Sociodemographic and spatiotemporal profiles of hepatitis-A in the state of Pará, Brazil, based on reported notified cases

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Ethics approval and consents: the study used secondary data available for public unrestricted access; without identifying the individuals. The results were aggregated at the municipality level; therefore, without having to go through the Brazilian Research Ethics Committee (CEP); in accordance with Law No. 12;527/2011 that ensures public access to information (http://www.planalto.gov.br/ccivil_03/_ato2011-2014 /2011/lei/ l12527.htm). The Geoprocessing Laboratory of the Evandro Chagas Institute of the Ministry of Health of Brazil has the authorization of the Public Health Secretariat of the State of Pará (SESPA) for the use and publication of data from the Information System for Notifiable Diseases (SINAN) and Epidemiological Surveillance Information System (SIVEP). The Geoprocessing Laboratory of the Evandro Chagas Institute (of the Ministry of Health of Brazil) is authorized to use and publish the data analysis. Data availability is made by the respective data sources. The data processing scripts can be made available on demand for possible interested parties. We also declare that the applied algorithms, data and data analyses can be made available upon request.

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Abstract

Hepatitis-A virus is a worldwide healthcare problem, mainly affecting countries with poor sanitary and socioeconomic conditions. This communication evaluates the spatiotemporal variability of the disease's socioepidemiological profile in one of the endemic Brazilian regions (Pará State) prior to (2008-2013) and after (2014-2017) the launch of the national public vaccination programme. Hepatitis-A epidemiological reports concerning Pará State - Brazil - were used for this study including municipality-level data of the disease's reported positive notification cases (PNCs). The analyses involved socioepidemiological profiling and space-time scan statistics. A total of 5500 PNCs were reported in the study period. On average, PNCs decreased over time throughout the state, with strongest drops after 2015. The PNCs were specific for gender, race/ethnic origin and age group. The predominant gender and race/ethnic groups was male and brown, respectively. While children were the most susceptible age group prior to 2015, there was a shift towards older ages (young and adults) in later years. Those found to be the most affected by the disease, as shown by space-time scan statistics, were people in densely populated municipalities with unsatisfactory sanitary conditions and also less well covered by the public vaccination programme. Despite drops in the number of hepatitis-A PNCs, thanks to the national vaccination programme, the disease still persists in Pará State and elsewhere in Brazil. The present study reinforces the need of continuous prevention and control strategies for effective control and erradication of hepatitis-A.

Introduction

Viral hepatitis is a worldwide healthcare problem caused by five morphologically and antigenically distinct viruses, which are either food-borne (A and E) or parenteral (B, C and D) (Mahboobi *et al*., 2012). According to the World Health Organization (WHO), these infections are responsible for approximately 1.4 million deaths per year around the world, whether from acute infection or hepatitis-related liver cancer and cirrhosis, with hepatitis-A (HAV) alone being the cause of approximately 70,000 deaths annually (WHO, 2016a). According to the Ministry of Health (*Ministério da Saúde* - MS) around 1.7% of all reported deaths between 2000 and 2016 in Brazil were related to HAV (MS, 2018a).

The prevalence of HAV infection increases with age, something which compromises effective public infection incidence assessments (Nunes *et al*., 2014). It can cause debilitating symptoms and lead to acute liver failure associated with high mortality (WHO, 2019). HAV also poses a great threat to women in the gestational period, since it can result in uterine contraction, potentially causing premature birth (Elinav *et al*., 2006). Transmission can occur through direct contact between a susceptible and an infected person, though the faecal-oral route is the most common pathway (WHO, 2011). Consequently, distribution of the disease is intimately related to sanitation (WHO, 2016a), social interaction (Clemens *et al*., 2000; Jacobsen and Koopman, 2005) and environmental conditions (Paula *et al*., 2001; Parashar *et al*., 2011). HAV transmission may also be specific to certain population groups, such as age, literacy, gender, as well being seasonal (WHO, 2009a; MS, 2018b).

Climate change is expected to intensify as a result of unmitigated environmental changes (WHO, 2009b), something that can lead to increased infectious-disease burdens in the future (UN, 2007), especially for water-borne diseases like HAV (Pal *et al*., 2016; Bahrami *et al*., 2020; Desbordes, 2021). Given the tendency of impacts of this kind targeting children, the poor and women (WHO, 2014), new healthcare policies and strategies should be promoted to encompass differences in populations, *e.g*., gender (Marcheggiani *et al*., 2010). HAV is considered endemic in Brazil, where it mainly affects children, teenagers and young adults (Clemens *et al*., 2000; MS, 2002). Between 2005 and 2009, the disease was considered the predominant form of hepatitis in Brazil (Ximenes *et al*., 2010; Zorzetto, 2011). Nowadays, its endemicity is considered of intermediate risk nationwide (Vitral *et al*., 2014), while the northern and mid-western regions are considered having higher than average HAV infection incidence (Zago-Gomes *et al*., 2005; MS, 2018a). In the northern region, the mortality rate due to this infection has been increasing since 2013. Indeed, its mortality has doubled between 2012 and 2016 to reach 35 cases per million inhabitants (MS, 2018a).

