in methodological characteristics and outcomes, highlighting a drastic decline in the last decades. Future studies should identify HDV prevalence estimates in other regions of the continent and identify risk factors.

Keywords: Hepatitis delta virus; Anti-HDV; Prevalence; South America; Epidemiology.

INTRODUCTION

Hepatitis delta virus (HDV) infection can cause acute or chronic hepatitis. HDV is a defective virus capable of multiplying only in hepatitis B virus (HBV) infected hepatocytes, requiring HBV surface antigen (HBsAg) as its envelope protein[1]. Diagnostic assays using antibodies against HDV antigen (anti-HD) performed on HBsAg carriers are reliable sources of information on HDV epidemiology and molecular tests (HDV-RNA) are indicated for active infection confirmation. It is estimated that 18 million HBsAg carriers around the world also have anti-HDV antibody, representing 5% of HBV infected individuals. However, this estimate presents a range of substantial uncertainty since not all are tested for HDV infection[1, 2].

HDV infection is ubiquitous worldwide, but its distribution pattern is not uniform [1-12]. Even in endemic areas, anti-HDV prevalence differs greatly depending on geographical region, such as in the Eastern Mediterranean[5], sub-Saharan Africa[12], Iran[4], and Turkey[6]. In Latin America, HDV has been associated with acute and chronic infection, particularly severe and fulminant hepatitis. The study area was based on articles already reporting high HDV endemicity in South America, since the 1980s[13-19]. There are relatively few data on HDV prevalence in South American countries and most of them are regional cross-sectional studies[1, 2, 20-22]. To date, there has been no HDV infection prevalence estimate for South America. Therefore, a systematic review with meta-analysis was planned to provide a clearer and more comprehensive

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presentation of published data on HDV prevalence among HBsAg carriers in South American countries.

METHODS

Study design

All methods of this systematic review and meta-analysis were conducted according to the MOOSE (Meta-analyses of Observational Studies in Epidemiology) guidelines and reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist[23, 24].

Study area

South America extends across 17,819,100 km² (12% terrestrial surface) and comprises 6% of the world population. It encompasses the following countries: Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Guyana, Paraguay, Peru, Suriname, Uruguay, and Venezuela. Also, the following independent territories are part of the continent: French Guiana, Falkland Island and South Georgia and the South Sandwich Islands.

Relevant article search strategy

An algorithm was developed to search for articles containing the topic of interest by combining the following key descriptors and medical terms (MeSH); "hepatitis D" OR "HDV" OR "hepatitis Delta virus" OR "anti-HD" and "prevalence" OR "seroprevalence" OR "epidemiology". This was adapted to predefined electronic databases (PubMed, SciELO, Lilacs, Capes, and Virtual Health Library). Each country/independent territory name was added individually. The time frame included all published articles until 31st December 2017 and searches were conducted for articles published in English, Portuguese and Spanish.

In addition, a limited manual search of cross-references was conducted to identify all published articles on HDV prevalence. Thus, identified articles were selected first by their titles and abstracts, according to inclusion and exclusion criteria by five researchers independently and duplicates removed. Relevant articles were read in full.

Inclusion criteria

- Any study reporting HDV prevalence.
- Clearly stated information about number of HBV-infected people and HDV diagnosis based on anti-HDV antibody presence or molecular tests.
- Case series, cross-sectional, case control, or cohort appropriated studies.
- People residing in any South American country and no criteria regarding size, gender or age.
- Published data in five electronic databases.

Exclusion criteria

- Studies conducted in populations residing outside South America.
- Studies designed as case reports, reviews, comments, and editorials.
- Studies with no primary data and/or explicit description of laboratory methods.
- Studies about HDV genotyping.

Quality assessment and data extraction of studies

Each paper was quality assessed according to the GRADE approach[25] and a scoring system was established considering: study design, population group, sampling method, HDV diagnostic method, anti-HDV prevalence outcome, endemic region and relative risk measure or reported odds ratios. Points ranged from 0 to 2 points on evaluation by two researchers individually, with a partial blinding process. Consensus was used to resolve misunderstandings in appraisals by investigators. Quality level was arbitrarily categorized as very low (0–2.5), low (2.6–5.0), moderate (5.1–7.5), and high (7.6–9.5). A five-point minimum score was established for an article to be included in the meta-analysis.

General information (authors, year, country), primary data (study design, target population, positive HBsAg, and anti-HDV case number) were extracted from each included article in the meta-analysis (met the eligibility criteria). One researcher checked all extracted data for accuracy.

Statistical analysis

Data analysis was performed using the "metan" and "metaprop" packages in Stata version 11.0 (StataCorp LLC, College Station, TX, USA) [26, 27]. Study primary data were computed to establish individual HDV prevalence and confidence intervals (95%CI) were calculated using the Wilson method. Publication bias was verified through a funnel plot and Egger's test. Study heterogeneity was evaluated using the chi-squared test based on the Q statistic and calculated by I^2. Pooled anti-HDV prevalence was calculated using DerSimonian-Laird's random-effects model with Freeman-Tukey's double arcsine transformation, based on the heterogeneity test result. Forest plot and descriptive tables were used to display the main results.

Meta-regression was performed using the residual maximum-likelihood model to examine for heterogeneity sources related to study country or design, selected population, specific geographic area, data collection decade, anti-HDV diagnostic method, HDV/HBV infection risk, and quality assessment. Methodological and clinical heterogeneity due to groups and potentially non-representative samples were investigated with sensitivity analysis with Tau^2 showing variation between subgroups.

RESULTS

Search outcomes

A total of 405 records were found in the searched databases, but only 171 of them were retained after duplicates were removed. Further evaluation excluded 91 titles because they were not related to anti-HDV prevalence in South American countries. Twenty four articles were not made available by the authors. Fifty-five articles were selected based on inclusion and exclusion criteria after full text reading. Two very low-quality studies (4.5 score) were excluded[15,19]. Therefore, only 31 of 33 eligible articles with 71,733 participants were included in the final phase for quantitative analysis (meta-analysis) as shown by the flowchart (**Figure 1**) and **Table 1**.

