Temporal trends of Acute Hepatitis A in Brazil and its regions

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Research Article

Keywords: Hepatitis A, Hepatitis A virus, Epidemiology, Trends

Posted Date: August 30th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1986565/v1

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Abstract

**Background:** Hepatitis A are responsible for 126,000,000 cases of acute viral hepatitis distributed heterogeneously worldwide, high disability-adjusted life year (DALY) rates, especially in low-income countries. Data related to Hepatitis A provides information to improve control-measures and identify population at risk. This study aims to analyze temporal trends of Hepatitis A in Brazil and its regions from 2007 to 2018, based on official notification data.

**Methods:** Data related to Hepatitis A reported cases from 2017 to 2018 were fitted to a join point model by Brazilian regions, Age Groups and Gender, allowing the calculation of Average Annual Percentage Change (AAPC) and Annual Percentage Change (APC) to estimate trends of Hepatitis A in Brazil.

**Findings:** From 2007 to 2018, 65,284 Hepatitis A cases notified in Brazil were available for analysis. The Northeast region reported 18,732 (28.69%) cases, followed by North 18,430 (28.23%), Southeast 14,073 (21.55%), South 7,909 (12.11%) and Central-West 6,140 (9.4%), respectively. Temporal trend analysis showed that Hepatitis A incidence decreased from 2007 to 2016 in all Brazilian regions for individuals with less than 20 years and increased in South and Southeast in males between 10 and 39 years after 2016.

**Conclusions:** Hepatitis A endemicity is heterogeneous among Brazilian regions. In addition, an unexpected outbreak of HAV among Southeast and South adult males in 2016 resembles the outbreak in Europe, revealing a vulnerable population that should be prioritized by vaccination programs and control measures.

Introduction

In 2015, Hepatitis A was responsible for 126,000,000 cases of acute viral hepatitis distributed heterogeneously worldwide, with more than 7,000 deaths due to liver failure. Although deaths related do Hepatitis A Virus (HAV) infection correspond to a small fraction of deaths related to viral hepatitis, HAV have high disability-adjusted life year (DALY) rates, especially in low-income countries (1-3).

The World Health Organization (WHO) classifies Hepatitis A endemicity as High, Intermediate or Low according to the Regional Endemicity Index (REI). This index is composed of children's immunity ratio, defined as the proportion of children between 10 - 14 years immune to HAV (Anti HAV IgG positive), and the adult susceptibility ratio, defined as the proportion of adults between 35 - 44 years who are at risk of HAV infection (Anti HAV IgG negative) (4,5).

High-endemic regions, like South Asia and Sub-Saharan Africa have high Child Immunity and low Adult Susceptibility ratios and are marked by poor sanitary conditions favoring HAV transmission. In contrast, low-endemic regions, like Western Europe and North America, have low Child Immunity and High Adult susceptibility ratios, and are characterized by better hygiene and sanitary conditions and high-socio-demographic development (4,5). Tropical Latin America is classified as an intermediate endemic region, with medium Child Immunity and Low Adult Susceptibility ratios (4). Although Brazil is located in Tropical Latin America, its continental extension and socio-demographic heterogeneity impose a particular setting related to HAV infection, with some estates resembling high developed regions while others low developed ones.

In 2016, low-endemicity regions faced an unexpected increase in Acute Hepatitis A cases. Over 4,000 cases related to three different strains of HAV were reported across the European Union, most of which in unvaccinated adult men who have sex with men (MSM) (6,7).

In the following years, other countries also identified increasing notification of HAV cases unrelated to travel in MSM. Based on these reports, authors suggested that sexual transmission was the main route of transmission in high-susceptible populations (7,8), posing a new prevention challenge to countries with low or intermediate Hepatitis A endemicity.

In Brazil, Acute Hepatitis A is a compulsorily notifiable disease, meaning that its occurrence is monitored by health assistance services, which must report demographic, clinical and laboratory information of each identified case to compose the Viral Hepatitis Database of the National Reportable Disease Information System (SINAN) (9).

In 2016, this database registered an increase of Acute Hepatitis A cases, mainly in the South and Southeast regions, which could be related to the European outbreak. This article intends to explore this hypothesis.

Methods

Hepatitis A data extracted from SINAN Viral Hepatitis database (SINAN Net – Version 5.0) for the period of 2007 to 2018 were anonymized, reviewed and depurated to constitute the study database. The following variables were used:

- Indexing number – serving as an index variable for the database,
• dates of birth and notification,
• state of notification,
• gender,
• Anti-HAV IgM – marked as Reagent, Not-reagent, Undetermined and Not realized

**Case definition:**

Acute HAV Infection (or Acute Hepatitis A): Anti HAV IgM reagent.