The anti-HAV vaccine has been available in Brazil through private health agencies since 1992 (MS, 2013), and only after 2014 did it make it into the Brazilian National Vaccination Calendar of the Unique Health System (*Sistema Único de Saúde* - SUS) for children between 12 months and 2 years of age (MS, 2014). The vaccine is indicated for vulnerable people, such as those with immunodeficiency, chronic liver disease, coagulopathy, cystic fibrosis, those with HIV infection aged ≤13 years, carriers of hepatitis B or C virus, organ donors, *etc*. (MS, 2006; WHO, 2009a; Sartori *et al*., 2012; Paraná and Schinoni, 2013). Universal vaccination is recommended for countries with intermediate-level endemicity, such as Brazil (WHO, 2000; Sartori *et al*., 2012). The distribution of HAV infection incidence in Brazil is irregular (Ximenes *et al*., 2010; Zorzetto, 2011; MS, 2018a). In the North, the incidence rate is nearly 7 times higher than the national average (Brasil and Ministério da Saúde, 2021; MS, 2018a), which is reflected by the increasing HAV-related mortality rates there (MS, 2018a). The disease is mostly concentrated in the states Pará and Amazonas (Dutra *et al*., 2018).

Despite improved sanitary conditions in Brazil (Velasco, 2017), the situation in Pará State is yet precarious (AMAE, 2014; Borja, 2014; Aguiar *et al*., 2020), which constitutes a social problem that can result in high morbidity (Rodrigues *et al*., 2010). Given Pará's trend towards an older population distribution (Campos and Gonçalves, 2018) and HAV's positive association with age (Hollinger and Ticehurst, 1996), more cases of the disease can be expected in the future. Based on the current sanitary conditions in Pará, its historical HAV record and current level of incidence, continuous monitoring is important for predicting future disease burdens and trends (Daw *et al*., 2014). Furthermore, though the general control measures are clear, effective strategies must also consider the epidemiologic specifics of each region. HAV infections as well as other infectious diseases can quickly spread over political borders by means of migration (Tuite *et al*., 2018) or by goods transportation, *i.e*. mainly food and water (Saker *et al*., 2002; WHO, 2011; Kurup *et al*., 2019). For some countries, HAV appears to be more closely related to developed regions, especially for those with high population densities (O'Brien and Xagoraraki, 2019), while for other countries, such as Brazil, it appears to be more closely related to less developed regions (Stoitsova *et al*., 2015; Pal *et al*., 2016; Santos *et al*., 2019; Bahrami *et al*., 2020). Therefore, it is utterly important to account for the spatiotemporal dynamics of this and other water-borne diseases (Desbordes, 2021) in order to achieve a better understanding of the main transmission patterns leading to more effective control strategies (Zimmerman *et al*., 2011; WHO, 2014).

Given the importance of effective prevention and control of HAV in places with poor sanitary condition, a retrospective spatiotemporal epidemiological approach (Zhu *et al*., 2018) could reveal priority measures enabling meaningful input from key stakeholders (Stoitsova *et al*., 2015; WHO, 2016b; Kurup *et al*., 2019). With this in mind, we applied a longitudinal study approach as described by Coggon *et al*. (1997). The spatiotemporal distribution of notified cases of HAV infection was analysed considering the period before (2008-2013) and after (2014-2017) the launch of the vaccination programme for the general public. These analyses were conducted in two steps starting with a study of the temporal variations in the sociodemographic profile of reported HAV cases in the study area, followed by assessment of space and space-time characteristics of these cases.

Materials and methods

Study area

As seen in Figure 1, the study area comprised the whole state of Pará. According to the Brazilian Institute of Geography and Statistics (IBGE), Pará is located in the northern region of Brazil, encompassing a territorial area of 1.2 million km^2 with six mesoregions, 22 microregions and 144 municipalities (IBGE, 2017). The state has an human development index (HDI) of 0.646, with gross income index (GII) of 0.646, a life expectancy index (LEI) of 0.789, and an education index (EI) of 0.528 (IBGE, 2013). Pará had an estimated 8.37 million residents (4% of the Brazilian population) in 2017 (IBGE, 2019a).

