

Trends and spatial distribution of Hepatitis D in the North of Brazil, 2009-2018: an ecological study

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Abstract

Objective: To analyze the annual incidence of hepatitis D cases in both Brazil and the Brazilian Northern region between 2009 and 2018. **Methods:** This was an ecological study of hepatitis cases notified on the Notifiable Health Conditions Information System (SINAN), analyzed by sex, age groups, and Northern region states. Temporal trend analysis was performed using the Prais-Winsten method to estimate incident rate annual percent change (APC). **Results:** In the period studied, 2,710 cases were reported in Brazil, 74.5% of them in the Northern region and 71.5% in Amazonas, Acre and Rondonia alone. APC showed a downward trend in Brazil as a whole (-21.6% – 95%CI -3.8;-36.2%), in the Northern region (-28.5% – 95%CI -5.2;-46.1%), in Amazonas (-34.1% – 95%CI -0.8;-56.2%) and in Acre (-37.6% – 95%CI -18.0;-52.6%). Cases decreased in age groups below 40 years old. **Conclusion:** There was a downward trend in incidence in the Western Amazon, impacting incidence in Brazil as a whole. This fall was led by younger people, probably due to hepatitis B vaccination.

Keywords: Hepatitis D; Neglected Diseases; Time Series Studies; Epidemiological Monitoring; Incidence; Amazonian Ecosystem.

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Introduction

Hepatitis D is caused by a defective virus, which only infects humans in the presence of hepatitis B virus infection.¹ The disease can lead individuals with hepatitis B to liver failure more rapidly. It is a neglected disease and primarily affects developing countries.^{2,3} The Amazon is one of the regions with the highest hepatitis B and D endemicity in the world.^{4,5} In Brazil, cases outside the Northern region are reported sporadically, being more common in states bordering the region.^{6,7}

Low levels of education, lack of access to health care, and absence of symptoms are some factors that delay diagnosis and care for vulnerable populations.^{4,6,8,9} Despite the regional difficulties, efforts have been made to control the disease, ensuring the supply of vaccines and medicines to the most remote communities. In recent years, a drop in hepatitis B prevalence has been observed throughout Brazil^{9,10} and as a consequence, it is possible that a reduction in hepatitis D prevalence levels is also occurring. Analysis of case notifications can indicate whether implementing hepatitis B control measures has helped in the fight against hepatitis D.

The Amazon is one of the regions with the highest hepatitis B and D endemicity in the world.

The objective of this study was to analyze annual incidence of hepatitis D cases in both Brazil and the Brazilian Northern region between 2009 and 2018.

Methods

This was an ecological study which analyzed time series of reported cases of hepatitis D, by municipality of residence, between 2009 and 2018, considering Brazil as a whole and all states in the country's Northern region. Information was obtained in absolute numbers of cases per state, sex (male; female) and age (divided into three age groups, in years: <20; 20-39; ≥40). These data were entered into electronic spreadsheets. Official free access Ministry of Health data were accessed online on September 20, 2020 via the Notifiable Health Conditions Information System (SINAN) and the Ministry's Health Surveillance Secretariat website.^{11,12} Notified cases were considered

and analyzed as acute and chronic. The municipalities with the highest number of notifications were represented on a map.

The calculation of detection rates (cases/population) per 100,000 inhabitants was performed using population estimates based on Brazilian Institute of Geography and Statistics (IBGE) data.¹³ The extracted data and calculated rates were input to electronic spreadsheets (Microsoft Office Excel, version 2016). In order to test temporal trend, by state and age group, nonparametric linear models were created using the Prais-Winsten method,¹⁴ using logarithmic data transformation (Stata 6.0 - Statacorp, College Station, USA, 1999). The trends were classified as increasing, decreasing or stationary, when the β coefficients were, respectively, significantly positive, significantly negative or not significant. Annual percent change (APC) was calculated using the β regression coefficient according to the following formula:

$$VPA = (-1 + 10^{\beta}) * 100$$

95% confidence intervals (95%CI) were calculated for APC. Statistical significance was set at <0.05. The Durbin-Watson statistic (DW) was used to rule out results with autocorrelation.