**Statistical analysis:**

Cases from 1 to 89 years old at notification were stratified by 10 years interval. Population age stratified data from the Brazilian Institute of Geography and Statistics (Instituto Brasileiro de Geografia e Estatística - IBGE) allowed the calculation of the national and regional notification rate of Hepatitis A, defined as cases per 100,000 inhabitants by gender and age group.

Data were fitted to a joinpoint regression model, with up to 2 joinpoints and constant variance. The model, selected by Schwarz Information Criteria (BIC) (10), allowed estimation of temporal trends of Hepatitis A incidence through the Annual Percent Change (APC) for time segments (e.g. from 2007 to 2014) and Average Annual Percent Change (AAPC) for the full time period (2007 to 2018), both expressed in percentages followed by its value with 95% CI (11). The terms ‘increase’ and ‘decrease’ were used to describe temporal trends when APC or AAPC achieved statistical significance (p < 0.05), otherwise, the term ‘stable’ was used. The Joinpoint Regression Program 4.7.0.0 was used for the analysis.

**Results**

In Brazil, 65,284 Hepatitis A cases were reported from 2007 to 2018. Northeast region reported 18,732 (28.69%) cases while North 18,430 (28.23%), Southeast 14,073 (21.55%), South 7,909 (12.11%) and Central-West 6,140 (9.4%). The larger notification rate, cases per 100,000 inhabitants, was observed in the North from 2007 (13.91) to 2016 (1.64), when the Southeast surpassed all other regions until the last year of the study.

Trend analysis estimated that the overall incidence of Hepatitis A in Brazil decreased 17.5% from 2007 to 2018. This pattern was found in all Brazilian regions, except to Southeast where the overall incidence remained stable in the full period. In addition, no joinpoints are identified in Central-West, one joinpoint was identified in 2014 in North, Northeast, and South, and one joinpoint was identified in 2016 in Southeast.

Regarding North, Northeast and South models, the incidence of HAV remained stable from 2007 to 2014 in the North and decreased 18.5% and 27.7% in the Northeast and South, respectively. From 2014 to 2018, HAV incidence decreased 52.4% in the North, 45.8% in the Northeast and remained stable in the South region. As for Southeast model, Hepatitis A incidence decreased 15.7% from 2007 to 2016 and remained stable from 2016 to 2018. See Table 1 for details.

<table>
<thead>
<tr>
<th>Brazilian region</th>
<th>AAPC with 95% CI</th>
<th>APC with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>-17.5 (-22.3 to -12.4)</td>
<td>-1.7 (-15.0 to 13.7)</td>
</tr>
<tr>
<td>North</td>
<td>-24.5 (-33.7 to -14.1)</td>
<td>2007 to 2014: -1.7 (-15.0 to 13.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2014 to 2018: -52.4 (-66.3 to -32.9)</td>
</tr>
<tr>
<td>Northeast</td>
<td>-29.7 (-35.5 to -23.5)</td>
<td>2007 to 2014: -18.5 (-26 to -10.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2014 to 2018: -45.8 (-56.8 to -32.0)</td>
</tr>
<tr>
<td>Central-West</td>
<td>-25.1 (-30.8 to -18.9)</td>
<td>-</td>
</tr>
<tr>
<td>Southeast</td>
<td>-2.6 (-12.4 to 8.2)</td>
<td>2007 to 2016: -15.7 (-20.6 to -10.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2016 to 2018: 86.6 (2.4 to 256.7)</td>
</tr>
<tr>
<td>South</td>
<td>-18.4 (-23.2 to -13.4)</td>
<td>2007 to 2014: -27.7 (32.5 to -22.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2014 to 2018: 0.8 (-14.1 to 18.4)</td>
</tr>
</tbody>
</table>

(Table 1)
Age group analysis reveals that the overall incidence of Hepatitis A in Brazil decreased from 2007 to 2018 in individuals with less than 20 years and remained stable in individuals with more than 20 years. For individuals below 20 years, the incidence of Hepatitis A remained stable from 2007 to 2014. Thereafter, it decreased 59.3% and 43.3% in age groups 1 to 9 and 10 to 19, respectively. For individuals between 20 and 40 years old, the incidence remained stable until 2016, when it increased 56.1% and 55.4% for the age groups 20 to 29 and 30 to 39, respectively. Figure 1 illustrates these findings and Table 2 shows the details of the analysis.

### Table 2
AAPC and APC values, expressed as percentages, of Brazil for age groups below 40 years. In bold, values that achieved statistical significance (p < 0.05).