TABLE 1: Data of articles included in the meta-analysis on the prevalence of HDV infection in South America (1985–2015).

Year	Authors	Data date	Country	Design	Target population w	Anti-HDV diagnostic method	HDV-RNA	Crude sample size (n)	Positive HBsAg (n)	Positive anti-HDV (n)	HDV/HBsAg prevalence (%)	Quality total (score)
1985	Ljunggren KE, et al. [13]	1985	Colombia	case control	hospitalized patients	radio immunoassay	NA	564	34	6	17.65	7.5
1988	Fonseca JC, et al.[15]	1981 – 1985	Brazil	cross-sectional	health-care workers	enzyme immunoassays	NA	574	96	33	34.38	7.5
1991	Soares MCP, Bensabath G[17]	1990	Brazil	cross-sectional	native indigenous communities	NA	NA	436	288	144	50.00	5.5
1991	Indacochea S, et al.[19]	1991	Peru	cross-sectional	general population	ELISA	NA	214	21	10	47.62	5.0
1991	Torres JR, Mondolfi A[18]	1975; 1986	Venezuela	cross-sectional	native indigenous communities	radio immunoassay	NA	116	28	17	60.71	6.0
1992	Da Fonseca JC, et al.[14]	NA	Brazil	case series	hospitalized patients	enzyme immunoassays	1 HDV	11	9	4	44.44	5.8
1992	Hadler SC, et al. [16]	1983 – 1988	Venezuela	cohort	native indigenous communities	enzyme immunoassays	NA	248	216	109	50.46	7.0
1994	Soares MC, et al.[22]	1992	Brazil	cross-sectional	native indigenous communities	enzyme immunoassays	NA	339	53	0	0.00	5.0
1995	Arboleda M, et al.[20]	1995	Brazil	cross-sectional	general population	ELISA	NA	798	13	5	38.46	6.5
1996	Azevedo RA, et al.[21]	1996	Brazil	cross-sectional	native indigenous communities	enzyme immunoassays	NA	255	14	0	0.00	5.0
1996	Casey JL, et al. [28]	1992 – 1993	Peru	cross-sectional	hospitalized patients	enzyme immunoassays	32 HDV-3	88	77	54	70.13	8.0
1997	Chang J, et al.[29]	1997	Peru	cross-sectional	general population	ELISA	NA	224	6	1	16.67	5.5
1999	Oliveira MLA, et al.[30]	1994 – 1995	Argentina	case control	HIV-infected patients	enzyme immunoassays	NA	484	73	9	12.33	5.5
1999	Fainboim H, et al.[31]	1992 – 1996	Bolivia	cross-sectional	native indigenous communities	enzyme immunoassays	NA	751	9	2	22.22	5.5
1999	León P, et al.[32]	1999	Brazil	cross-sectional	injecting drug users	enzyme immunoassays	NA	102	8	0	0.00	6.0
2000	Manock SR, et al.[33]	1998	Ecuador	cross-sectional	native indigenous communities	ELISA	14 HDV	173	47	15	31.91	6.5
2001	De Paula VS, et al.[34]	1997	Brazil	cross-sectional	general population	ELISA	NA	349	18	12	66.67	7.0
2001	Braga WS, et al. [35]	2001	Brazil	cross-sectional	native indigenous communities	ELISA	NA	688	67	9	13.43	7.5
2002	Segovia M, et al.[36]	2000	Peru	cross-sectional	school Community	ELISA	NA	130	18	3	16.67	7.5
2005	Viana S, et al.[37]	2002	Brazil	cross-sectional	general population	ELISA	NA	2656	89	47	52.81	6.0
2006	Cabezas S, et al. [38]	1996	Peru	cross-sectional	native indigenous communities	ELISA	NA	870	82	32	39.02	8.5
2007	Nunes HM, et al.[39]	2003 – 2005	Brazil	cross-sectional	native indigenous communities	ELISA	NA	258	10	0	0.00	5.0
2010	Duarte MC, et al.[40]	2002 – 2004	Venezuela	cross-sectional	native indigenous communities	enzyme immunoassays	NA	645	54	6	11.11	5.5
2011	Mendes-Correa MC, et al.[41]	2006 – 2007	Brazil	cross-sectional	HIV-infected patients	ELISA	1 HDV-1	154	86	1	11.16	5.0
2011	Barros LM, et al.[42]	2008 – 2010	Brazil	cross-sectional	hospitalized patients	ELISA	1 HDV-3; 2 HDV-8	133	133	5	33.76	5.0
2011	Alvarado-Mora MV, et al.[43]	2011	Colombia	cross-sectional	native indigenous communities	ELISA	NA	696	35	9	25.71	6.0
2012	Delfino CM, et al.[44]	2012	Argentina	cross-sectional	native indigenous communities	ELISA	3 HDV-1	297	5	0	0.00	7.5
2012	Braga WSM, et al.[45]	2006	Brazil	cross-sectional	rural population	ELISA	NA	787	93	39	41.94	5.5

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TABLE 1: Continuation.

Year	Authors	Data date	Country	Design	Target population w	Anti-HDV diagnostic method	HDV-RNA	Crude sample size (n)	Positive HBsAg (n)	Positive anti-HDV (n)	HDV/HBsAg prevalence (%)	Quality total (score)
2014	Delfino CM, et al.[46]	2003 – 2009	Argentina	cross-sectional	blood donors	ELISA	1 HDV-1	56983	109	1	0.92	6.0
2014	Freitas SZ, et al. [47]	2009 – 2011	Brazil	cross-sectional	HIV-infected patients	ELISA	NA	848	21	0	0.00	6.0
2015	Di Filippo Villa D, et al.[48]	2015	Colombia	cross-sectional	native indigenous communities	ELISA	6 HDV-3	862	23	10	43.48	8.0

ELISA: Enzyme-Linked Immunosorbent Assay; **HBsAg:** Hepatitis B antigen; **anti-HDV:** Hepatitis D virus antibody; **HIV:** Human immunodeficiency virus; **NA:** not available.

