Is the aging of acute hepatitis B occurring in Brazil?

Está ocorrendo envelhecimento da hepatite B aguda no Brasil?

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ABSTRACT

Introduction: The prevalence of hepatitis B virus (HBV) infection has been declining nationwide throughout Brazil since the introduction of universal child vaccination. The vaccine is currently available for all ages. However, most of the adult population has not been vaccinated and may still be susceptible to it. Most of the cases reported to the Brazilian Notifiable Diseases Information System (*Sistema de Informação de Agravos de Notificação* - SINAN) are chronic, a consequence of early exposure in life. However, acute cases are the result of current transmission and may reveal the current dynamics of HBV circulation. **Objective:** To evaluate whether there is a change in the age distribution of acute hepatitis B in Brazil. **Methods:** To analyze the historical series of reported cases and incidence rates of acute hepatitis B by age group between 2007 and 2018, based on data reported to SINAN. Temporal trend was tested with non-parametric Cusick test. **Results:** The incidence rate fell from 1.02 (/ 100,000 inhabitants) in 2007 to 0.67 in 2018 (p=0.01). The drop was significant at all ages, except under 15 and over 60. The highest incidences (≅1.0 / 100,000 inhab.) occurred between 20 and 59 years old. **Conclusion:** There is a progressive "aging" of acute hepatitis B cases in the country, probably due to the vaccine protection of younger people. A considerable portion of the older population is susceptible to HBV and may be exposed, especially by sexual route. Control measures such as vaccination and guidance for safe sex are needed.

Keywords: acute hepatitis B; hepatitis B virus; aging; Brazil; incidence.

RESUMO

Introdução: A prevalência da infecção pelo vírus da hepatite B (HBV) vem diminuindo em todo o Brasil desde a introdução da vacinação universal de crianças. Atualmente a vacina está disponível para todas as idades, porém a maior parte da população brasileira não foi vacinada e pode ainda ser suscetível. A maioria dos casos notificados ao Sistema de Informação de Agravos de Notificação (SINAN) é crônica, consequência de contágio antigo. Contudo os casos agudos são fruto de transmissão atual e podem revelar-nos a dinâmica atual da circulação do HBV. **Objetivo:** Avaliar se há mudança na distribuição etária da incidência da hepatite B aguda no Brasil. **Métodos:** Analisar a série histórica de casos notificados e as taxas de incidência de hepatite B aguda por faixa etária entre 2007 e 2018, tendo como base os dados notificados ao SINAN. Testar tendência temporal pelo teste não paramétrico de Cusick. **Resultados:** Houve queda da taxa de incidência de 1,02 (/100.000 hab.), em 2007, para 0,67, em 2018 (p=0,01). A queda foi significativa em todas as idades, exceto abaixo dos 15 e acima dos 60 anos. As maiores incidências (≅1,0/100.000 hab.) ocorreram entre 20 e 59 anos. **Conclusão:** Há progressivo "envelhecimento" dos casos agudos de hepatite B no país, provavelmente pela proteção dos mais jovens por vacina. Parcela considerável da população mais idosa é suscetível ao HBV e continua exposta, principalmente por via sexual. São necessárias medidas de controle, como vacinação e orientação para prática de sexo seguro.

Palavras-chave: hepatite; vírus da hepatite B; envelhecimento; Brasil; incidência.

INTRODUCTION

According to the global report on hepatitis from the World Health Organization (WHO),[1] chronic hepatitis B affects around 257 million people worldwide, and it is responsible for more than 800,000 deaths per year, as a result of complications from liver cirrhosis and hepatocellular carcinoma.

Infection with hepatitis B virus (HBV) has a heterogeneous distribution in Brazil, with regions of low, moderate, and high prevalence. Hyper-endemic regions were identified in the second half of the 20th century, with emphasis on the Western Amazon, but also the mountain region of Espírito Santo State, and the west of Santa Catarina and Paraná States.[2]

Hepatitis B is an immunopreventable disease, which has an effective vaccine, produced by genetic engineering. Countries that have implemented vaccination in children have shown a significant drop in the incidence of new cases.[3] The WHO advocates for all nations to start vaccination early, applying the first dose while still in the maternity ward. In Brazil, mass vaccination of children was introduced into public health in 1998. Currently, the vaccine is produced in the country and is available to the population of any age (Ordinance MS No. 1.533, of 08/18/2016). Studies conducted over the last two decades have shown a significant drop in the prevalence of HBV infection across the country.[4,5] However, there are difficulties to access remote locations, such as riverside communities in the Amazon, *quilombola* communities in the C*errado* and in the innermost part of the Northeast, in addition to vulnerable groups in cities, such as homeless people, with a deficit in vaccination coverage.