The northern region has precarious sanitary conditions, with less than 50% of its municipalities with access to proper sanitation (de Aguiar *et al*., 2020). The region has more diseases related to inadequate sanitation than the rest of the country, and Pará scores highest in this respect among all the northern states (de Aguiar *et al*., 2020). Despite its natural water abundance, the whole northern region lacks regulated water supply, which impinges on personal hygiene (de Aguiar *et al*., 2020). According to the national water authority (*Agência Nacional de Águas e Saneamento Básico* - ANA), Pará's water bodies have no public management directives, no state planning, or there is not even a public billing policy for water usage (ANA, 2013a). The water sources are mostly superficial, which makes them susceptible to contamination by sewage, residential septic tanks and leaching (Vasconcelos *et al*., 2016), which contributes to the spread of water-borne diseases. Only 25% of all Pará's municipalities have 55% or more of its sewage collected and treated, while half of them rely on mainly non-treated sewage (ANA, 2013b). The remaining 25% are municipalities that lack any kind of sewage treatment or disposability. Pará is segmented into six Planning Hydrographic Units (PHU), with specific pressure levels (Lima *et al*., 2010).

Data sources

Hepatitis A-infected cases

Patient data, obtained from the Notifiable Disease Information System (SINAN) of the Ministry of Health, consisted of Pará residents with HAV infection covering the period January 2008 to December 2017. All data obtained were without personal names and addresses to ensure and maintain the confidentiality of the study. The annual incidence by municipality was derived from the number of reported positive notification cases (PNCs) per population number times 100,000. The annual population data in each municipality was retrieved from IBGE. The equation for aggregating the data by municipality and year takes the form:

$$Incidence_{(year,municipality)} = \frac{PNC_{(year,municipality)}}{Population\ size_{(year,municipality)}} * 100{,}000 \quad (1)$$

Demographic data and education

The PNC data were aggregated according to age, gender, race/ethnicity and education-level. Age made up five groups: child 0-11; teenager 12-18; young 19-29; adult 30-59; and elderly 60+ following the classification proposed by Santos *et al*. (2019). Race/ethnicity encompassed the following groups: black; brown; ignored; indigenous; white and yellow; while the education levels were classified into 11 groups (according to SINAN): illiterate; incomplete elementary school; completed elementary school; incomplete middle school; completed middle school; incomplete high school; completed high school; incomplete under graduation; completed under graduation; ignored; and non-applicable (N/A).

Sociodemographic data

The population coverage by the annual HAV vaccination and the annual number of live births per municipality data were obtained from the Information Technology Department of the Public Health Care System (*Departamento de Informática do Sistema Único de Saúde* - DATASUS) platform (MS, 2019). Data comprised the annual vaccination per municipality for the period between 2014 and 2017. Prior to 2014, the Brazilian Government provided the anti-HAV vaccine only for vulnerable individuals as described above. Consequently, there was an extremely low vaccination coverage countrywide, with less than 1% of children between 1 and 4 years old vaccinated.

Annual municipality sanitation data were obtained from the Brazilian National Sanitation System (SNIS) that covers the treated sewage percentage per municipality per year. The SNIS variable code (IN046) is an index based on the assumption that the sewage generated volume is the same as the volume of consumed water (SNIS, 2014). It is related to the sewage volume treated (ES006), the exported treated gross sewage volume (ES015), the treated water volume (AG019), and the consumed water volume (AG010) as given by the equation:

$$\mathrm{IN046} = \frac{(ES006 + ES015)}{(AG010 + AG019)} * 100 \quad (2)$$

The Brazilian Ministry of Health provides financial support for eliminating sexually transmitted diseases (STDs), the human immunodeficiency virus (HIV) and hepatitis. The budget destined for the development of socioeconomic plans, policies and respective managements in Pará State were obtained for the period