Results

A total of 2,710 hepatitis D cases were reported for Brazil as a whole between 2009 and 2018, 1,529 (56.4%) of which were male. In the Northern region, 2,019 (74.5%) cases were reported, 1,283 (63.5%) of which were male. In Brazil as a whole and also in the Northern region, cases increased until 2011, maintained a plateau until 2014, and fell after that period (Table 1).

Regarding age, the time series show a decrease in the incidence of hepatitis D cases in Brazil in the under-20 age groups (APC=-43.4% - 95%CI -55.5;-28.0 - p-value=0.001) and the 20-39 age groups (APC=-29.1% - 95%CI -43.5;-11.0 - p-value=0.008). The fall in incidence in those aged over 40 was not statistically significant (APC=-4.9% - 95%CI -23.4;18.1 - p-value=0.605)

The annual hepatitis D detection rate in the Northern region ranged from 0.23 to 1.27 per 100,000 inhabitants, this being higher than the national rate, which ranged from 0.06 to 0.20/100,000 inhab. Most cases in the North (1,189) were reported in Amazonas (58.9%) and Acre (29.2%), which was also in first

place with regard to case concentration, with detection rates ranging from 1.8 to 13.2/100,000 inhab. (Table 1). Together, Pará, Roraima, Amapá and Tocantins had 82 cases (4,1%), with low detection rates (Figure 1).

Time-series analysis (Table 1) showed a decreasing trend in annual hepatitis D incidence from 2009 to 2018 for Brazil as a whole (p-value=0.025), the Northern region (p-value=0.025), and the states of Acre (p-value=0.004) and Amazonas (p-value<0.05). Durbin-Watson statistics showed that there was no autocorrelation. In relation to the other Northern region states, there was either no statistical significance or autocorrelation occurred. When adding together the other four regions of Brazil, the detection rate was very low and showed no rising or falling trend in the period (p-value=0.339).

Among the 60 cases notified as being acute hepatitis D, Amazonas (36) and Acre (12) accounted for the majority, while only 16 cases (26.7%) were detected after 2013.

Analysis by municipality of residence showed that in Acre, 82.7% of hepatitis D cases were concentrated in six municipalities, especially Rio Branco -226 (43.8%), and Cruzeiro do Sul, 143 (27.5%). In Amazonas, 78% of cases were concentrated in eight municipalities. In Rondônia, 64 (40.2%) cases were recorded in Porto Velho (Figure 2).

Discussion

The present study showed a fall in hepatitis D case detection in Brazil as a whole, as a consequence of the decrease in the Northern region, where the disease has been identified as endemic since the 1970s.¹⁵ This trend was significant especially among younger people. In the period between 2009 and 2018, there was a higher proportion of notifications in the states that correspond to the southwestern part of the Western Amazon (Acre, Amazonas and Rondônia), where Brazil's highest prevalence rates are found.^{1,4,8} Time series analysis showed a significant drop in the detection rate in Acre and Amazonas, influencing the hepatitis D figures for the Northern region and for Brazil as a whole.

Some authors,^{6,8} when studying rural communities in the last decade, have identified high hepatitis D prevalence among people with hepatitis B, raising concern about the endemic control of the disease. However, hepatitis B numbers have been falling in

the Brazil,⁹ probably due to improved biosecurity measures, donor screening, and above all because of universal vaccination of children.^{9,10} With the progressive control of hepatitis B in Brazil, one would expect an equal effect with regard to hepatitis D, given that it is dependent on the former.

Data that corroborates the impression of gradual control and the importance of vaccination is the "aging" of cases, with a significant falling trend in the age group up to 39, but not above that age. The younger segments of the Brazilian population are those that have benefited most from vaccination, because they have been vaccinated for longer. Vaccination for all ages was only released a few years ago. The progressive decrease in the detection of acute hepatitis D cases also suggests gradual control of the disease.