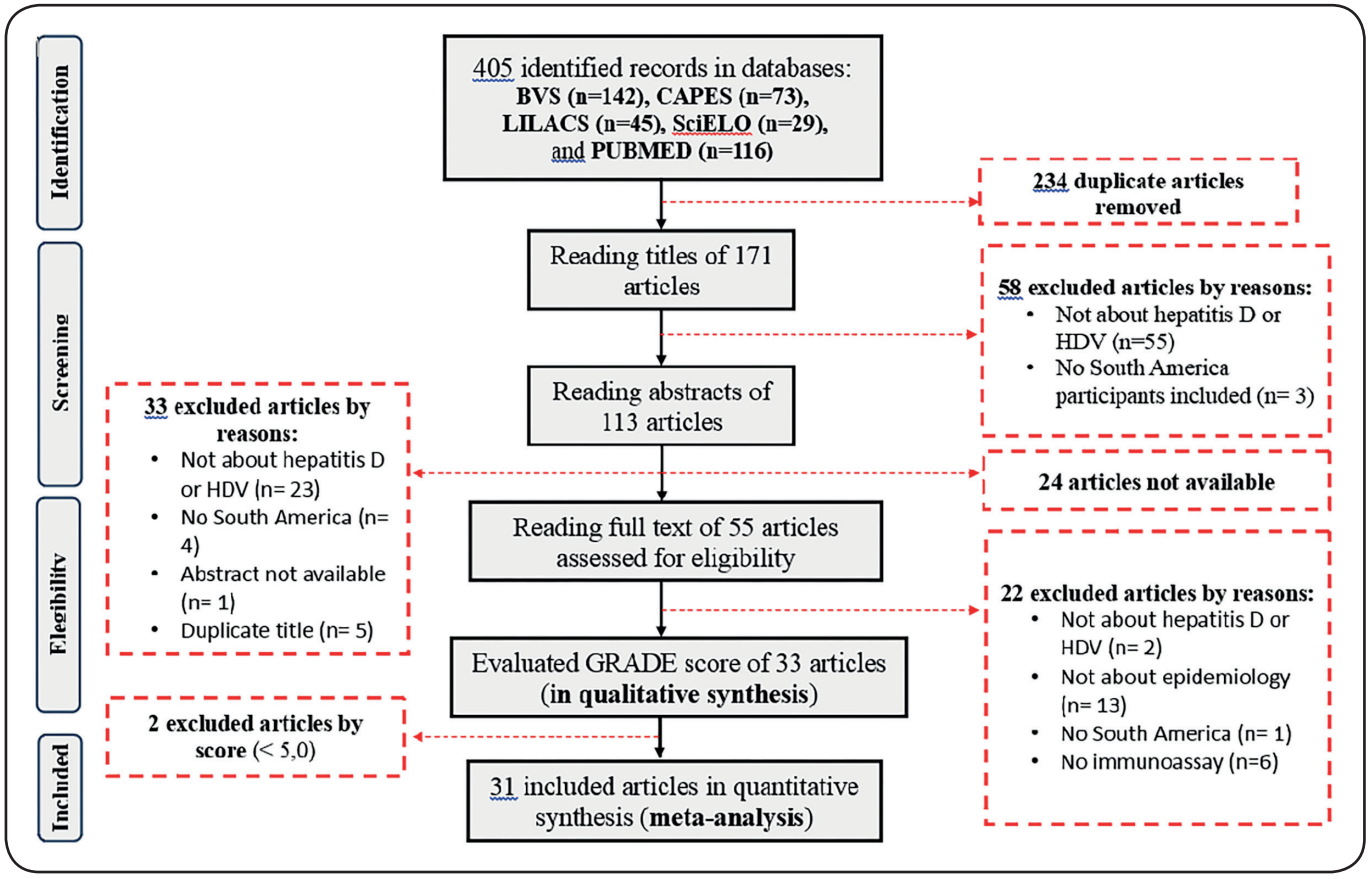

FIGURE 1: Systematic flow for article selection for inclusion in review and meta-analysis on HDV prevalence in South America

Characteristics of included articles

Of the thirty one studies included in the meta-analysis, nine different population groups were described in seven out of the 12 South American countries during a period spanning from 1985 to 2015 (**Figure 2**). Participants were recruited in various epidemiological contexts: through specific or general community surveys, blood bank, during testing of health professionals, in HIV clinics, drug treatment centers and in university hospitals (patients with liver disease). No studies on HDV infection prevalence were found in Chile, Guyana, Suriname, Paraguay, Uruguay, French Guiana, Falkland Island and South Georgia, and the South Sandwich Islands published until 2017.

Overall, the quality of reviewed studies showed a moderate score (median: 6.0, range from 4.5 to 8.5). Most studies (17/31; 54.84%) published data from "convenience samples" such as native indigenous or rural communities, hospitalized or HIV-infected patients and health-care workers. These selected participants had not been representative of regional populations and no country in the study was sampled nationally. A summary of articles included in the systematic review and meta-analysis with quality score is shown in **Table 1**.