OBJECTIVE

Assess the dynamics of HBV infection the incidence of new cases, reported as "acute hepatitis". The separation of acute and chronic cases must be analyzed, since chronic cases represent infections that took place many years ago. Thus, the notification of chronic hepatitis B cases does not reflect the current state of HBV circulation in a human society. To this end, the analysis of acute incident cases is more appropriate.

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METHODS

This is a study of secondary data, considering as a unit of analysis the notifications made throughout the Brazilian territory from 2007 to 2018 on the incidence of acute hepatitis B. Official data from the Brazilian Ministry of Health were accessed through electronic addresses of the Notifiable Diseases Information System (*Sistema de Informação de Agravos de Notificação* - SINAN) (www.tabnet.datasus.gov.br) and the Health Surveillance Secretariat (indicatorshepatites.aids.gov.br). The classification of cases made in the notification forms and registered in SINAN was used as an *acute* and *fulminating* "clinical form" and *hepatitis B* "etiology". The incidences were calculated using the country`s population estimates year by year, according to the Brazilian Institute of Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística* - IBGE). The distribution of cases by age group was also analyzed.

For time trend testing, of increase or decrease in notifications for each age group, the non-parametric test developed by Cusick was used, an extension of the Wilcoxon test,[6] available in the software Stata 6.0 (Statacorp, College Station, USA) using the *nptrend* function. The degree of statistical significance was set at <0.05.

The research protocol was not submitted to the Research Ethics Committee on Human Beings because it is an analysis of secondary data on information of public domain.

RESULTS

A total of 21,277 cases of acute hepatitis B was reported between 2007 and 2018 to SINAN, corresponding to 13.9% of notifications of HBV infection. When the sum of acute and chronic cases is made, there is no increasing or decreasing in the historical series, portraying stability in the number of cases reported annually between 2007 and 2018 (p=0.304). When only acute cases are considered, there is a downward trend in notifications over time (p=0.026) (**Table 1**).

The incidence rate of acute hepatitis B in Brazil shows a statistically significant downward trend, having varied from 1.02/100,000 inhabitants in 2007 to 0.67/100,000 inhabitants (provisional number) in 2018 (p=0.01). **Tabela 2** shows the incidence rates by age group. Under 15 years old, the rates are below 0.20/100,000 inhabitants, remaining stable (<2% of cases). Drop in the incidence of notifications is significant in the 15 to 19 and 20 to 39 age groups (p=0.002). In the 40 to 59 age group, there is also a significant decrease (p=0.038). There was no decrease among individuals aged >60, with the incidence of notifications being 0.66/100,000 inhabitants in 2007 and 0.58/100,000 inhabitants in 2018. Most acute cases (63.8 and 62.6%) occurred in individuals aged <40 in 2007 and 2008, respectively. This ratio fell progressively, reaching 50 and 48% in 2017 and 2018 (**Figure 1**).

Table 1 – Absolute number of cases of total, chronic, and acute hepatitis B reported to the Brazilian Notifiable Diseases Information System (*Sistema de Informação de Agravos de Notificação* – SINAN), 2007 to 2018, and statistical calculation of temporal trend using the Cusick test.

Year	Cases		
	Acute	Chronic	Total
2007	1,931	9,503	11,434
2008	1,868	9,214	11,082
2009	1,993	10,070	12,063
2010	1,748	9,871	11,619
2011	1,757	11,208	12,965
2012	1,684	11,117	12,801
2013	2,077	13,526	15,603
2014	1,952	13,904	15,856
2015	1,615	12,214	13,829
2016	1,673	11,773	13,446
2017	1,582	10,862	12,444
2018	1,397	8,267	9,664
Cusick*	-2.22	+1.03	+1.03
p-value	0.026	0.304	0.304

*Positive values of the non-parametric Cusick test show an upward trend. Negative values indicate a downward trend. P≥0.05 indicates stability.

Table 2 – Incidence rate of notifications of cases of acute hepatitis B (/100,000 inhabitants) to the Brazilian Notifiable Diseases Information System (*Sistema de Informação de Agravos de Notificação* – SINAN), 2007 to 2018, and statistical calculation of temporal trend using the Cusick test.

