

## Scientific evidence on hepatitis Delta in Brazil: integrative literature review

Evidências científicas sobre a hepatite Delta no Brasil: revisão integrativa da literatura

Marcelo Siqueira de Oliveira<sup>1</sup>  
Suiane da Costa Negreiros do Valle<sup>1</sup>  
Rodrigo Medeiros de Souza<sup>1</sup>  
Romeu Paulo Martins Silva<sup>2</sup>  
Elisabeth Níglio de Figueiredo<sup>3</sup>  
Mônica Taminato<sup>3</sup>  
Dayana Fram<sup>3</sup>

### Keywords

Hepatitis D; Hepatitis B; Brazil

### Descritores

Hepatite D; Hepatite B; Brasil

### Submitted

November 8, 2017

### Accepted

December 4, 2017

### Corresponding author

Marcelo Siqueira de Oliveira  
Gleba Formoso, Lote 245, 69980-000,  
Cruzeiro do Sul, AC, Brazil.  
marcelo.oliveira@ufac.br

### DOI

<http://dx.doi.org/10.1590/1982-0194201700091>

### Abstract

**Objective:** Describe the level of scientific evidence on infections by the hepatitis Delta virus (HDV) in Brazil.

**Methods:** Integrative literature review, with research in the databases of the Medical Literature Analysis and Retrieval System Online, Latin American and Caribbean Center on Health Sciences Information, Scientific Electronic Library Online and Scopus, with analysis focusing on the leveling of the methodological rigor according to the model of Melnyk and Fineout-Overholt.

**Results:** The search revealed an average of two publications a year between 1987 and 2017. We selected 33 articles, the majority (91%) presented level of evidence VI. The publications were concentrated in the area of tropical medicine (46%) and virology (15%). The authors of 85% of the studies were medical professionals and the most common design was the descriptive/cross-sectional (69.6%).

**Conclusion:** Scientific literature on HDV infections in Brazil is focused on prevalence studies, showing incipency regarding the production of studies with stricter guidelines, such as clinical trials.

### Resumo

**Objetivo:** Descrever o nível de evidência científica sobre a infecção por vírus da hepatite Delta (VHD) no Brasil.

**Métodos:** Revisão integrativa da literatura, com buscas realizadas nas bases de dados do *Medical Literature Analysis and Retrieval System Online*, *Literatura Latino-americana e do Caribe em Ciências da Saúde*, *Scientific Electronic Library Online* e *Scopus*, com análise centrada no nivelamento do rigor metodológico de acordo com o modelo de Melnyk e Fineout-Overholt.

**Resultados:** A busca revelou uma média de duas publicações por ano no intervalo entre 1987 e 2017. Foram selecionados 33 artigos, tendo a maioria (91%) apresentado nível de evidência VI. As publicações ficaram concentradas em periódicos da área de medicina tropical (46%) e virologia (15%). Dos trabalhos, 85% tinha profissional médico com autor e o delineamento mais encontrado foi o descritivo/transversal (69,6%).

**Conclusão:** A produção científica sobre a infecção por VHD no Brasil está centrada em estudos de prevalência, mostrando-se incipiente quanto à produção de estudos com delineamentos mais rígidos como ensaios clínicos.

<sup>1</sup>Multidisciplinary Center, Universidade Federal do Acre, Cruzeiro do Sul, AC, Brazil.

<sup>2</sup>Center of Health and Sports Sciences, Universidade Federal do Acre, Rio Branco, AC, Brazil.

<sup>3</sup>Escola Paulista de Enfermagem, Universidade Federal de São Paulo, São Paulo, SP, Brazil.

**Conflict of interest:** Fram DM is associate editor of the Acta Paulista of Nursing and did not participate in the evaluation process of the manuscript.



## Introduction

By analyzing the serum of patients infected with the hepatitis B virus (HBV), the Italian researcher Mario Rizzetto described a new antigen-antibody system in the 1970's, the system was named antigen/antibody Delta.<sup>(1)</sup> Subsequent studies revealed that the discovery was not of another component of HBV, but of a new virus: the hepatitis Delta virus (HDV).<sup>(2)</sup>

The HDV needs the HBV to infect humans, because it uses the surface antigen (HBsAg) on the process of pathogenesis.<sup>(2)</sup> The viral structure is composed by a single-stranded ribonucleic acid (RNA)<sup>(3)</sup>, measuring between 35nm and 37nm, it produces two antigens of known clinical importance: the small Delta antigen (HDAg-S), which acts in the process of viral replication, and the large Delta antigen (HDAg-L) which, through the interaction with HBsAg, acts on the assembly of RNA.<sup>(4)</sup>

HDV infection occurs by parenteral exposure and is considered a co-infection when it occurs on the primary or acute phase of HBV infection and as a superinfection when it occurs in chronic hepatitis B.<sup>(2)</sup>

The interaction between the HDV and HBV is not fully understood yet, especially due to the fact that both viruses compete for HBsAg to assemble new viral structures.<sup>(5)</sup> Furthermore, studies indicate that the HDV is related to the early development of serious conditions of hepatic diseases, such as: Cirrhosis, hepatocellular carcinoma (HCC) and fulminant hepatitis.<sup>(6,7)</sup>

The hepatitis cases caused by HDV associated with HBV represent a serious worldwide public health problem, generating continuous demands to health services, in addition to considerable losses in the quality of life of infected patients, also showing high mortality rates.<sup>(8)</sup>

This kind of infection is distributed around the globe; HBV, the required element for HDV infection, is estimated to have already infected 2 billion individuals worldwide, of which 300 to 400 million are chronic carriers and 15 to 20 million are infected with the HDV<sup>(2,9)</sup>, with an annual number of deaths estimated between 620,000 and 1 million.<sup>(10)</sup>

The HDV has worldwide distribution with variable prevalence. Two countries of Central Europe, Romania and Hungary, present, respectively, 47.6% and 13.9% of patients with positive HBsAg infected with HDV. West and central Africa, present infection ranging from 1.3% in Nigeria to 66% in Gabon. 20% of patients with positive HBsAg in Egypt are infected. In Asia, the prevalence reaches 66.7% in Taiwan and 82% in Mongolia.<sup>(4)</sup> The distribution in South America is variable, but high indicators are found across the entire Amazon basin, especially in the Western Brazilian Amazon, where the seropositivity to HDV can reach up to 85% of patients with positive HBsAg in some communities.<sup>(4,8,11)</sup>