The municipalities in the state of Amazonas with most case notifications are close to the border with Acre, as are the two most affected municipalities in Rondônia. The confluence of these municipalities corresponds to the area through which the tributaries of the Juruá, Purus and Madeira rivers flow, historically identified as the most endemic area for hepatitis B and D in Brazil.^{2,3,8}

The limitations of this study are inherent to disease notification systems, universally subject to underreporting and inconsistencies. This becomes of greater concern in the Amazon, due to logistical difficulties for surveillance actions and provision of health care in hard-to-reach areas with precarious conditions for conservation of supplies and equipment. There is furthermore the aggravating factor of the chronic lack of reagents for hepatitis D diagnosis, since the test kits are expensive and difficult to obtain, due to it being neglected disease and receiving little investment from the biomedical supplies industry.^{2,3} The true number of cases is probably higher than the number of notified cases, especially because the disease can remain asymptomatic for long periods. However, there is no tendency for underreporting to increase, since the Brazilian epidemiological surveillance system has been improving recent decades.¹⁶

Using the Prais-Winsten technique for modeling time series can be misleading due to autocorrelation of residuals, especially in small series.¹⁴ To avoid this error, we used the Durbin-Watson statistic and disregarded series that had autocorrelation.

Another limitation of the study lies in not knowing where and when these people were infected. However,

Table 1 – Prais-Winsten trend analysis of the hepatitis D detection rate (case per 100,000 inhab.) and annual percent change, by Northern region state, Northern region and Brazil, 2009-2018

Period	Acre		Amazonas		Rondônia		Pará		Roraima		Amapá		Tocantins		Norte		Brazil		Other regions of Brazil ^a	
	n	Rate	n	Rate	n	Rate	n	Rate	n	Rate	n	Rate	n	Rate	n	Rate	n	Rate	n	Rate
2009	91	13.17	125	3.68	12	0.80	2	0.03	4	0.95	0	0.00	2	0.15	236	1.00	299	0.16	63	0.04
2010	64	8.72	155	4.45	13	0.83	3	0.04	3	0.66	0	0.00	0	0.00	238	0.98	294	0.15	56	0.03
2011	91	12.19	197	5.57	11	0.70	5	0.07	8	1.74	0	0.00	2	0.14	314	1.27	391	0.20	77	0.05
2012	63	8.30	128	3.56	18	1.13	3	0.04	6	1.28	4	0.57	0	0.00	222	0.89	308	0.16	86	0.05
2013	75	9.66	197	5.17	11	0.64	4	0.05	3	0.61	0	0.00	1	0.07	291	1.13	369	0.18	78	0.04
2014	99	12.53	174	4.49	7	0.40	6	0.07	2	0.40	2	0.27	2	0.13	292	1.12	360	0.18	68	0.04
2015	39	4.85	82	2.08	48	2.71	3	0.04	0	0.00	0	0.00	0	0.00	172	0.67	250	0.12	78	0.04
2016	33	4.04	16	0.40	10	0.56	1	0.01	0	0.00	1	0.13	0	0.00	61	0.23	132	0.06	71	0.04
2017	15	1.81	52	1.28	16	0.89	2	0.02	0	0.00	3	0.38	1	0.06	89	0.33	162	0.08	73	0.04
2018	19	2.19	63	1.54	13	0.74	4	0.05	3	0.52	1	0.12	1	0.06	104	0.38	145	0.07	41	0.04
APC ^b (%)	-37.6	-34.1	-34.1	-34.1	-0.3	-0.3	-6.1	-6.1	-19.3	-19.3	-28.7	-28.7	-20.1	-20.1	-28.5	-28.5	-21.6	-21.6	-0.23	-0.23
95%CI ^c	-52.6;-18.0	-56.2;-0.8	-56.2;-0.8	-56.2;-0.8	-27.4;36.9	-27.4;36.9	-34.5;34.7	-34.5;34.7	-45.7;19.9	-45.7;19.9	-57.4;19.3	-57.4;19.3	-20.2;-20.0	-20.2;-20.0	-46.1;-5.2	-46.1;-5.2	-36.2;-3.8	-36.2;-3.8	-0.76;0.29	-0.76;0.29
p-value	0.004	0.047	0.047	0.047	0.982	0.982	0.697	0.697	0.222	0.222	0.128	0.128	0.000	0.000	0.025	0.025	0.025	0.025	0.339	0.339
DW ^d	1.96	1.77	1.77	1.77	2.33	2.33	1.62	1.62	1.61	1.61	0.99 ^e	0.99 ^e	0.84 ^e	0.84 ^e	1.68	1.68	1.69	1.69	1.42	1.42