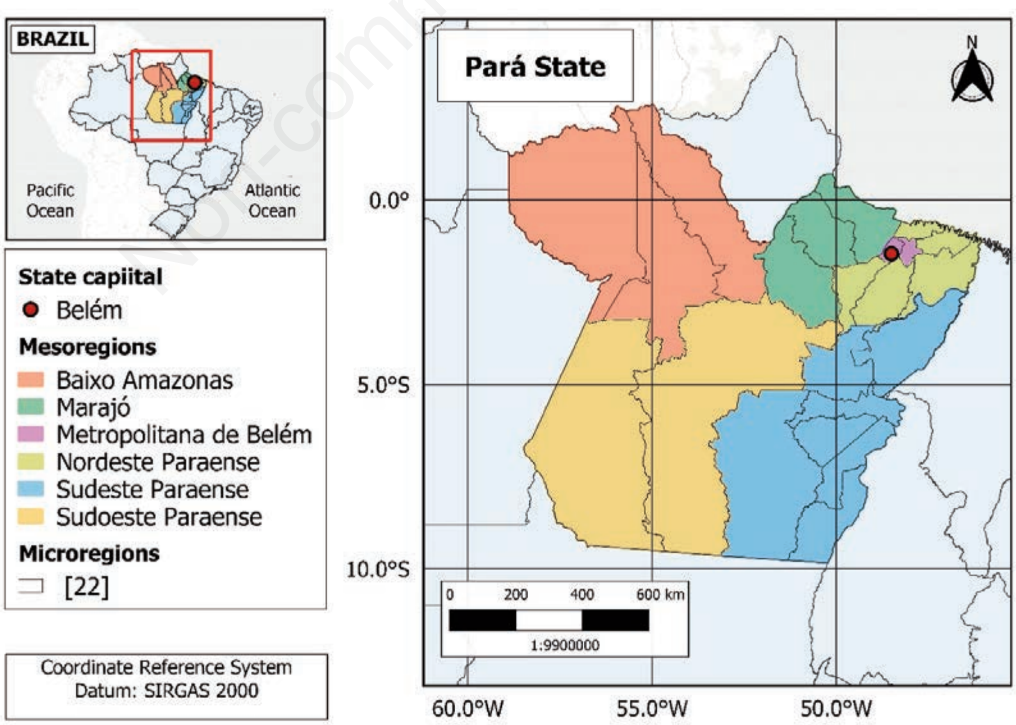

Figure 1. Map showing the state of Pará with its meso and microregions comprising the study area. Data source: IBGE (IBGE, 2019b). Figure generated from QGIS software (version 3.18).

between 2014 and 2017 (Brasil, 2019). This dataset, which includes public health-related investments, was applied to investigate temporal trends in the Brazilian Federal Government's investments for Pará in this respect. The data discriminated type, year, month, and municipality of investment. Since 2013, Mojuí dos Campos, that was previously part of Santarem Municipality in northwest Pará, became a municipality on its own. This resulted in an increase of the total number of municipalities in Pará from 143 to 144. Therefore, all sociodemographic data prior to 2013 were gathered for 143 municipalities and after that period for 144 municipalities. Geospatial data for all Brazilian political administrative subunits (*i.e.* mesoregions; microregions; and municipalities) were obtained from IBGE (2019b).

Spatiotemporal analyses

An incidence analysis was applied to assess the trend and seasonality of HAV transmission across the state of Pará. A candle plot (box plots for each year) was used to visualize the temporal trend of HAV incidence. The box-plot whiskers were evaluated using the standard equation of 1.5 times the interquartile range (IQR) that was evaluated as the difference between the 3rd and 1st quartiles of the data distribution. Under Gaussian distribution supposition, the IQR range represents 99.7% of the data distribution (Krzywinski and Altman, 2014). The box-plot analysis was performed using Python (Version 3.x) programming language.

The annual average incidence of HAV infections in Pará State was statistically compared by the ANOVA test. The statistical significance, when achieved, was checked by a post-hoc Tukey's pairwise, multi-comparison test (Lock *et al*., 2017) to indicate the most dissimilar annual groups (Bussab and Morettin, 2010). PNC occurrence was evaluated with respect to residential zone, gender, education, race/ethnicity, and age, while also paying attention to its temporal variation with respect to potential changes derived from the national public vaccination programme. Pair-wise analyses were assessed between the number of PNCs reported from January 2008 to December 2014 (*i.e.* including the first year of the public vaccination programme) and that of PNC reports after January 2015 to December 2017.

The temporal aspect of the HAV incidence was evaluated by the Pearson's cross-correlation analysis. This analysis was performed using Python (Version 3.x) programming language, and α=10% was considered statistically significant. The annual variation of HAV incidence; as well as municipality sanitation efforts, and the vaccination coverage by municipality were evaluated by multi-plot (FacetGrids) maps generated by Python (Version 3.x) programming language. Each figure had their colour-ramp and respective colour-bar scaled for common minimum and maximum thresholds (MinT and MaxT, respectively) towards the whole study period (2008-2017) for better assessment of the temporal variability. The adopted MinT is the minimum value of the given evaluated parameter (*i.e*., incidence) of the whole time-series data. The MaxT is the median value of all municipalities' specific annual maxima. Therefore, for the evaluation of MaxT, two steps were required: i) obtain an annual time-series of all maximum values for a given variable (*i*) from all municipality-specific data; and ii) extract the median of that maximum time-series. This algorithm allowed us to easily assess potential areas of interest for this variable without excessively squeezing or extending the data's colorimetric colour-range.