Dating back to the mid-18th century, historical accounts record deaths of members of the French Royal Academy of Science by a disease described acute icteric fever, during an expedition through the Amazon River, in Brazil.<sup>(12)</sup> During the second half of the 20th century, studies describe a serious icteric condition, of rapid evolution and with death records of five days after the initial symptoms in the city of Lábrea, in the interior of the state of Amazonas. The condition was initially named as Labrea black fever,<sup>(13)</sup> but the cases were investigated and in 1987 it was confirmed that the Labrea black fever was, in fact, fulminant hepatitis caused by infection of the HDV in patients with HBV.<sup>(14)</sup>

Nowadays, despite the infection being recorded throughout the Brazilian territory and 77% of the cases occurring in the northern region, researchers claim that despite the high endemic indicators of HDV infection, the condition is neglected by health services.<sup>(15)</sup>

Given the Brazilian context, resources available from the Brazilian Unified Health System and recognizing HDV infection as a major public health problem, the objective of this study was to, through an integrative review: describe the level of scientific evidence on HDV infection in Brazil to provide awareness on the theme to health professionals and public administrators, as well as serving as a parameter of good research and assistance practices for the development of health policies.

## Methods

Integrative literature review with the theme “level of scientific evidence on HDV infection in Brazil” between the years of 1987 and 2017. The search was performed in September 2017 and went through six methodological steps, according to criteria outlined in national and international scientific literature (Figure 1).<sup>(16-19)</sup>

The first stage was to elaborate the guiding question: “what is the level of scientific evidence on HDV infection in Brazil?”. Then, we set the keywords according to the Health Sciences Descriptors (DeCS) and the Medical Subject Headings (MeSH), they are: Hepatitis D; Hepatitis B and Brazil.

On the second stage we defined the databases for searching and the eligibility criteria. For this, were considered eligible the scientific articles found through the descriptors defined on the first step, published in English, Portuguese and Spanish, the search was restricted to the Brazilian territory, the approach focused on hepatitis D or HDV and abstract available in the following databases: Medical

Literature Analysis and Retrieval System Online (Medline), Latin American and Caribbean Center on Health Sciences Information (LILACS), Scientific Electronic Library Online (SciELO) and Scopus (Elsevier).

For the third stage we considered the formulation of a framework proposed by Souza, Silva and Carvalho<sup>(19)</sup> to organize the database and present the results (Chart 1), in addition to the classification of evidence models based on the model of Melnyk and Fineout-Overholt.<sup>(20)</sup>

Evidence from systematic review or meta-analysis of all relevant randomized clinical trials controlled or from clinical guidelines based on systematic reviews of randomized controlled clinical trials:

I-Evidence from at least one controlled and well-designed randomized clinical trial;

II-Evidence from clinical trials well designed without randomization;

III- Evidence from well-designed cohort and case-control studies;

IV- Evidence from systematic review of descriptive and qualitative studies;

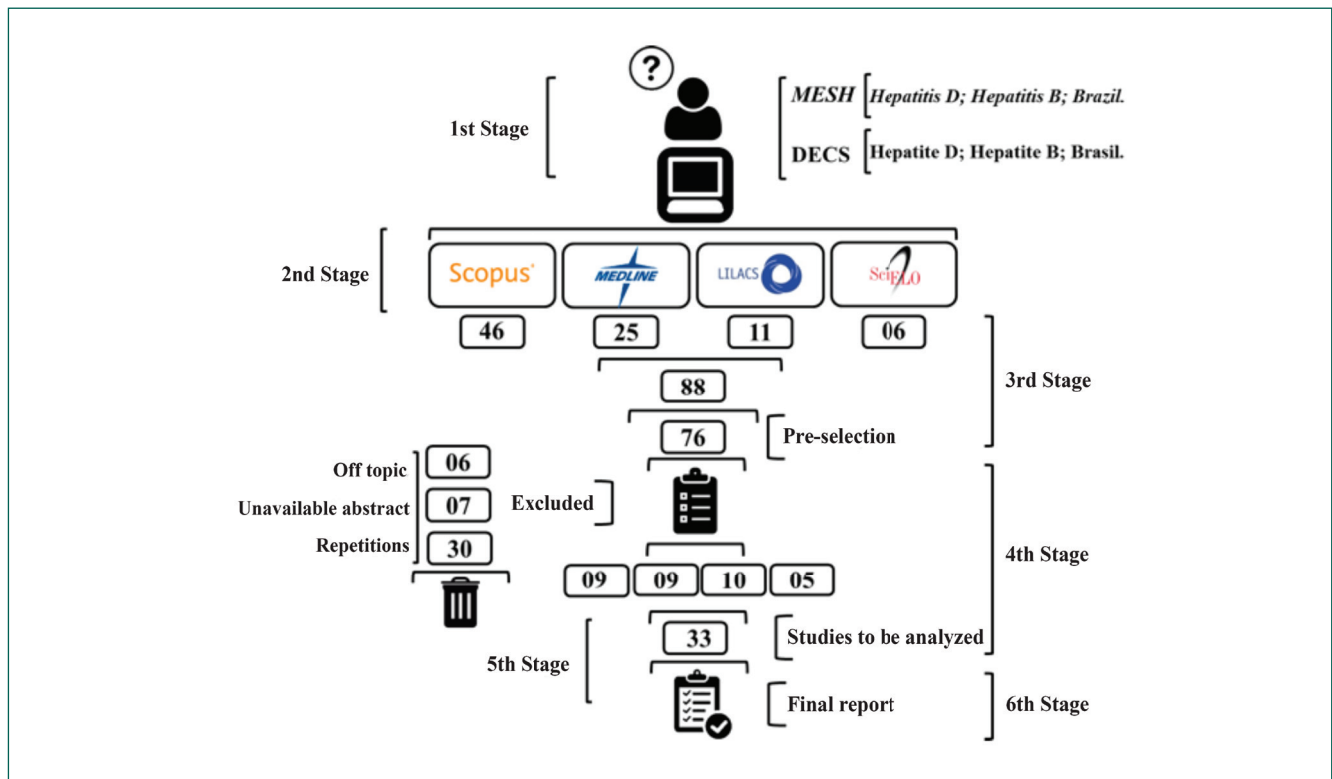


Figure 1. Methodological stages of the research

**Chart 1.** Characterization of publications on hepatitis D in Brazil, according to reference, thematic considerations, type of study and level of evidence