a) Other regions of Brazil: data for the other Brazilian regions except the Northern region. Variation from 63 (2009) to 41 (2018) cases, with a maximum of 86 (2012); b) APC: Annual percent change; c) 95%CI: 95% confidence interval; d) DW: Durbin-Watson statistic for assessing autocorrelation. In the case of these time series models, with ten observations and two terms (year and intercept), autocorrelation is discarded if the statistic is between 1.3 and 2.7; e) Analysis that presented autocorrelation.

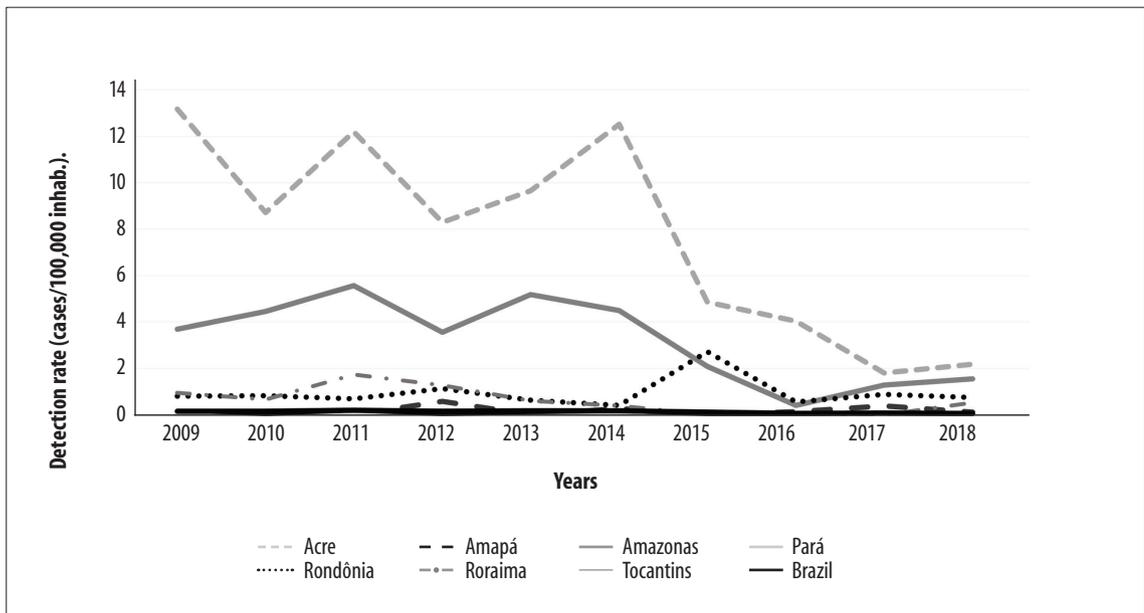
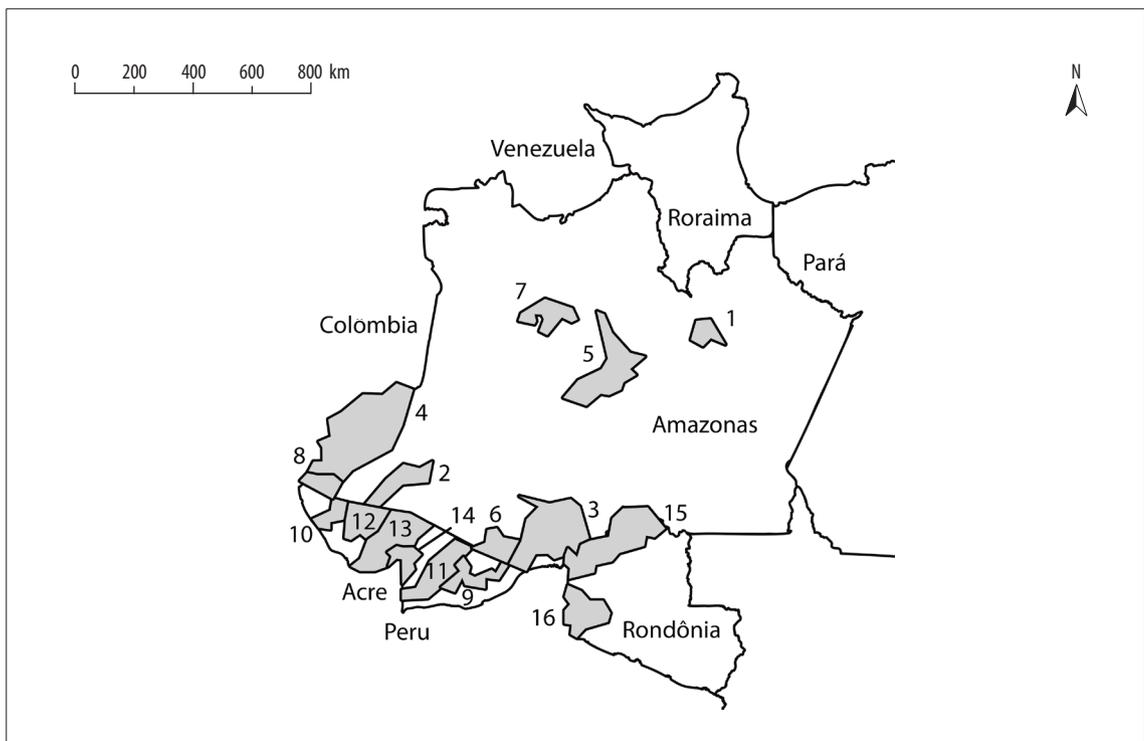