Space-time scan statistics

Space-time scan statistics was applied in order to investigate the most likely clusters and respective temporal windows with the largest log likelihood ratios (LLRs) (Kulldorff, 1997; Pellegrini and Kulldorff, 2016) for the two periods (before and after public vaccination). The detected clusters and LLRs were evaluated by the equation:

$$\mathrm{LLR} = \log\left\{\left(\frac{C}{n}\right)^{c} * \left[\frac{(C-c)}{(C-n)}\right]^{(C-c)}\right\} \tag{3}$$

where C stands for the total number of cases; c, for the number of observed cases inside the window; and n for the number of expected cases inside the window. Statistical significance was evaluated with the Monte Carlo simulation method (replications set at 999 and the significance level at P=0.05). The maximum radius of the window was set at 50% of the total population at risk and the time (maximum height of the cylinder) at 50% of the total study period. For this, a discrete Poisson-based model was applied, in which the number of PNCs in an area would be Poisson distributed according to a known underlying population at risk (Kulldorff *et al*., 1998; Kulldorff, 2001). The null hypothesis assumed that the relative risk (RR) of the incidence is the same within the space and the time domains. The spatial-scan statistic was calculated with the SatScan software (Kulldorf *et al*., 1998) using the municipality centroids as coordinate references (Pellegrini and Kulldorff, 2016).

Results

Temporal analysis

The number of PNCs of HAV infections in Pará State and the calculated incidence ranged from 717 and 9.79, respectively, in 2008 to 52 and 0.62, respectively, in 2017 (Table 1). The highest values reached 809 and 10.38, respectively, in 2012, *i.e.* the years before the public vaccination programme started (MS, 2014). A total of 5500 PNCs with an annual mean of 550 cases and a calculated incidence of 7.09 was reported in the study period. The PNC annual mean and median varied around 5 and 1 cases, respectively, during the study period. With respect to incidence (Figure 2), the annual values were deemed significant based on the ANOVA test ($P=8.65*10^{-07}$ at $<\alpha=0.05$). According to the Tukey multi-compar-

Table 1. Annual variation of hepatitis-A presence and positive notified new cases in Pará State, Brazil 2008-2017.

Year	PNC (no.)	Incidence
2008	717	9.79
2009	636	8.53
2010	445	5.98
2011	718	9.34
2012	809	10.38
2013	693	8.70
2014	790	9.78
2015	492	6.02
2016	148	1.79
2017	52	0.62

PNC, positive notification cases.

ison test, major changes in incidence were observed between 2009-2010, 2014-2013, 2014-2015, and 2015-2016 (Table 2).

Regarding land use and HAV infections during the study period, the urban number of PNCs dominated. It comprised 69.8% of all reported cases corresponding to an average of 2.4 times higher presence than the rural PNCs, and 154 times higher than the peri-urban cases (Table 3). However, with ratios below two for both, urban and rural PNCs were similar in 2012, 2013 and 2015. For other years, the disparity was higher, especially in 2009, when the number of urban PNCs reached a level nearly 3 times higher than that in the rural areas, which was the highest observed during the study.

With respect to race/ethnicity in Pará, the number of PNCs were predominantly found among brown people with an average percentage of 79.8% for the study period as a whole; followed by white people with 11.4%; and black people with 4.0%; while yellow people achieved the lowest number of infections, with 0.6% (Figure 3). The age distribution varied on an annual basis (Table 4). In 2015, prior to vaccination programme, the cases were mainly children (with 54.7%), followed by teenagers (19.8%), young (14.4%), adults (8.9), and elderly (2.2%).

As presented in Figure 4, the spatial distribution of the PNC's age groups not only varied during the study period but was also influenced by the shift in age groups towards more PNCs in the elderly groups (municipalities in warmer colours). Prior to 2015, children were the most commonly infected group; few municipalities had many other HAV infected age groups, and solely two municipalities (Curuá and Ourém) showed a predominance among the elderly. In the following years (after 2015), young and adult dominated, and solely one municipality (*Novo Repartimento*) had many PNCs among the elderly. There was also a notably decrease in PNCs throughout the study area. During this period, the predominant age groups were mostly young and adult, which was

Table 2. Tukey's pair-wise multi-comparison for hepatitis-A incidence in Pará State, Brazil.