Reference	Thematic considerations	Type of study	Evidence level
Souto FJD. A hepatite B e os movimentos migratórios no Estado de Mato Grosso, Brasil. Rev Soc Bras Med Trop. 2004; 37(Suppl 2):63-8.	Literature review on the relation between migratory cycles and the prevalence of hepatitis B and Delta on the north of the state of Mato Grosso - Brazil. <sup>(21)</sup>	Literature review	VI
Braga WSM. Infecção pelos vírus das hepatites B e D entre grupos indígenas da Amazônia Brasileira: aspectos epidemiológicos. Rev Soc Bras Med Trop. 2004; 37(Suppl 2):9-13.	Discusses epidemiological aspects of HBV and HDV infection among indigenous groups in Amazon. <sup>(22)</sup>	Literature review	VI
Braga WSM, Castilho M da C, Borges FG, Leão JRDT, Martinho AC de S, Rodrigues IS, et al. Hepatitis D virus infection in the Western Brazilian Amazon - far from a vanishing disease. Rev Soc Bras Med Trop. 2012; 45(6):691-5.	Investigates the prevalence of HDV infection through the total antibody (Anti-HD). <sup>(23)</sup>	Cross-sectional study (descriptive)	VI
Paraná R, Vitvitski L, Pereira JE. Hepatotropic viruses in the Brazilian Amazon: a health threat. Braz J Infect Dis. 2008; 12(3):253-6.	Reviews clinical and epidemiological studies on HBV and HDV infection and their respective genotypes F and III, addressing the existing relation between these and the severity of hepatic disease in the Amazon region. <sup>(24)</sup>	Study of Literature Review	VI
Braga WSM, Brasil LM, Souza RAB, Castilho MC, Fonseca JC. Ocorrência da infecção pelo vírus da hepatite B (VHB) e delta (VHD) em sete grupos indígenas do Estado do Amazonas. Rev Soc Bras Med Trop. 2001; 34(4):349-55.	Observes the distribution of cases of hepatitis B and D among indigenous ethnic groups in the Western Brazilian Amazon. <sup>(25)</sup>	Cross-sectional study (descriptive)	VI
Braga WSM, Castilho MC, Santos ICV, Moura MAS, Segurado AC. Low prevalence of hepatitis B virus, hepatitis D virus and hepatitis C virus among patients with human immunodeficiency virus or acquired immunodeficiency syndrome in the Brazilian Amazon basin. Rev Soc Bras Med Trop. 2006; 39(6):519-22.	Assesses the prevalence of co-infection among human immunodeficiency virus and viral hepatitis B, C and D in the Western Brazilian Amazon. <sup>(26)</sup>	Cross-sectional study (descriptive)	VI
Oliveira MLA, Bastos FI, Telles PR, Yoshida CFT, Schatzmayr HG, Paetzold U, et al. Prevalence and risk factors for HBV, HCV and HDV infections among injecting drug users from Rio de Janeiro, Brazil. Braz J Med Biol Res. 1999; 32(9):1107-14.	Assesses the prevalence and the determinants of risk for infections with hepatitis B, C and D among injection drug users in Rio de Janeiro, Brazil. <sup>(27)</sup>	Cross-sectional study (descriptive)	VI
Azevedo RA, Silva AE, Ferraz MLG, Marcopito LF, Baruzzi RG. Prevalência dos marcadores sorológicos dos vírus da hepatite B e D em crianças das tribos Caiabi e Tucaramãe do parque indígena do Xingu, Brasil central. Rev Soc Bras Med Trop. 1996; 29(5):431-9.	Studies the prevalence of serological markers of hepatitis B and delta in indigenous children from 0 to 14 years living in the Xingu Indigenous Park. <sup>(28)</sup>	Cross-sectional study (descriptive)	VI
Andrade ZA, Lesbordes JL, Ravisse P, Paraná R, Prata A, Barberino JS, et al. Fulminant hepatitis with microvesicular steatosis (a histologic comparison of cases occurring in Brazil - Labrea hepatitis - and in central Africa - Bangui hepatitis). Rev Soc Bras Med Trop. 1992; 25(3):155-60.	Compares cases of fulminant hepatitis in the Western Brazilian Amazon and in Central Africa by associating the HBV and HDV infections. <sup>(29)</sup>	Cross-sectional study (descriptive)	VI
Fonseca JC, Ferreira LCL, Brasil LM, Castilho MC, Moss R, Barone M. Fulminant Labrea hepatitis - The role of hepatitis A (HAV), B (HBV), C (HCV), AND D (HDV) infection. (Preliminary report). Fulminant Labrea Hepat - Role Hepat HAV B HBV C HCV HDV Infect Prelim Rep. 1992; 34(6):609-12.	Describes the participation of HDV infection on the etiopathogenesis of Labrea hepatitis, Western Brazilian Amazon. <sup>(30)</sup>	Cross-sectional study (descriptive)	VI
Botelho-Souza LF, Souza Vieira D, de Oliveira dos Santos A, Cunha Pereira AV, Villalobos-Salcedo JM. Characterization of the Genotypic Profile of Hepatitis Delta Virus: Isolation of HDV Genotype-1 in the Western Amazon Region of Brazil. Intervirology. 2015; 58(3):166-71.	Assesses the genotypic and clinical characteristics of individuals with the genotype 1 HDV in the Western Brazilian Amazon. <sup>(31)</sup>	Case-control study	IV