Studies included in the meta-analysis suggested a trend towards publication bias by funnel plot, with evidence confirmed by linear regression (Egger's test, $p<0.001$), whereas Begg's

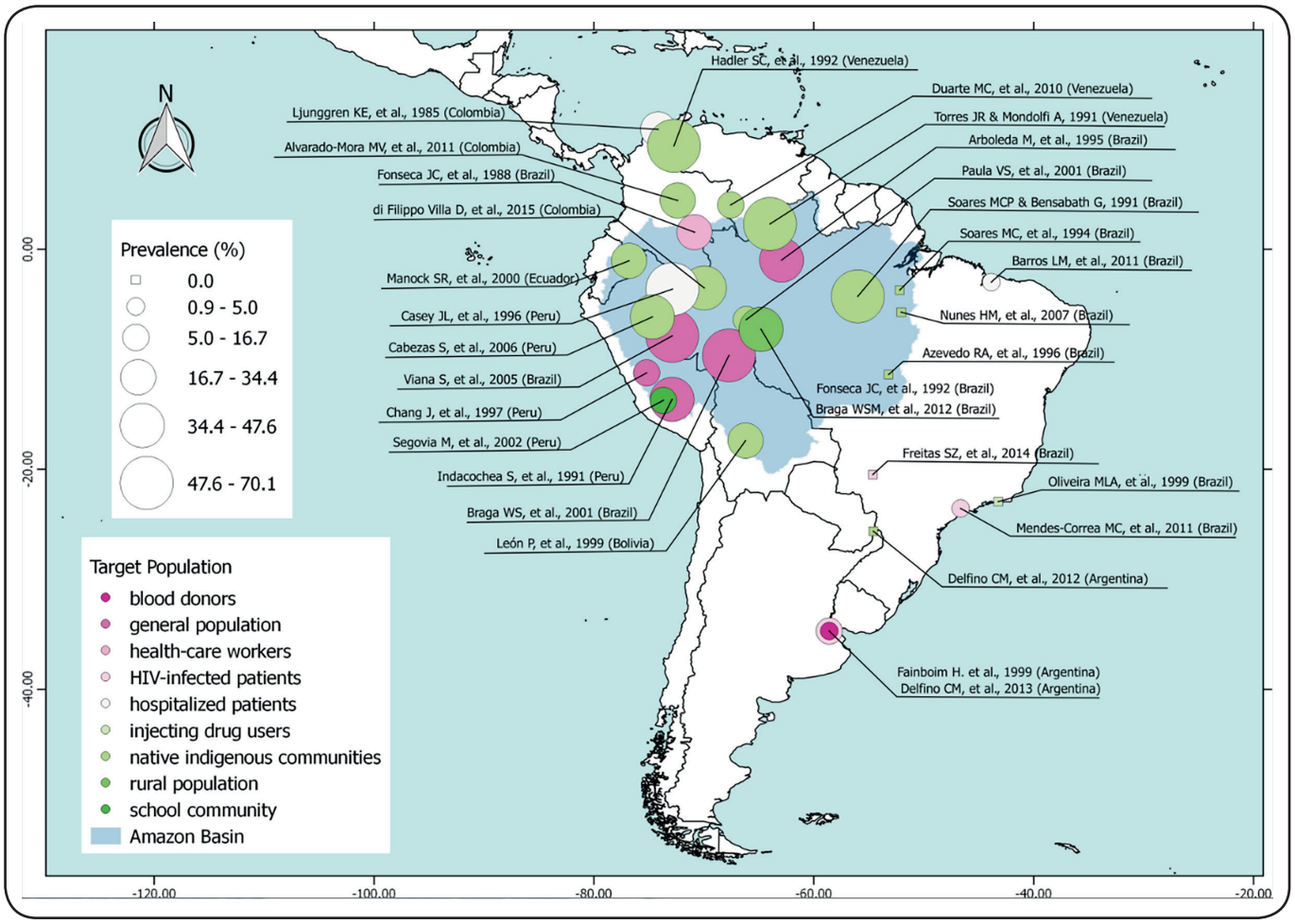

FIGURE 2: Geographic distribution of anti-HDV prevalence in several populations and South America countries, by study and year of publication.

test yielded p=0.024. This was depicted graphically by funnel plot which incorporated the trim and fill method, and showed asymmetry of reported anti-HDV prevalence by various studies. Some studies also indicated presence of high heterogeneity (p<0.001); thus, the random-effect meta-analysis model was therefore adopted.

Overall pooled HDV infection prevalence

Although 71,733 participants were included in this meta-analysis, only 2.56% of them exhibited HBsAg-positive marker (target population of this study). Anti-HDV marker positivity rate ranged from 0.45% to 54.00% for the analyzed studies (**Table 2**). Pooled anti-HDV prevalence at 22.37% (95%CI: 13.72–32.26) among 1,835 HBsAg carriers (in South American) was estimated by the random effects meta-analysis model, in which individual study variances had been stabilized by Freeman-Tukey's double-arc transformation method. There was significantly high heterogeneity among the included studies (I^2=94.79%; Cochran's Q=575.94; p< 0.001).

Source of heterogeneity and subgroup analysis

The influence of multiple factors on studies' heterogeneity was analyzed by meta-regression analysis, suggesting that there was a strong association between HDV infection prevalence with collected data decade (coefficient 0.53, 95%CI: 0.19–1.07, p=0.019), geographic area (coefficient -1.10, 95%CI: -1.84 to -0.22, p=0.008) and study quality (coefficient -0.89; 95%CI: -1.81 to -0.29, p=0.023). Publication bias was found for all group analyses, except for the HDV/HBV infection risk group (p=0.447).

HDV prevalence rate was 3.70% for six articles categorized in the low-quality group, while at the opposite extreme this was 51.53% for three classified as high quality, which constituted a significant variation among studies (p<0.001) (**Figure 3A**). Meanwhile, anti-HDV prevalence in the moderate quality group, which consisted of a significant number of articles (22/31, 70.97%), was estimated to be 25.34% among HBsAg positive patients, close to the group estimated prevalence (22.37%).