Pair	P-value	Significance*
2009-2008	0.84	No
2010-2009	0.01	Yes
2011-2010	1.00	No
2012-2011	0.31	No
2013-2012	1.00	No
2014-2013	0.04	Yes
2015-2014	0.02	Yes
2016-2015	0.03	Yes
2017-2016	1.00	No

*alpha=10%.

Table 3. Annual percentage distribution of positive notified new cases of hepatitis-A per type of residential zone in Pará State, Brazil (2008-2017).

Year	Peri urban (%)	Rural (%)	Urban (%)
2008	1.29	27.00	71.71
2009	1.31	21.48	77.21
2010	0.47	29.34	70.19
2011	0.14	30.80	69.05
2012	0.00	33.60	66.40
2013	0.00	36.12	63.88
2014	0.13	30.20	69.67
2015	0.42	33.61	65.97
2016	1.42	26.95	71.63
2017	0.00	28.00	72.00

Table 4. Annual age group distribution of the positive notification cases of hepatitis-A in Pará State, Brazil (2008-2017).

Age group (%)	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Child	57.6	53.7	53.6	58.7	53.6	54.5	52.4	52.9	42.6	12.8
Teenager	18.1	19.6	19.8	19.9	20.9	19.5	20.8	20.3	20.9	6.4
Young	14.1	16.2	12.3	12.5	13.7	15.2	17.4	13.7	20.2	36.2
Adult	8.4	8.3	11.6	7.1	9.3	9.1	6.9	10.8	12.4	34.0
Elder	1.8	2.3	2.7	1.8	2.4	1.7	2.4	2.2	3.9	10.6

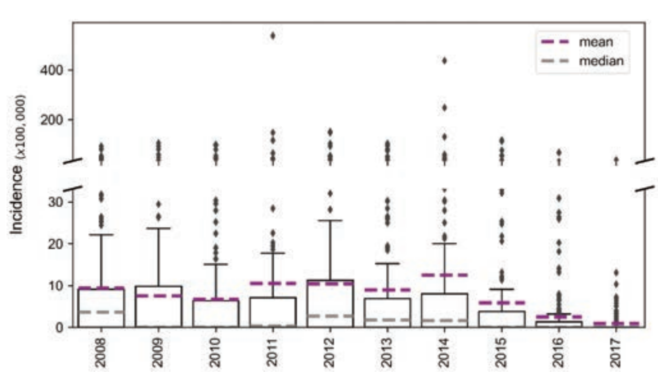

Figure 2. Box-plot distribution of the hepatitis-A incidence in Pará State, Brazil 2008-2017. The annual incidence by municipality was derived from the number of reported positive notification cases per municipality and year per population size for these places and years times 100,000; the annual population data in each municipality was retrieved from IBGE; the epidemiological data was retrieved from the Brazil's Ministry of Health Notifiable Disease Information System (SINAN). Figure created using Python version 3.8.

most evident at the southern municipalities. Lastly, PNC predominance among the elderly was solely detected in one municipality (*Novo Repartimento*).

With respect to literacy levels, the number of PNCs was predominantly found among N/A, incomplete elementary school and incomplete middle school people despite gender (Figure 5). On average, despite literacy level or period studied, men denoted higher values than women. Highest PNCs values per literacy group, gender and year were observed for the years 2011, 2012 and 2013 for both genders; an evidence which reinforce that HAV transmission can be specific to certain population groups, particularly for literacy, and gender, as well as being seasonally specific (WHO, 2009a; MS, 2018b).