Kay A, Melo da Silva E, Pedreira H, Negreiros S, Lobato C, Braga W, et al. HBV/HDV co-infection in the Western Brazilian Amazonia: an intriguing mutation among HDV genotype 3 carriers. J Viral Hepat. 2014; 21(12):921-4.	Studies the genotypic characterization of patients infected with HBV and HDV in the Western Brazilian Amazon. <sup>(32)</sup>	Cross-sectional study (descriptive)	VI
Crispim MAE, Fraiji NA, Campello SC, Schriefer NA, Stefani MMA, Kiesslich D. Molecular epidemiology of hepatitis B and hepatitis delta viruses circulating in the Western Amazon region, North Brazil. BMC Infect Dis. 2014; 14:94.	Describes the genotypes of HBV and HDV in the Western Brazilian Amazon. <sup>(6)</sup>	Cross-sectional study (descriptive)	VI
Mendes-Correa MC, Gomes-Gouveia MS, Alvarado-Mora MV, Da Silva MH, Lázari C, Cavalcanti NCS, et al. Hepatitis delta in HIV/HBV co-infected patients in Brazil: is it important? Int J Infect Dis. 2011; 15(12):e828-32.	Assesses the prevalence of HDV among patients co-infected with human immunodeficiency virus (HIV) and HBV in São Paulo, southeastern Brazil. <sup>(33)</sup>	Cross-sectional study (descriptive)	VI
Gomes-Gouveia MS, Soares MCP, Bensabath G, de Carvalho-Mello IMVG, Brito EMF, Souza OSC, et al. Hepatitis B virus and hepatitis delta virus genotypes in outbreaks of fulminant hepatitis (Labrea black fever) in the western Brazilian Amazon region. J Gen Virol. 2009; 90(11):2638-43.	Describes the genotypes of HBV and HDV that circulate among the cases of fulminant hepatitis in the Brazilian Amazon Basin. <sup>(34)</sup>	Cross-sectional study (descriptive)	VI
Nunes HM, Monteiro MRCC, Soares MCP. Prevalência dos marcadores sorológicos dos vírus das hepatites B e D na área indígena Apyterewa, do grupo Parakanã, Pará, Brasil. Cad Saúde Pública. 2007; 23(11):2756-66.	Studies the prevalence of HBV and HDV among the indigenous ethnicity Parakanã and assesses the impact of vaccination against hepatitis B starting in 1995 in the Apyterewa village in the state of Pará, Brazil. <sup>(35)</sup>	Cross-sectional study (descriptive)	VI
Viana S, Paraná R, Moreira RC, Comprí AP, Macedo V. High prevalence of hepatitis b virus and hepatitis d virus in the western brazilian amazon. Am J Trop Med Hyg. 2005; 73(4):808-14.	Studies the prevalence of markers for hepatitis caused by HBV and HDV in the Western Brazilian Amazon. <sup>(36)</sup>	Cross-sectional study (descriptive)	VI
Arboleda M, Castilho MC, Fonseca JF, Albuquerque BC, Saboia RC, Yoshida CFT. Epidemiological aspects of hepatitis B and D virus infection in the northern region of Amazonas, Brazil. Trans R Soc Trop Med Hyg. 1995; 89(5):481-3.	Identifies epidemiological patterns and risk factors for HBV and HDV infections in Barcelos, at the Rio Negro basin, Amazon region. <sup>(37)</sup>	Cross-sectional study (descriptive)	VI
Soares MC, Menezes RC, Martins SJ, Bensabath G. Epidemiologia dos vírus das hepatites B, C e D na tribo indígena parakanã, Amazônia Oriental Brasileira. Bol Oficina Sanit Panam. 1994; 124-35.	Studies the prevalence of infection with the hepatitis B, C and D viruses and describes its transmission among the indigenous ethnicity Parakanã in the state of Pará, Brazil. <sup>(38)</sup>	Cross-sectional study (descriptive)	VI
Dantas LC, Genzini T, Miranda MP, Santos RG, Siqueira NG, Weirich J, et al. Liver transplantation in a patient with hepatitis B, C and D coinfection associated with hepatocellular carcinoma: a management strategy for a rare condition. Case report. Sao Paulo Med J. 2015; 133(6):525-30.	Presents a case report of a patient with hepatitis B, C and D subjected to antiviral treatment and liver transplantation. <sup>(39)</sup>	Case report	VI
Fonseca JC. Hepatite D. Rev Soc Bras Med Trop. 2002; 35(2):181-90.	Presents a literature review on viral hepatitis of type D, showing aspects of the epidemiology, pathogenesis, diagnosis and treatment. <sup>(40)</sup>	Literature review	VI
Ribeiro LC, Souto FJD. Hepatite Delta no Estado de Mato Grosso: apresentação de cinco casos. Rev Soc Bras Med Trop. 2000; 33(6):599-602.	Presents a report of five cases of severe hepatitis Delta in the state of Mato Grosso, Brazil. <sup>(41)</sup>	Case report	VI
Oliveira MS, Silva RPM, Valle SCN, Figueiredo EN, Fram D. Chronic hepatitis B and D: prognosis according to Child-Pugh score. Rev Bras Enferm. 2017; 70(5):1048-53.	Compares patients with chronic hepatitis B to patients superinfected by the D virus according to the Child-Pugh score. <sup>(8)</sup>	Cross-sectional study (descriptive)	VI