Figure 1 – Hepatitis D detection rate (cases per 100,000 inhab.) in the states of the Northern region and in Brazil, 2009-2018



Note: Municipality of residence and respective notified cases: 1. Manaus (404); 2. Eirunepé (149); 3. Lábrea (123); 4. Atalaia do Norte (100); 5. Coari (54); 6. Boca do Acre (45); 7. Fonte Boa (38); 8. Guajará (17); 9. Rio Branco (226); 10. Cruzeiro do Sul (143); 11. Sena Madureira (41); 12. Tarauacá (39); 13. Feijó (25); 14. Santa Rosa do Purus (15); 15. Porto Velho (64); and 16. Guajará-Mirim (7).

Figure 2 – Brazilian Western Amazon, showing the municipalities of residence of cases in the three Brazilian states with most hepatitis D notifications, 2009-2018

cases reported as being acute are an indication of recent infection. As has been shown here, these cases are decreasing.

Despite the falling trend, hepatitis D continues to be detected, mainly among older people. Many of these cases are the result of old infections, often identified only in advanced stages. In addition to strengthening hepatitis B vaccination, it is important to increase active tracing of hepatitis D cases among people with hepatitis B, in order to being treatment at early stages of the disease.

Analysis of hepatitis D incidence in the Northern region between 2009 and 2018 suggests that the disease is declining, especially in the younger strata of its population. The hepatitis B vaccination effort,

which began decades ago, may be the reason for this improvement. Maintaining high levels of vaccination coverage, including among the older strata of the population, should be encouraged as a key strategy to achieve elimination of the disease in the region.

Authors' contributions

Yamada ABF, Freitas PL, Silva RF and Souto FJD took part in the concept and design of the study, reviewing the literature, compiling, analyzing and interpreting the data. All the authors have approved the final version of the manuscript and are responsible for all aspects thereof, including the veracity of the information and the analyses performed.

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