The Brazilian Ministry of Health surveillance financial grant

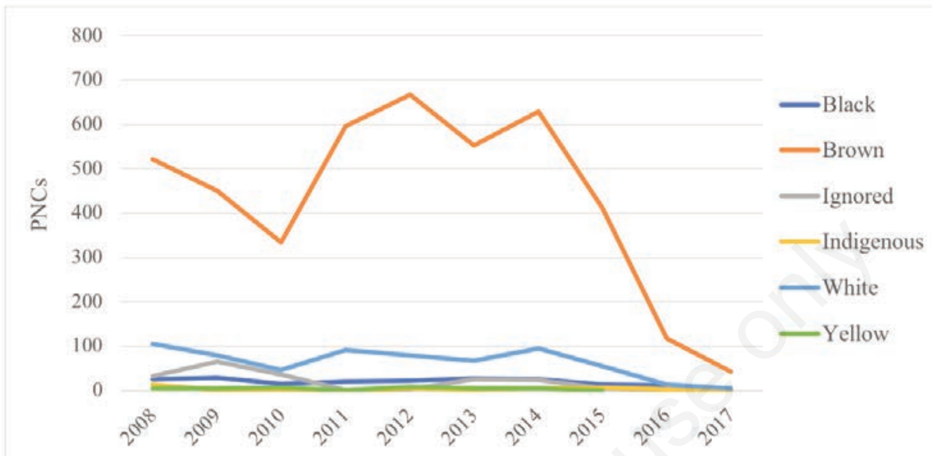

Figure 3. Annual hepatitis-A positive notifiable cases per race/ethnicity in Pará State, Brazil. Data from Brazil's Ministry of Health Notifiable Diseases Information System (SINAN). Figure created using Excel Microsoft Office.

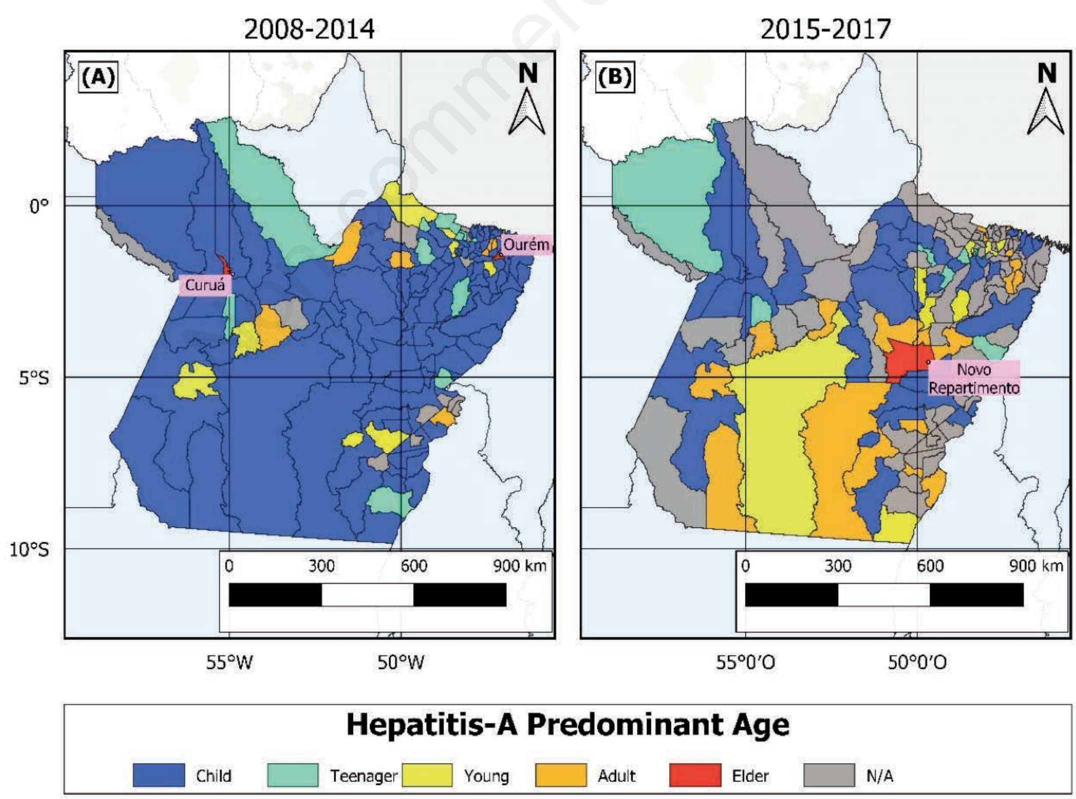

Figure 4. Distribution of the predominant hepatitis-A infections among age groups before (in A) and after (in B) vaccination. Pink boxes give the names of the municipalities where hepatitis-A dominated in the elderly. Figure created using QGIS version 3.18.

(namely, BMH-FG) was constant for the period analysed (Figure 6), but differences between municipalities could vary considerably with a range from 2500 R$ per year up to nearly 34,000 R$. A significant (P<α for alpha=0.05) low cross-correlation (<2%) was observed for the surveillance financial support and the calculated HAV incidence between 1 up to 4 years of temporal shift (no. lags - years) (Figure 7). These findings alone reinforce the need of continuous prevention and control strategies for effective control and erradication of the HAV, and an urge for a revaluation of this Brazilian financial support programme towards a more effective strategy. Pará's annual HAV incidence spatial distribution varied during the study period (Figure 8), with higher incidences observed in Marajó (2008), Sudeste do Pará (2009, 2010, 2016, and 2017), Baixo Amazonas (2011, 2012, 2014 and 2015), and Nordeste do Pará (2013) mesoregions (Table 5 and Figure 9). These mesoregions notably present relatively more underdeveloped sanitation conditions, which may have facilitated disease transmission (IBGE, 2008; SNIS, 2019). Municipality sewage treatment percentage relative to the consumed water index (IN046) denoted small spatial variation between 2008 and 2017 (Figure 10), with variations no higher than 10% between years. For 2016 and 2017, the maximum IN046 values were found in Altamira municipality with a constant value of 80%. Annual HAV vaccination percentage per municipality for the study area denoted a tem-