continua

continuação

Reference	Thematic considerations	Type of study	Evidence level
Paula V, Arruda M, Vitral C, Gaspar A. Seroprevalence of viral hepatitis in riverine communities from the Western Region of the Brazilian Amazon Basin. <i>Mem Inst Oswaldo Cruz.</i> 2001; 96(8):1123-8.	Investigates the presence of infection by hepatitis viruses A, B, C, D and E in communities living along the rivers Purus and Acre in the states of Acre and Amazonas, Amazon basin. <sup>(42)</sup>	Prevalence study (descriptive)	VI
Chachá SGF, Gomes-Gouvêa MS, Malta FM, Ferreira S da C, Villanova MG, Souza FF, et al. Distribution of HBV subgenotypes in Ribeirão Preto, Southeastern Brazil: a region with history of intense Italian immigration. <i>Braz J Infect Dis.</i> 2017; 21(4):424-32.	Determines the genotypes and subgenus of HBV circulating in southeastern Brazil and compares the genetic sequences found to HBV sequences previously described in the world. <sup>(43)</sup>	Case-control	IV
Braga WSM, de Oliveira CMC, de Araújo JR, Castilho MC, Rocha JM, Gimaque JB de L, et al. Chronic HDV/HBV co-infection: Predictors of disease stage – a case series of HDV-3 patients. <i>J Hepatol.</i> 2014; 61(6):1205-11.	Describes predictors of patients with chronic hepatitis B co-infected by HDV. <sup>(44)</sup>	Cross-sectional study (descriptive)	VI
Botelho-Souza LF, dos Santos A de O, Borzacov LM, Honda ER, Villalobos-Salcedo JM, Vieira DS. Development of a reverse transcription quantitative real-time PCR-based system for rapid detection and quantitation of hepatitis delta virus in the western Amazon region of Brazil. <i>J Virol Methods.</i> 2014; 197:19-24.	develops a to detect and quantify the abundance of HDV particles in serum samples, based on quantitative reverse PCR (RT-qPCR). <sup>(45)</sup>	Clinical trial	III
Barros LMF, Gomes-Gouvêa MS, Pinho JRR, Alvarado-Mora MV, Dos Santos A, Mendes-Corrêa MCJ, et al. Hepatitis Delta virus genotype 8 infection in Northeast Brazil: Inheritance from African slaves? <i>Virus Res.</i> 2011; 160(1-2):333-9.	Assesses the seroprevalence of HDV among chronic carriers of HBsAg in the state of Maranhão, northeast Brazil. <sup>(46)</sup>	Cross-sectional study (descriptive)	VI
Gomes-Gouvêa MS, Soares MCP, de Carvalho Mello IMVG, Brito EMF, Moia LJMP, Bensabath G, et al. Hepatitis D and B virus genotypes in chronically infected patients from the Eastern Amazon Basin. <i>Acta Trop.</i> 2008; 106(3):149-55.	Describes the genotypes of HBV and HDV housed in chronically infected patients in the Amazon Basin, Brazil. <sup>(47)</sup>	Cross-sectional study (descriptive)	VI
Fonseca JC. Hepatite fulminante na Amazônia brasileira. <i>Rev Soc Bras Med Trop.</i> 2004; 37(Suppl 2):93-5.	The author makes a review and update on the results of research involving hepatitis of Lábrea hepatitis and other percussion caps of brazilian Western Amazonia, with emphasis on epidemiological, clinical and histopathologic features and viral etiology, such as hepatitis viruses B and D <sup>(48)</sup>	Literature review	VI
Fonseca JC, Simonetti SRR, Schatzmayr HG, Castejón MJ, Cesário ALO, Simonetti JP. Prevalence of infection with hepatitis delta virus (HDV) among carriers of hepatitis B surface antigen in Amazonas State, Brazil. <i>Trans R Soc Trop Med Hyg.</i> 1988; 82(3):469-71.	Performs an enzyme immunoassay to investigate HDV infection among individuals HBsAg asymptomatic. <sup>(49)</sup>	Cross-sectional study (descriptive)	VI
Bensabath G. Hepatitis Delta virus infection and Labrea hepatitis: prevalence and role in fulminant hepatitis in the amazon basin. <i>JAMA.</i> 1987; 258(4):479.	Studies the epidemiology of HDV infection to confirm its role on causing fulminant Labrea hepatitis, District of Boca do Acre, Amazon Basin, Brazil. <sup>(14)</sup>	Cross-sectional study (descriptive)	VI
Strauss E, Gayotto LCC, da Silva LC, Alves VAF, Carrilho F, Chamone DAF, et al. Unexpected low prevalence of delta antibodies in the east Amazon region and São Paulo: evidence for regional differences in the epidemiology of delta hepatitis virus within Brazil. <i>Trans R Soc Trop Med Hyg.</i> 1987; 81(1):73-4.	Investigates antibodies (anti-HD) for HDV among symptomatic and asymptomatic carriers of HBsAg in Eastern Amazon (states of Pará and Amapá) and São Paulo, Brazil. <sup>(50)</sup>	Cross-sectional study (descriptive)	VI

V- Evidence from a single descriptive or qualitative study;

IV- Evidence from the opinion of authorities and/or from a report of committees of experts.

During the fourth stage we read the abstracts and applied the eligibility criteria, as set by the protocol on figure 1, the result was 33 selected studies.

On the fifth stage the discussion of data found was had and on the sixth stage we built the descriptive document of this review.

## Results

The selected studies are summarized (Chart 1), considering information such as title, author(s), journal in which it was published, thematic considerations and the classification of the level of evidence.

The studies analyzed (Chart 1) were organized to facilitate the better reading of the results. The select-

ed studies were published between the years of 1987 and 2017; there were no studies selected for the years 1993, 1997, 1998, 2003, 2010, 2013 and 2016. We observed an average publication of two studies per year on the other years, and 2014 presented the greater volume of publications, with four studies.

Observing the academic training of the main author of the study, 85% of the studies were from medical professionals, 6% from biomedical professionals, 3% from nurses, 3% from pharmacists/biochemists and 3% from biologists.

The research were published in eight categories of journals, 46% of the area of tropical medicine, 15% of the area of virology, 12% of the area of infectious diseases, 9% of the area of medical sciences, 9% of the area of public health, 3% of the area of hepatology, 3% of the area of nursing and 3% of the area of biomedicine.

Regarding research design, 69.6% were cross-sectional studies, 15.2% were literature re-

views, 6.1% were case-control studies, 6.1% were case reports and 3% were clinical trials.

By classifying the level of evidence according to the method adopted, we observed that: 91% of the studies were of type VI, i.e., evidence derived from a single descriptive or qualitative study; 6% were of type IV, evidences from well designed cohort and case-control studies; and 3% of type III, i.e., evidences from well designed clinical trials without randomization.

## Discussion

The result of this integrative review depicts the scientific production on HDV infection in Brazil over the past three decades, and, despite being a major cause of severe complications of hepatic disease in patients with hepatitis B and variable distribution, with areas of high prevalence on the country,<sup>(2, 51, 52)</sup> the results demonstrate a discrete scientific production.