The four oldest studies had their data collected in the 1980s[14,16-18] and had the highest HDV infection prevalence in the meta-analysis (**Figure 3B**), contributing to overestimated pooled HDV infection prevalence; however, a cumulative meta-analysis could confirm that the epidemiological profile of this virus has undergone significant changes (p<0.001), with successive reductions since 1990s.

Nearly all analyzed studies reported cross-sectional observational design (27/31; 87.10%), although the presence of other designs had been observed (cohort, case control and case series). Anti-HDV prevalence also varied considerably by HDV screening method, suggesting one probable methodological heterogeneity cause among studies (p<0.001). In addition, many studies had not clearly identified how many cases were positive for anti-HDV in serologic screening, nor did they include HDV infection confirmation by antibody retesting or HDV-RNA detection. Eight studies detected HDV-RNA presence in 60 seropositive participants (10.29% with active infection).

TABLE 2: Summary meta-analysis of studies on HDV prevalence in South American region (1985-2015), using random effects model and Freeman-Tukey transformations.

Category	Subgroups	Reviewed studies (n)	References	Positive anti-HDV cases (n)	Positive HBsAg (n)	Pooled HDV prevalence (%)	95% Confidence Interval	I^2 (%)	P (heterogenity)	95% prediction intervals	p (difference subgroups)
Quality assessment											
	Low	6	[19, 21, 22, 39, 41, 42]	16	317	3.70	0.00% - 13.25%	84.84	<0.001	0.00 - 0.48	
	Moderate	22	[13-18, 20, 29-37, 40, 43-47]	471	1336	25.34	15.99% - 35.86%	92.81	<0.001	0.00 - 0.76	
	High	3	[28, 38, 48]	96	182	51.53	29.45% - 73.31%	NE	NE	NE	<0.001
Study design											
	Case series	1	[14]	4	9	44.44	18.88% - 73.33%	NE	NE	NE	
	Control case	2	[13, 31]	15	107	13.82	7.72% - 21.21%	NE	NE	NE	
	Cohort	1	[16]	109	216	50.46	43.85% - 57.06%	NE	NE	NE	
	Cross-sectional	27	27 [15, 17-22, 28-30, 32-48]	455	1503	21.34	11.93% - 32.37%	94.93	<0.001	0.00 - 0.82	<0.001
Data decade											
	1980	4	[13, 15, 16, 18]	165	374	40.29	25.47% - 56.05%	85.83	<0.001	0.00 - 0.98	
	1990	15	[14, 17, 19-22, 28-34, 38]	297	753	28.01	15.16% - 42.76%	92.56	<0.001	0.00 - 0.86	
	2000	8	[35-37, 39-42, 45-47]	106	526	13.58	2.05% - 31.55%	95.62	<0.001	0.00 - 0.85	
	2010	4	[42, 43, 47, 48]	15	182	6.97	0.00% - 29.70%	87.43	<0.001	0.00 - 1.00	0.043
Country's location											
	Argentina	3	[31, 44, 46]	10	187	2.62	0.00% -15.93%	NE	NE	NE	
	Bolivia	1	[32]	2	9	22.22	6.32% - 54.74%	NE	NE	NE	
	Brazil	15	[14, 15, 17, 20-22, 30, 34, 35, 37, 39, 41, 42, 45, 47]	299	998	17.26	6.10% - 31.89%	95.80	<0.001	0.00 - 0.83	
	Colombia	3	[13, 43, 48]	25	92	27.48	14.73% - 42.27%	NE	NE	NE	
	Ecuador	1	[33]	15	47	31.91	20.40% - 46.17%	NE	NE	NE	
	Peru	5	[19, 28, 29, 36, 38]	100	204	40.56	20.68% - 62.01%	85.74	<0.001	0.00 - 1.00	
	Venezuela	3	[16, 18, 40]	132	298	38.82	12.40% - 69.01%	NE	NE	NE	0.035

Continue....

TABLE 2: Continuation.

Category	Subgroups	Reviewed studies (n)	References	Positive anti-HDV cases (n)	Positive HBsAg (n)	Pooled HDV prevalence (%)	95% Confidence Interval	I^2 (%)	P (heterogenity)	95% prediction intervals	p (difference subgroups)
Specific geografic area											
	Amazon basin	24	[13-22, 28, 29, 32-40, 43, 45, 48]	420	1033	32.12	20.95% - 42.21%	90.84	<0.001	0.00 - 0.89	
	Another area (outside Amazon)	7	[30, 31, 41, 42, 44, 46, 47]	163	802	11.27	1.83% - 25.68%	95.66	<0.001	0.00 - 0.77	0.027
Selected population											
	Blood donors	1	[46]	1	109	0.92	0.16% - 5.01%	NE	NE	NE	
	General population	5	[19, 20, 29, 34, 37]	75	147	49.99	38.83% - 61.14%	24.56	0.26	0.24 - 0.76	
	HIV-infected patients	3	[31, 41, 47]	10	180	3.30	0.00% - 13.35%	NE	NE	NE	
	Health-care workers	1	[15]	33	96	34.38	25.64% - 44.31%	NE	NE	NE	
	Hospitalized patients	4	[13, 14, 28, 42]	69	253	30.18	0.72 - 74.43%	97.57	<0.001	0.00 - 1.00	
	Injecting drug users	1	[30]	0	8	0.00	0.00% - 32.44%	NE	NE	NE	
	Native indigenous communities	14	[16-18, 21, 22, 32, 33, 35, 38-40, 43, 44, 48]	353	931	22.20	11.38% - 35.08%	93.14	<0.001	0.00 - 0.76	
	Rural population	1	[45]	39	93	41.94	32.42% - 52.09%	NE	NE	NE	
	School community	1	[36]	3	18	16.67	5.84% - 39.22%	NE	NE	NE	<0.001
HDV/HBV infection											
	Low risk*	7	[20, 29, 34, 36, 37, 45, 46]	79	274	31.22	6.98% - 61.96%	95.10	<0.001	0.00 - 1.00	
	High risk†	24	[13-18, 21, 22, 28, 30-35, 38-44, 47, 48]	504	1561	20.18	11.21% - 30.76%	94.88	<0.001	0.00 - 0.77	0.447
Anti-HDV diagnostic method											
	ELISA	18	[19, 20, 29, 33-39, 41-43, 45-48]	199	876	20.36	9.82% - 33.13%	95.23	<0.001	0.00 - 0.90	
	Enzyme immunoassays	10	[14-16, 21, 22, 28, 30-32, 40]	217	609	20.14	5.96% - 39.03%	93.55	<0.001	0.00 - 0.80	
	Radioimmunoassay	2	[13, 18]	23	62	35.83	24.14% - 48.39%	NE	NE	NE	
	NA	1	[17]	144	288	50.00	44.26% - 55.74%	NE	NE	NE	<0.001
Overall random pooled	**All studies**	**31**	**[13-22, 28-48]**	**583**	**1835**	**22.37**	**13.72% - 32.26%**	**94.79**	**<0.001**	**0.00 - 0.80**	**<0.001**