Year	<5	5–14	15–19	20–39	40–59	>60	Total
2007	0.09	0.12	0.73	1.66	1.44	0.66	1.02
2008	0.09	0.02	0.69	1.61	1.40	0.64	0.97
2009	0.10	0.10	0.74	1.64	1.41	0.83	1.03
2010	0.04	0.10	0.55	1.43	1.25	0.68	0.89
2011	0.12	0.08	0.61	1.25	1.31	0.81	0.89
2012	0.17	0	0.51	1.32	1.29	0.83	0.84
2013	0.13	0.08	0.61	1.50	1.52	0.85	1.03
2014	0.13	0.08	0.45	1.31	1.50	0.91	0.96
2015	0.13	0.03	0.31	1.10	1.25	0.72	0.79
2016	0.07	0.04	0.32	1.17	1.21	0.77	0.81
2017	0.11	0.01	0.35	1.03	1.18	0.77	0.76
2018	0.06	0.03	0.21	0.91	1.10	0.58	0.67
Cusick*	+0.27	-1.72	-3.04	-3.06	-2.07	+0.19	-2.59
valor p	0.786	0.085	0.002	0.002	0.038	0.851	0.010

*Positive values of the non-parametric Cusick test show an upward trend. Negative values indicate a downward trend. A value of p≥0.05 indicates stability.

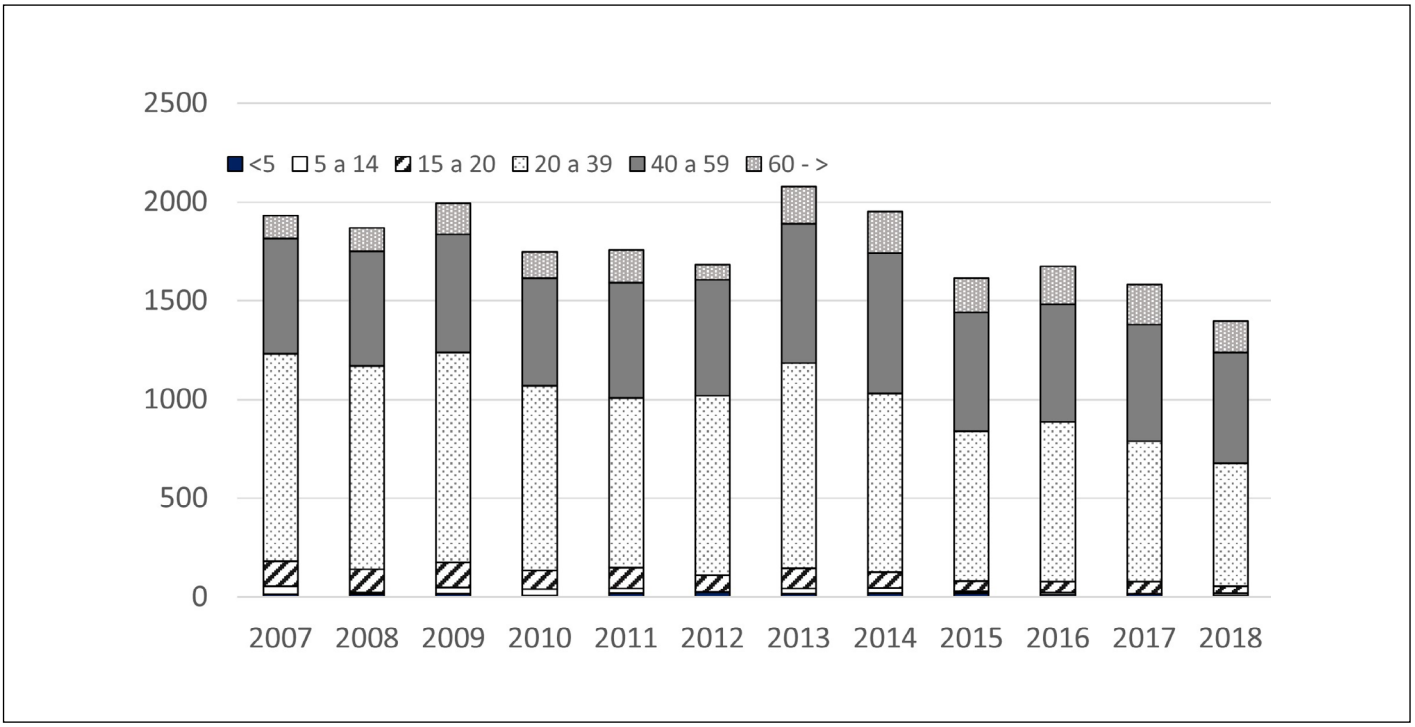

Figure 1 – Cases of acute hepatitis B reported to the Brazilian Notifiable Diseases Information System (*Sistema de Informação de Agravos de Notificação* – SINAN) between 2007 and 2018. Note that cases up to 39 years old were 63% of the total in the initial years. In 2017 and 2018, they make up no more than 50% of cases.