Of the studies identified in this review, 91% correspond to the level of evidence VI, i.e., studies with descriptive cross-sectional design, most of them focused on the analysis of prevalence, resulting on a low level of evidence.<sup>(18,20)</sup>

The main areas of production are concentrated in tropical medicine journals. Brazil is a tropical country and still bears a high burden of communicable diseases.<sup>(53)</sup> Although advances on the control of vaccine-preventable diseases and HIV infection are seen on the last two decades, infectious diseases still constitute a serious public health problem in the country.<sup>(54)</sup>

Most studies, 85%, have a medical professional as the primary author, although it is a theme inherent to the practice of medicine, due to the need for scientific research to produce good clinical practices;<sup>(55)</sup> other areas of the multidisciplinary field of health hold equal importance on the need for scientific production as a guiding mechanism for the improvement of care, especially when preventable harms, such as hepatitis D, are considered, an argument that contrasts with researchers who claim, for example,

that the scientific production of nursing is still incipient in Brazil.<sup>(56)</sup>

However, initiatives such as the national program for the prevention and control of viral hepatitis, which seeks the systematization of the programmatic actions in health, providing the nursing professional with protagonism and autonomy to manage care on the three levels of health care. Due to the professional assignment, there is interest in constructing health strategies from new knowledge, both in care and adequacy of public policies.<sup>(57)</sup>

The World Health Organization recognizes the HBV infection, a necessary condition for the HDV infection, as a public health problem that requires urgent response, reiterating the importance of prevention, particularly through vaccine strategies, this highlights the importance of the nurse as a transforming agent in this health-disease-curing process.<sup>(58)</sup>

However, to evaluate the quality of scientific production in health it is necessary to consider the structural and promotion conditions existing in Brazil for higher ranked classifications. This goes beyond the theme of this integrative review. Stimulating undergraduate research was only implemented in Brazil in 1988 and despite the advances in recent decades, the Brazilian scientific production faces obstacles regarding the quality of the studies produced, something directly related to the scarcity of resources.<sup>(59)</sup>

Additionally, when the object of analysis is a theme like HDV infection, aspects related to the quality of care and to the rational use of resources, both in the public and private sectors, end up exerting pressure on health professionals who lack contextualized scientific evidence for better performance practices.<sup>(60)</sup>

The production of scientific evidence, such as meta-analytic reviews or randomized clinical trials, does not exclude the importance of descriptive studies and the value of personal experiences, but evidences to care for patients subject to the evolution to severe conditions, such as those infected with HDV, are of fundamental importance to make the best clinical decisions.<sup>(55)</sup> However, we note that all of the epidemiological studies and the data on

information systems must be used to understand hepatitis B and D in the country, and to support the development of individual and collective interventions that minimize the influence of the disease on the population.

Despite the importance of study reviews to synthesize research results or even the production of relevant research, actions must go beyond simply stimulating scientific production, but fundamentally, using the results of these studies as transforming elements in clinical practice.<sup>(60)</sup>

## Conclusion

We conclude that the scientific literature on HDV infection in Brazil is centered on research with descriptive/cross-sectional design, being incipient on studies with higher levels of evidence. This information points to the need for further research focused on the definition of risk factors, drug and therapeutic analysis and the effectiveness of prevention and control programs, to sustain the adoption of innovations in public policies and healthcare.

## Collaborations

Oliveira MS, Valle SCN, Souza RM, Silva RPM, Figueiredo EM, Taminato M e Fram D contributed to the design of the manuscript, in writing the study, with critical and relevant review of the intellectual content and with the approval of the final version to be published.

## References

- Rizzetto M, Canese MG, Aricò S, Crivelli O, Trepo C, Bonino F, et al. Immunofluorescence detection of new antigen-antibody system (delta/anti-delta) associated to hepatitis B virus in liver and in serum of HBsAg carriers. *Gut*. 1977; 18(12):997-1003.
- Wedemeyer H, Manns MP. Epidemiology, pathogenesis and management of hepatitis D: update and challenges ahead. *Nat Rev Gastroenterol Hepatol*. 2010; 7(1):31-40.
- Rizzetto M. Hepatitis D Virus: Introduction and Epidemiology. *Cold Spring Harb Perspect Med*. 2015; 5(7):a021576.
- Alfaiate D, Dény P, Durantel D. Hepatitis delta virus: From biological and medical aspects to current and investigational therapeutic options. *Antiviral Res*. 2015; 122:112-29.
- Huang CR. Hepatitis D virus infection, replication and cross-talk with the hepatitis B virus. *World J Gastroenterol*. 2014; 20(40):14589.
- Rizzetto M, Alavian SM. Hepatitis Delta. *Clin Liver Dis*. 2013; 17(3):475-87.
- De Oliveira MS, Do Valle SD, Silva RP, De Figueiredo EN. Hepatite B e a superinfecção por vírus D em pacientes crônicos na Amazônia ocidental brasileira. *Rev Epidemiol Control Infec [Internet]*. 2015[citado 2016 Abr 17];5(2). Disponível em: <http://online.unisc.br/seer/index.php/epidemiologia/article/view/5442>.
- Crispim MA, Fraiji NA, Campello SC, Schriefer NA, Stefani MM, Kieślisch D. Molecular epidemiology of hepatitis B and hepatitis delta viruses circulating in the Western Amazon region, North Brazil. *BMC Infect Dis*. 2014; 14:94.
- Oliveira MS, Silva RP, Valle SD, Figueiredo EN, Fram D. Chronic hepatitis B and D: prognosis according to Child-Pugh score. *Rev Bras Enferm*. 2017; 70(5):1048-53.
- Scaglione SJ, Lok AS. Effectiveness of hepatitis B treatment in clinical practice. *Gastroenterology*. 2012; 142(6):1360-8.
- di Filippo Villa D, Cortes-Mancera F, Payares E, Montes N, de la Hoz F, Arbelaez MP, et al. Hepatitis D virus and hepatitis B virus infection in Amerindian communities of the Amazonas state, Colombia. *Virol J*. 2015; 12:172.
- Fonseca JC. Histórico das hepatites virais. *Rev Soc Bras Med Trop*. 2010; 43(3):322-30.
- Fonseca JC, Ferreira LC, Guerra AL, Passos LM, Simonetti JP. Hepatite fulminante e febre negra de Lábrea: estudo de 5 casos procedentes de Codajás, Amazonas, Brasil. *Rev Soc Bras Med Trop*. 1983; 16(3):144-7.
- Bensabath G. Hepatitis Delta virus infection and Labrea hepatitis: prevalence and role in fulminant hepatitis in the Amazon Basin. *JAMA*. 1987; 258(4):479.
- Cicero MF, Pena NM, Santana LC, Arnold R, Azevedo RG, Leal ES, et al. Is Hepatitis Delta infections important in Brazil? *BMC Infect Dis [Internet]*. 2016 [cited 2017 Sep 28];16(1). Available from: <http://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-016-1856-9>.
- Alcalá Pompeo D, Rossi LA, Galvão CM. Revisão integrativa: etapa inicial do processo de validação de diagnóstico de enfermagem. *Acta Paul Enferm*. 2009; 22(4):434-8.
- Hopia H, Latvala E, Liimatainen L. Reviewing the methodology of an integrative review. *Scand J Caring Sci*. 2016; 30(4):662-9.
- Mendes KD, Silveira RC, Galvão CM. Revisão integrativa: método de pesquisa para a incorporação de evidências na saúde e na enfermagem. *Texto Contexto Enferm*. 2008; 17(4):758-64.
- Souza MT de, Silva MD, Carvalho R. Integrative review: what is it? How to do it? *einstein (São Paulo)*. 2010; 8(1):102-6.
- Melnik BM, Fineout-Overholt E. Evidencebased practice in nursing & healthcare. A guide to best practice. Philadelphia: Lippincot Williams & Wilkins; 2005. Making the case for evidence based practice. p.239-344.
- Souto FJ. A hepatite B e os movimentos migratórios no Estado de Mato Grosso, Brasil. *Rev Soc Bras Med Trop*. 2004; 37(Suppl 2):63-8.
- Braga WS. Infecção pelos vírus das hepatites B e D entre grupos indígenas da Amazônia brasileira: aspectos epidemiológicos. *Rev Soc Bras Med Trop*. 2004; 37(Suppl 2):9-13.
- Braga WS, Castilho M da C, Borges FG, Leão JR, Martinho AC, Rodrigues IS, et al. Hepatitis D virus infection in the Western Brazilian Amazon - far from a vanishing disease. *Rev Soc Bras Med Trop*. 2012; 45(6):691-5.