NE: not estimable because of insufficient observations number. *** Low risk:** general population, blood donors, rural population and school communities. **† High risk:** health-care workers, HIV-infected patients, injecting drug users, hospitalized patients and native indigenous communities.

Anti-HDV marker seroprevalence varied significantly between South American countries (p=0.035) as shown in **Figure 4A**. A single study conducted in native indigenous communities of Ecuador also estimated a high HDV infection prevalence (31.91%) in 2000[27]. Most of the studies (15/31, 48.39%) were conducted in Brazil, covering the largest number of participants (998), although HDV prevalence was estimated at 17.26% (95%CI: 6.10–31.89). The findings showed about three times higher HDV infection prevalence for a specific geographic area (31.12% in the Amazon Basin) compared to 11.27% in other studied areas (**Figure 4B**).

The target populations (HBsAg positive) were significantly associated with HDV seroprevalence (p<0.001). Five articles revealed high anti-HDV rate (49.99%) in the general population; in contrast, a very low rate (0.92%) was observed in another study conducted among blood donors. The pooled HDV prevalence was 22.20% among native indigenous communities from 14 studies in five countries. Among three studies in which patient HIV status was reported, the HDV seroprevalence was 3.30%. Surprisingly, no HDV infection case was reported in one study with injecting drug users from Rio de Janeiro, Brazil[28], whereas in another study conducted in a school community in Peru, the anti-HDV prevalence was 16.67%[29].

DISCUSSION

This is the first systematic review to perform a meta-analysis on HDV infection prevalence in several populations, whose focus was on South America. Only a large regional epidemiological study could estimate with precision overall HDV infection prevalence in South America. This review is important for the better understanding of current HDV-infection geographical distribution between South American countries, notably, in highly endemic areas and with acute and chronic cases recorded over a 30-year period[1, 2, 49, 50].

The study area was based on evidence that HDV is widespread throughout the world, with its prevalence rate varying widely in different geographic regions, which does not exactly match the HBV infection rate[1,2]. This is confirmed with cross-sectional studies conducted since 1980, evidencing a large difference in HDV prevalence in America under several epidemiological contexts[9,13,15,45,51]. However, this review sought to estimate an overall prevalence encompassing all South American countries, which has demonstrated high rates of HDV infection within this subcontinent, according to other previous studies[10,17-19,28,34].

This review found a heterogeneous anti-HDV positive geographical distribution in South America, with low and high antibody prevalence differing between areas even within the same country[13,18,28,29,34,35,40,48]. One reason for these variations may be limited sample size in some studies, without previous sample calculation. Another explanation would be different criteria established for participant inclusion[1].