<table>
<thead>
<tr>
<th>Age groups</th>
<th>AAPC with 95% CI</th>
<th>APC with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 9</td>
<td>-34.9 (−43.7 to -24.8)</td>
<td>2007 to 2014: -14.9 (−27.7 to 0.1)</td>
</tr>
<tr>
<td></td>
<td>2014 to 2018: -59.3 (−72.3 to -40.2)</td>
<td></td>
</tr>
<tr>
<td>10 to 19</td>
<td>-25.6 (−36.0 to -13.6)</td>
<td>2007 to 2014: -13.2 (−26.7 to 2.8)</td>
</tr>
<tr>
<td></td>
<td>2014 to 2018: -43.3 (−62.0 to -15.3)</td>
<td></td>
</tr>
<tr>
<td>20 to 29</td>
<td>-4.5 (-9.9 to 1.3)</td>
<td>2007 to 2016: -14.3 (−17.1 to -11.5)</td>
</tr>
<tr>
<td></td>
<td>2016 to 2018: 56.1 (9.0 to 123.4)</td>
<td></td>
</tr>
<tr>
<td>30 to 39</td>
<td>2.8 (-2.3 to 8.1)</td>
<td>2007 to 2016: -6.3 (−8.9 to -3.6)</td>
</tr>
<tr>
<td></td>
<td>2016 to 2018: 55.4 (13.9 111.9)</td>
<td></td>
</tr>
</tbody>
</table>

(Fig. 1)

The pattern encountered for age groups below 20 years is seen in all Brazilian regions with different intensities, while the pattern observed in individuals between 20 and 40 years old is seen in the Southeast and South.

(Table 2)

Age group analysis of Southeast detailed by Gender reveals that in males with 20 to 29 years, 30 to 39 and 40 to 49 years, the incidence of Hepatitis A from 2007 to 2018 increased 13.6%, 19.4% and 13.1%, respectively. Data fit a model with one joinpoint in 2016. From 2007 to 2016, HAV incidence decreased or remained stable according to age group, while from 2016 on, HAV incidence increased up to 252.5%. This pattern does not occur in females of the same age groups, where HAV incidence decreases or remains stable. See Table 3 for details.

### Table 3
AAPC values, expressed as percentages, of Southeast age groups below 40 years for Males and Females. In bold, values that achieved statistical significance (p < 0.05).

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Males (AAPC with 95% CI)</th>
<th>Females (AAPC with 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 9</td>
<td>-30.1 (-36.6 to -22.9)</td>
<td>-26.3 (-36.8 to -14.1)</td>
</tr>
<tr>
<td>10 to 19</td>
<td>-8.7 (-25.3 to 11.5)</td>
<td>-12.2 (-32.5 to 14.2)</td>
</tr>
<tr>
<td>20 to 29</td>
<td>13.6 (0.5 to 28.3)</td>
<td>1.4 (-14.3 to 20.0)</td>
</tr>
<tr>
<td>30 to 39</td>
<td>19.4 (7.8 to 32.2)</td>
<td>6.7 (-4.5 to 19.1)</td>
</tr>
<tr>
<td>40 to 49</td>
<td>13.1 (3.8 to 23.3)</td>
<td>4.4 (-0.4 to 9.4)</td>
</tr>
</tbody>
</table>

(Table 3)

South region also experienced an increase of 153.8% of Hepatitis A incidence from 2016 to 2018 in males between 20 and 29 years. Like Southeast region, this result was not observed in females.

**Discussion**

Trend estimates of hepatitis A incidence reveals two patterns: first for North, Northeast, and Central West regions where the overall incidence decreases, mainly after 2014, and second, for the Southeast and South regions, where incidence decreases until 2016, increasing mainly in males between 20 and 40 years old after 2016. Other authors also described similar results in a 2019 study that analyzed hepatitis A reported
cases in large-Brazilian cities (12). Both patterns can be explained by the Brazilian socio-demographic heterogeneity and by the improvements of national sanitation and the Brazilian vaccination program.

The North, Northeast and Central-West regions have the higher Gini Index (zero equals no social inequality), higher percentage of population without access to sanitation and without regular waste collection as compared to South and Southeast regions (13). These indexes are related to HAV main route of transmission - ingestion of contaminated food or water – therefore, it's expected that the first three regions behave as High Endemicity regions, i.e. high proportion of children immune to HAV and low adult susceptibility. The National Survey of Viral Hepatitis, published in 2008 (14), confirmed that the North, Northeast and Central-West regions are indeed high endemic regions for Hepatitis A. Regarding South and Southeast regions, only studies of sub populations are available (15) suggesting that both regions have low endemicity for Hepatitis A.