24. Paraná R, Vitvitski L, Pereira JE. Hepatotropic viruses in the Brazilian Amazon: a health threat. *Braz J Infect Dis.* 2008; 12(3):253-6.
25. Braga WS, Brasil LM, Souza RA de, Castilho MC, Fonseca JC. Ocorrência da infecção pelo vírus da hepatite B (VHB) e delta (VHD) em sete grupos indígenas do Estado do Amazonas. *Rev Soc Bras Med Trop.* 2001; 34(4):349-55.
26. Braga WS, Castilho MC, Santos IC, Moura MA, Segurado AC. Low prevalence of hepatitis B virus, hepatitis D virus and hepatitis C virus among patients with human immunodeficiency virus or acquired immunodeficiency syndrome in the Brazilian Amazon basin. *Rev Soc Bras Med Trop.* 2006; 39(6):519-22.
27. Oliveira ML, Bastos FI, Telles PR, Yoshida CF, Schatzmayr HG, Paetzold U, et al. Prevalence and risk factors for HBV, HCV and HDV infections among injecting drug users from Rio de Janeiro, Brazil. *Braz J Med Biol Res.* 1999; 32(9):1107-14.
28. Azevedo RA, Silva AE, Ferraz ML, Marcopito LF, Baruzzi RG. Prevalência dos marcadores sorológicos dos vírus da hepatite B e D em crianças das tribos Caiabietucarramãe do parque indígena do Xingu, Brasil central. *Rev Soc Bras Med Trop.* 1996; 29(5):431-9.
29. Andrade ZA, Lesbordes JL, Ravisse P, Paraná R, Prata A, Barberino JS, et al. Fulminant hepatitis with microvesicular steatosis (a histologic comparison of cases occurring in Brazil - Labrea hepatitis - and in central Africa - Bangui hepatitis). *Rev Soc Bras Med Trop.* 1992; 25(3):155-60.
30. Fonseca JC, Ferreira LC, Brasil LM, Castilho MC, Moss R, Barone M. Fulminant Labrea hepatitis - The role of hepatitis a (HAV), B (HBV), C (HCV), AND D (HDV) infection. (Preliminary report). Fulminant Labrea Hepat - Role Hepat HAV B HBV C HCV HDV. *Infect Prelim Rep.* 1992; 34(6):609-12.
31. Botelho-Souza LF, Souza Vieira D, de Oliveira dos Santos A, Cunha Pereira AV, Villalobos-Salcedo JM. Characterization of the genotypic profile of hepatitis delta virus: isolation of hdv genotype-1 in the western amazon region of Brazil. *Intervirology.* 2015; 58(3):166-71.
32. Kay A, Melo da Silva E, Pedreira H, Negreiros S, Lobato C, Braga W, et al. HBV/HDV co-infection in the Western Brazilian Amazonia: an intriguing mutation among HDV genotype 3 carriers. *J Viral Hepat.* 2014; 21(12):921-4.
33. Mendes-Correa MC, Gomes-Gouvêa MS, Alvarado-Mora MV, Da Silva MH, Lázari C, Cavalcanti NC, et al. Hepatitis delta in HIV/HDV co-infected patients in Brazil: is it important? *Int J Infect Dis.* 2011; 15(12):e828-32.
34. Gomes-Gouvea MS, Soares MC, Bensabath G, de Carvalho-Mello IM, Brito EM, Souza OS, et al. Hepatitis B virus and hepatitis delta virus genotypes in outbreaks of fulminant hepatitis (Labrea black fever) in the western Brazilian Amazon region. *J Gen Virol.* 2009; 90(11):2638-43.
35. Nunes HM, Monteiro MR, Soares M. Prevalência dos marcadores sorológicos dos vírus das hepatites B e D na área indígena Apyterewa, do grupo Parakanã, Pará, Brasil. *Cad Saúde Pública.* 2007; 23(11):2756-66.
36. Viana S, Paraná R, Moreira RC, Compri AP, Macedo V. High prevalence of hepatitis b virus and hepatitis d virus in the western brazilian amazon. *Am J Trop Med Hyg.* 2005; 73(4):808-14.
37. Arboleda M, Castilho MC, Fonseca JF, Albuquerque BC, Saboia RC, Yoshida CF. Epidemiological aspects of hepatitis B and D virus infection in the northern region of Amazonas, Brazil. *Trans R Soc Trop Med Hyg.* 1995; 89(5):481-3.
38. Soares MC, Menezes RC, Martins SJ, Bensabath G. Epidemiologia dos vírus das hepatites B, C e D na tribo indígena parakanã, Amazônia Oriental Brasileira. *Bol Oficina Sanit Panam.* 1994; 117(2):124-35.
39. Dantas LC, Genzini T, Miranda MP, Santos RG, Siqueira NG, Weirich J, et al. Liver transplantation in a patient with hepatitis B, C and D coinfection associated with hepatocellular carcinoma: a management strategy for a rare condition. *Case report. Sao Paulo Med J.* 2015; 133(6):525-30.
40. Fonseca JC. Hepatite D. *Rev Soc Bras Med Trop.* 2002; 35(2):181-90.
41. Ribeiro LC, Souto FJD. Hepatite Delta no Estado de Mato Grosso: apresentação de cinco casos. *Rev Soc Bras Med Trop.* 2000; 33(6):599-602.
42. Paula V, Arruda M, Vitral C, Gaspar A. Seroprevalence of viral hepatitis in riverine communities from the Western Region of the Brazilian Amazon Basin. *Mem Inst Oswaldo Cruz.* 2001; 96(8):1123-8.
43. Chachá SG, Gomes-Gouvêa MS, Malta F de M, Ferreira SC, Villanova MG, Souza FF, et al. Distribution of HBV subgenotypes in Ribeirão Preto, Southeastern Brazil: a region with history of intense Italian immigration. *Braz J Infect Dis.* 2017; 21(4):424-32.
44. Braga WS, de Oliveira CM, de Araújo JR, Castilho MC, Rocha JM, Gimaque JB, et al. Chronic HDV/HBV co-infection: Predictors of disease stage - a case series of HDV-3 patients. *J Hepatol.* 2014; 61(6):1205-11.
45. Botelho-Souza LF, dos Santos AO, Borzacov LM, Honda ER, Villalobos-Salcedo JM, Vieira DS. Development of a reverse transcription quantitative real-time PCR-based system for rapid detection and quantitation of hepatitis delta virus in the western Amazon region of Brazil. *J Virol Methods.* 2014; 197:19-24.
46. Barros LM, Gomes-Gouvêa MS, Pinho JR, Alvarado-Mora MV, Dos Santos A, Mendes-Corrêa MC, et al. Hepatitis Delta virus genotype 8 infection in Northeast Brazil: Inheritance from African slaves? *Virus Res.* 2011; 160(1-2):333-9.
47. Gomes-Gouvêa MS, Pereira Soares Mdo C, Guedes de Carvalho Mello IM, Brito EM, Pereira Moia Lde J, Bensabath G, et al. Hepatitis D and B virus genotypes in chronically infected patients from the Eastern Amazon Basin. *Acta Trop.* 2008; 106(3):149-55.
48. Fonseca JC. Hepatite fulminante na Amazônia brasileira. *Rev Soc Bras Med Trop.* 2004; 37(Suppl 2):93-5.
49. Fonseca JC, Simonetti SR, Schatzmayr HG, Castejón MJ, Cesário AL, Simonetti JP. Prevalence of infection with hepatitis delta virus (HDV) among carriers of hepatitis B surface antigen in Amazonas State, Brazil. *Trans R Soc Trop Med Hyg.* 1988; 82(3):469-71.
50. Strauss E, Gayotto LC, da Silva LC, Alves VA, Carrilho F, Chamone DA, et al. Unexpected low prevalence of delta antibodies in the east Amazon region and São Paulo: evidence for regional differences in the epidemiology of delta hepatitis virus within Brazil. *Trans R Soc Trop Med Hyg.* 1987; 81(1):73-4.
51. Alvarado-Mora MV, Romano CM, Gomes-Gouvêa MS, Gutierrez MF, Carrilho FJ, Pinho JR. Dynamics of Hepatitis D (delta) virus genotype 3 in the Amazon region of South America. *Infect Genet Evol.* 2011; 11(6):1462-8.
52. Silva AL, Vitorino RR, Esperidião-Antonio V, Santos ET, Santana LA, Henriques BD, et al. Hepatites virais: B, C e D: atualização. *Rev Soc Bras Clín Méd.* 2012; 10(3):206-18.
53. Mendes EV. As redes de atenção à saúde. *Ciênc Saúde Coletiva.* 2010; 15(5):2297-305.
54. Victora CG, Barreto ML, Leal MC, Monteiro CA, Schmidt MI, Paim J, et al. Condições de saúde e inovações nas políticas de saúde no Brasil: o caminho a percorrer. *Lancet.* 2011;(Supl Saúde no Brasil 6):90-102. DOI:10.1016/S0140-6736(11)60055-X.
55. Paolucci El Dib R. Como praticar a medicina baseada em evidências. *J Vasc Bras.* 2007; 6(1):1-4.