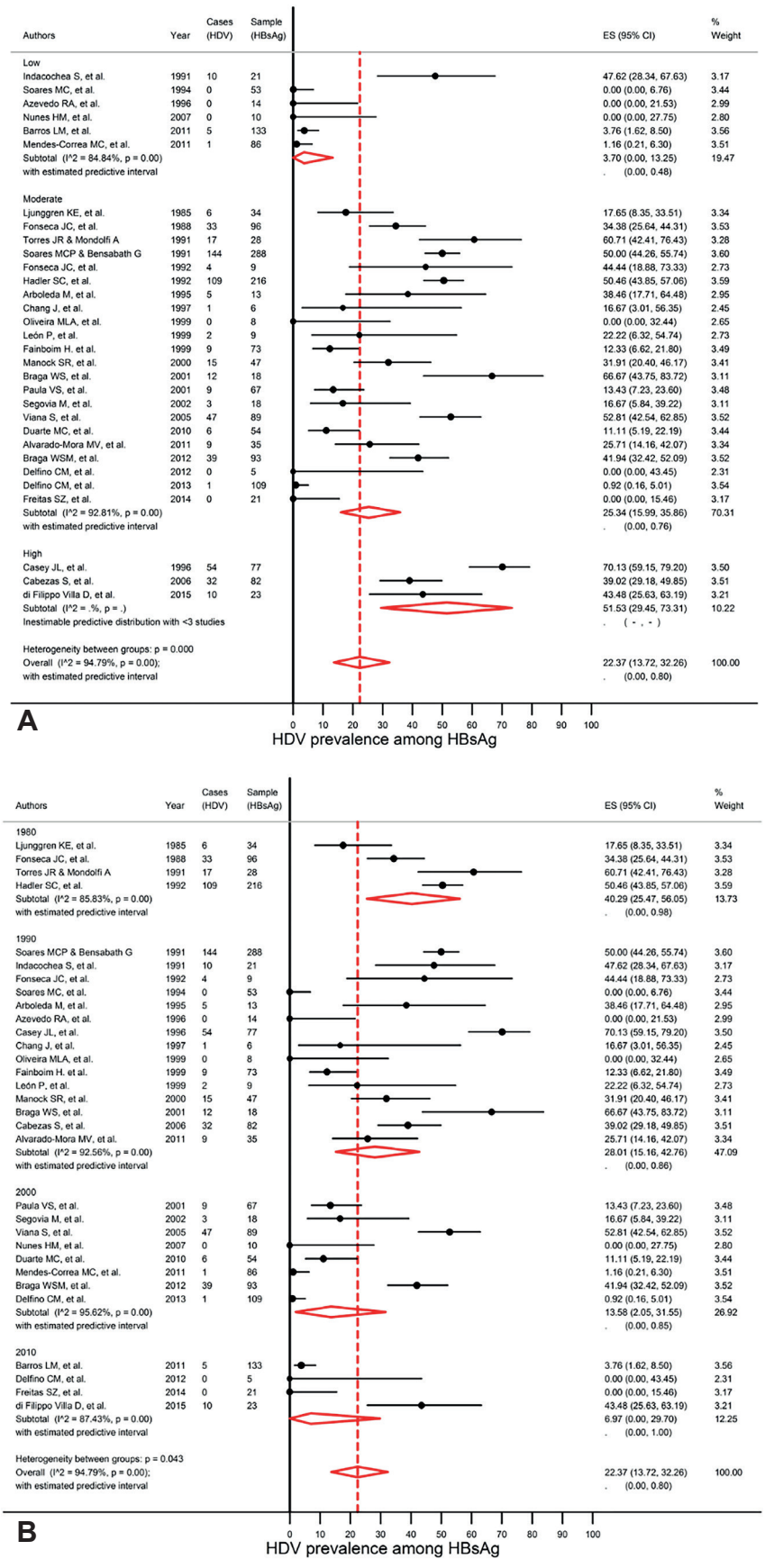

FIGURE 3: Forest plot of prevalence of HDV infection among HBsAg-positive carriers in South America region (1985-2015) by different subgroups: (A) quality assessment score and (B) decade of data for each study

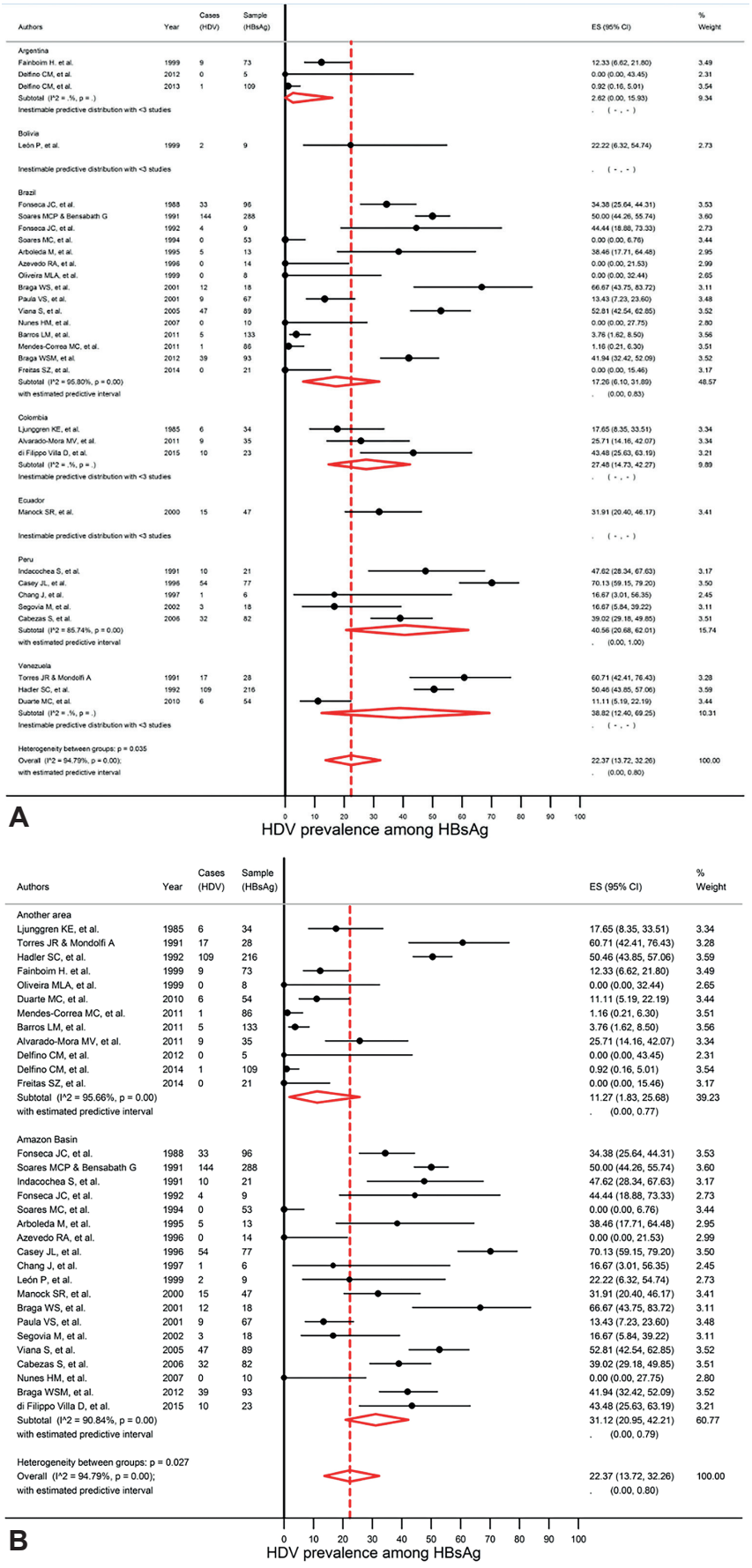

FIGURE 4: Forest plot of HDV infection prevalence among HBsAg-positive carriers (1985-2015) by different subgroups: (A) study country and (B) geographic area in South America region

These review findings indicate that most of the studies were directed to a specific area of South America, the Amazon Basin[10]. Recent studies suggest that high HDV infection cases in the Amazon Basin occurred due to geographic isolation, disseminating through restricted interaction to individuals and tribes[52]. Argentina was the only country identified by this review that does not belong to the Amazon Basin[31,44,46]. This systematic review shows that there were more than twice as many Brazilian articles compared to other countries[2,4,7-10,13,17,18,20,22,24,25,28,30]. On the other hand, all eligible articles pointed to local studies, so they were not representative of any of these countries' populations.