DISCUSSION

Official data indicate stabilization of the detection of cases of HBV infection from 2007 to 2018. However, there is a downward trend in the incidence of acute HBV infection in Brazil. Such trend seems to be a consequence of the gradual decrease in transmission over the last two decades due to vaccination. It is mainly reflected in the drop of incidence among young people.[7]

After the advent of infection by the human immunodeficiency virus (HIV), at the end of last century, concerns about biosafety and quality control of transfused blood in the country increased. Usage of disposable syringes and needles, greater control over sterilization modes in healthcare facilities and greater supervision in manicure salons and tattoo shops have reduced iatrogenic HBV infections. But, mainly, the beginning of the vaccination of children, about 20 years ago, created a cohort of Brazilians virtually free of HBV, as has been verified in cross-sectional studies.[4,5,7]

HBV infection can remain asymptomatic and unnoticed for several decades, sometimes manifesting itself as complications of liver cirrhosis or primary liver cancer. Analyzing the notifications of total HBV infections or cases reported as chronic does not show a decrease over the study period. Patients who are currently diagnosed with HBV infection were, in most past, infected a long time ago. Therefore, in order to know if there is an impact of the vaccination and sanitary improvements mentioned above, examining the dynamics of acute cases is needed, because they represent infected individuals weeks or a few months before the outbreak of symptoms. Data presented herein demonstrate that not only does acute hepatitis represent a small portion (<15%) of the detected cases, but is also falling in the population range from 15 to 59 years old. These results corroborate cross-sectional studies, which already pointed to a decrease in the prevalence of hepatitis B in all regions of the country.[4,5] The important decline in incidence among those aged 15 to 30 may be directly linked to the effect of vaccination. Among individuals aged 30 to 59, who did not directly benefit from vaccination, the effect of herd protection may be at the root of the decline in its incidence.[8]

The cases of acute hepatitis B decreased in all age groups, with the exception of extremes, in which there is a trend for stability in the study period. The incidence was already very low among children up to 15 years old, since the beginning of the study period. In 2007, there was certainly already a direct effect of HBV vaccination among younger people. Cases in patients under 15 that are still registered are sporadic (only 18, in 2017, and 20, in 2018, across the country) and may refer to the most vulnerable sections of the population and to regions with difficult access to achieve good vaccination coverage.

In populations with low or moderate prevalence of HBV infection, sexual transmission accounts for the majority of infections.[9] The Ministry of Health estimates that roughly 60% of HBV infections in Brazil were acquired by sexual contact in the last two decades.[10] The absence of a decline in cases over 60 years old may indicate that the increase in the population`s expectation and quality of life has extended their active sexual life, increasing the period of sexual exposure in a vulnerable

group, since vaccination is not a habit. The recent upsurge in sexually transmitted infections (STIs), with syphilis as the most dramatic example, suggests that the incidence of hepatitis B has not increased in the country thanks to the protection provided by vaccination.[11] However, the older strata of the population did not benefit from vaccination against HBV, which has only been released for all ages more recently. Vaccination coverage until 2017 was less than 33% in individuals over 50 years old.[12] The need to intensify prophylaxis strategies in the older age groups is evident, with vaccination and campaigns to practice safe sex with a barrier, aiming at controlling the disease by 2030.[1,13]

The main limitation of the present study is to be based on data from a national system of disease notifications, systematically subject to underreporting. In addition, there is a risk of inaccuracy in some of the diagnosis of individual cases, and there is no way to review individual patient records, which are not available in the system. In any case, this is the official information collected by the Brazilian epidemiological surveillance system, which serves to analyze the endemic behavior of diseases and to make decisions by health authorities. Even considering the possibility of underreporting and poor classification of some cases, the temporal trend should not have been influenced by these factors, since there is a progressive tendency to improve the system over time.

CONCLUSION

The present study, exploring official data from SINAN, shows a drop in the incidence of acute hepatitis B in Brazil between 2007 and 2018, probably thanks to the direct and herd protection effect due to vaccination, which started in 1998. However, the downward trend is lower in older sections of the population, especially over 60, in which the incidence rate remains stable. Consequently, the proportion of individuals over 40 among cases of acute hepatitis B in the country has been growing.

Participation of each author

Gustavo Henrique Vieira Carvalho, João Pedro Parreira Faria, Mauricio Aparecido Alexandre Silva and Francisco José Dutra Souto contributed to the study design and data interpretation. Gustavo Henrique Vieira Carvalho and Mauricio Aparecido Alexandre Silva created the figures and tables. Gustavo Henrique Vieira Carvalho and João Pedro Parreira Faria wrote the first version of the text. Francisco José Dutra Souto performed the statistical analysis and revised the first version of the text, giving it its final shape. All authors read and agreed with the final form of the article and its conclusions.

Financing

No need for funding because it is a study on secondary data.

Conflict of interests

Nothing to declare.

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Received on: 11.17.2019
Approved on: 04.17.2020