The Brazilian sanitation improvement observed between 2007 and 2017, which increased sewer extension from 184,000 km to 312,000 km and population with access to treated sewer from 32.5–46% (13), could have contributed to the observed decrease in Hepatitis A incidence from 2007 to 2014 in Brazil and some regions (Table 1).

Another improvement, and probably the most significant, relates to the Brazilian vaccination program. Vaccine against Hepatitis A is available in Brazil since 1990s, but only in 2014 it was incorporated into the National Immunization Program, encompassing infants from 15 to 24 months of age, with two doses with six months interval. In 2017, the program expanded to children with less than 5 years old (16), and vaccine coverage achieved more than 90% of the target population (17, 18). The decrease in Hepatitis A incidence observed after 2014, mainly in individuals with less than 20 years (Table 2), probably is a reflection of a successful vaccination program.

The second pattern observed in South and Southeast from 2016 to 2018, suggests the existence of a vulnerable population in these regions. As already discussed, both regions probably behave as low endemicity regions, therefore a high proportion of adults should be susceptible to Hepatitis A. The increase in HAV incidence observed after 2016 ,mainly in males between 20 and 40 years (Table 3), resembles the epidemiologic pattern found in Europe, world region with low endemicity, where most cases occurred in MSM (6–8). Although the data available for this study alone do not allow to evaluate this hypothesis, results published by others relating Hepatitis A from 2016 to 2018 point in this direction (19, 20).

Limitations of our work include the source of data and assumed hypothesis. Although revised, depurated and consisted, it's not possible to guarantee the absence of duplicate cases in the database. Additionally, the "steady state" hypothesis concerning the process of notification in Brazil is not confirmed. However, unlike chronic hepatitis, in the last decade no new treatments against Hepatitis A were developed or tracking campaigns realized, therefore, if the notification process remained constant ("steady state") from 2007 to 2018, it's possible to attribute reported cases variation to true change in population dynamics. As for strong points, our work analyzed Brazil and its macro-regions through a methodology used by other authors for temporal trends analysis of infectious diseases (21), allowing a proper comparison of world regions.

The results presented here reveal the success of vaccination programs and national sanitation improvement to control HAV transmission. Also, they suggest that Hepatitis A endemicity is heterogeneous within Brazilian regions, therefore, regional differences must be accounted for in the strategic planning of control measures. Following this line of thought, after the identification of new cases in 2016, the Brazilian government expanded the Hepatitis A Vaccination Program and, since 2018, it has started to encompass individuals who practices oro-anal sexual intercourse (22).

In conclusion, temporal trends point to regional differences related to Hepatitis A endemicity and the existence of an adult population exposed to Hepatitis A that should be prioritized by control programs.

Abbreviations

HAV: Hepatitis A Virus
SINAN: Brazilian National Notifiable Disease Reporting System
BIC: Bayesian Information Criteria
APC: Annual Percent Change
AAPC: Average Annual Percent Change

Declarations

Ethical approval:
This work was approved by the Ethical Research Committee of the Universidade Federal de São Paulo – UNIFESP.

Consent for publication:

Not applicable.

Availability of Data and Materials:

The datasets generated and/or analysed during the current study are available in the SINAN - Sistema Nacional de Agravos de Notificação repository, http://portalsinan.saude.gov.br/ - accessed in 06-11-2020.

Funding:

This study was partially supported by: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - CAPES (GG); National Council for Scientific and Technological Development - CNPq (MNB); Fundo Nacional de Saúde of the Brazilian Ministry of Health (FNS-MoH) – (Grant # TED 27/2015) (MNB); and by LIM01-HCFMUSP (MNB and LFL). Sponsors have no role on either study design, data analysis or writing of the manuscript.

Authors’ contributions:

All authors contributed to study design, data analysis and discussed the results. Giuliano Grandi and Marcelo Nascimento Burattini wrote the manuscript. The study was supervised by Marcelo Nascimento Burattini.

Acknowledgments:

We acknowledge Gerson F.M. Pereira and Fábio Mesquita for their helpful comments and for facilitating access to national data.

Competing Interests:

Authors declare they have no conflict of interest related to the work described in this manuscript.

Conflict of Interest:

Authors state that they have no conflicts of interest related to the material presented in this manuscript.

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Figures
Figure 1

Notification rates of Hepatitis A in Brazil. Square markers show age groups in which AAPC decreased and triangle markers show age groups in which APC increased from 2016 to 2018 and