The pooled HDV prevalence estimate was 22.37% (95%CI: 13.72–32.26) in South America by meta-analysis[13-22,28-48]. This geographical region is traditionally recognized as endemic for hepatitis delta and a higher frequency for this virus was previously expected[2]. Extreme caution should be exercised regarding the interpretation of the estimated prevalence for South America, due to selection biases observed during study review. These biases have been caused by the absence of information from several countries located far from the Amazon basin, as well as the use of data collected by studies conducted in the 1980s[1,2,5,6] and 1990s[3,4,7-17,21], which led to an overestimation of HDV infection cases in the studied area.

Pooled HDV infection prevalence found in South America have similar rates described in recent meta-analyses for other regions with high endemicity, as well as the Eastern Mediterranean Region (15% and 28% among asymptomatic HBsAg positive carriers and chronic hepatitis patients, respectively)[5] and in sub-Saharan Africa (7% in western Africa and 26% in central Africa)[12], but it exceeds Southeast Asia (8% in Iran)[4]. In South America, the estimated prevalence is closest to the mean of HDV prevalence reported in Turkey (27%)[6] and Mauritania (up to 30%) in West Africa[53].

The present study confirms a high pooled HDV infection prevalence in South America over more than three decades. HDV prevalence has demonstrated successive reductions over time, as seen in different areas of the world, currently close to the expected global rate at 5 to 10% among HBsAg carriers[3,8,10,49,54]. Stratified study analysis revealed a trend of successive reductions in pooled HDV prevalence over time in South America, from hyperendemic regions in the

80's and 90's (40.29% and 28.01%, respectively), to moderate endemic level in 2000 (13.58%), reaching values (6.97%) close to worldwide rates in 2010[1]. This change in HDV infection epidemiological profile was probably due to the vaccination policy against HBV initiated cross campaign form for Amazonas Brazilian state in 1989 and obligatory screening of blood and blood products for serum HBV markers[2]. The observed decline in prevalence rates is consistent with a recent review in which HDV infection prevalence decreased from 24% (1990) to 8.5% in Italy (2006).

Most of the studies included in this meta-analysis presented moderate methodological quality in relation to established criteria quality[1,2,4-7,9,12-20,23,26-30]. The information provided in this review revealed that almost all studies had cross-sectional designs[2-5,8-13,15-31] as they fit prevalence studies; therefore, they did not provide information on relative time of exposure and outcome. A strength of this review is that participant selection focused on HBV-infected individuals, notably positive HBsAg carriers because they were the target population who were more adequate and susceptible to HDV infection. This was chosen in consistency with previous studies showing that HDV requires obligatory HBV presence for its propagation to hepatocytes[1,2].

It is possible that the HDV prevalence reported in this evaluation may be overestimated, since the studies included in the meta-analysis were conducted with more vulnerable populations such as HIV-infected patients, hospitalized patients, health-care workers, injecting drug users and indigenous communities[1,2,4-8,10,11,13-18,21-27,30,31]. Discrepancies reported in the global epidemiology for HDV infection prevalence may be related to erroneous participant selection, generally not representative of general population or involving blood donors[1], reinforcing once again that this estimated HDV infection prevalence in meta-analysis is restricted to the populations studied.

This review had still others limitations. The estimate of pooled HDV infection prevalence in South America did not include unpublished data or official data sources. Additionally, there were no data available from seven countries (mainly outside Amazon Basin), and there was an absence of population-based studies. These reasons may directly interfere in pooled HDV infection prevalence calculations. The lack of standardized criteria for participant selection or even failure to report the gross number of HBV infected individuals in studies may induce inaccurate estimates or study exclusion. This fact constitutes further limitation to the inference drawn. In contrast, the search for articles reported in both English as in other native languages of the region (Portuguese and Spanish), increased the number of selected articles. Furthermore, the pooled HDV infection prevalence estimated for South America was accurate due to strong and reliable methodology (sample size of 1,835 HBV-infected included in random effects model) and statistical procedures used.

CONCLUSION

This systematic review provides evidence that hepatitis delta remains neglected in some South American areas, notably outside the Amazon Basin. The pooled anti-HDV prevalence was 22.37% covering several populations of seven South American countries through meta-analysis. In addition, the findings highlight a drastic decline in HDV prevalence over the last decades. In future studies, we plan to identify risk factors and evaluate HDV infection control measures.

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Conflict of Interest: The authors declare that there is no conflict of interest.

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Erratum

Revista da Sociedade Brasileira de Medicina Tropical/Journal of the Brazilian Society of Tropical Medicine
Title: Hepatitis Delta Prevalence in South America: A Systematic Review and Meta-Analysis
Vol.:52:e20180289: 2019 - doi: 10.1590/0037-8682-0289-2018 - **Table 1**

2011 Mendes-Correa MC, et al. Prevalence HDV/HBsAg = 11.16
Should read:
2011 Mendes-Correa MC, et al. Prevalence HDV/HBsAg = 1.16

2011 Barros LM, et al. - Prevalence HDV/HBsAg = 33.76
Should read:
2011 Barros LM, et al. - Prevalence HDV/HBsAg = 3.76