56. Morais AS, Nicole AG, Braga AT, Tronchin DMR, Melleiro MM. Qualidade e avaliação em saúde: publicações em periódicos de enfermagem nas últimas duas décadas. *Rev Enferm UERJ*. 2008; 16(3):404-9.
57. Brasil. Ministério da Saúde, Secretaria de Vigilância em Saúde. Manual de aconselhamento em hepatites virais. Brasília (DF): Ministério da Saúde; 2005. 52 p.
58. Organização Panamericana da Saúde (OPAS)/Organização Mundial da Saúde (OMS). Novos dados sobre hepatites destacam necessidade de uma resposta global urgente [Internet]. Brasília (DF); OPAS/OMS; 2017 [cited 2017 Oct 31]. Available from: [http://www.paho.org/bra/index.php?option=com\\_content&view=article&id=5404:novos-dados-sobre-hepatites-destacam-necessidade-de-uma-resposta-global-urgente&Itemid=812](http://www.paho.org/bra/index.php?option=com_content&view=article&id=5404:novos-dados-sobre-hepatites-destacam-necessidade-de-uma-resposta-global-urgente&Itemid=812).
59. Tenório MP, Beraldi G. Iniciação científica no Brasil e nos cursos de medicina. *Rev Assoc Médica Bras*. 2010; 56(4):390-3.
60. Sampaio RF, Mancini MC. Estudos de revisão sistemática: um guia para síntese criteriosa da evidência científica. *Rev Bras Fisioter*. 2007; 11(1):83-9.