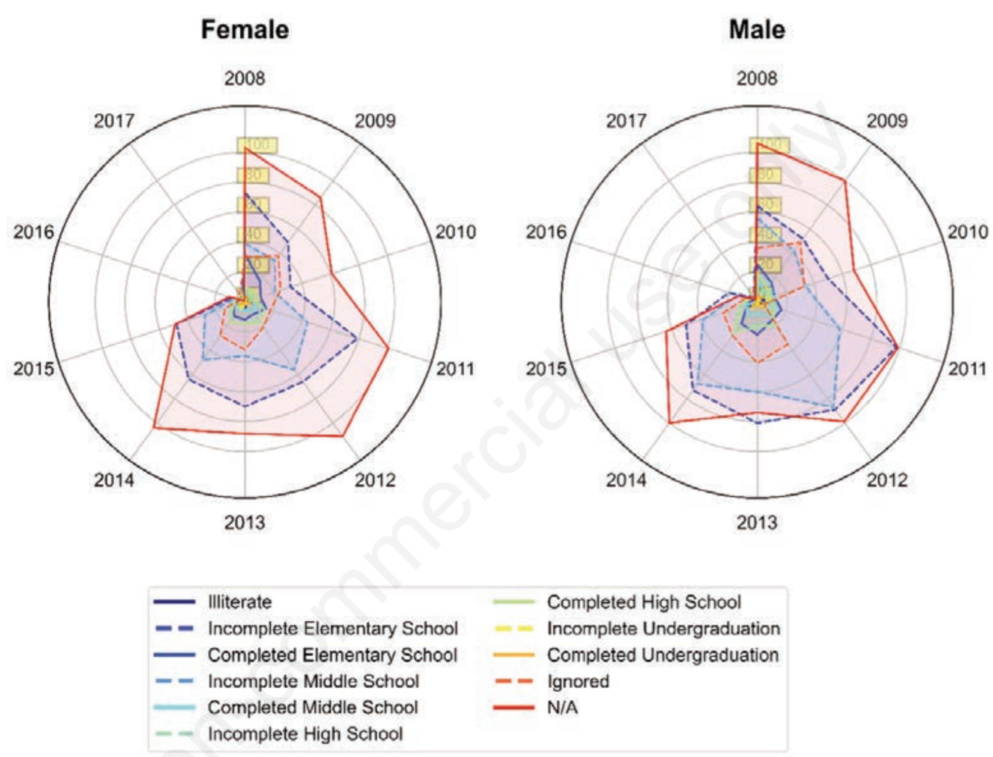

Figure 5. Annual hepatitis-A positive notifiable cases per gender and education group in Pará State, Brazil (2008-2017). Data from Brazil's Ministry of Health Notifiable Diseases Information System (SINAN); literacy groups from Brazilian Institute of Geography and Statistics (IBGE). Figure created using Python (Version 3.8).

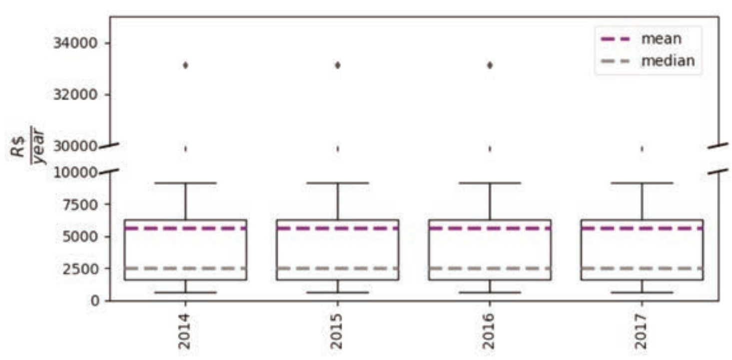

Figure 6. The annual Brazilian Ministry of Health surveillance financial grant (BMH-FG) municipality distribution for Pará. Figure created using Python version 3.8

poral positive increase, with initial coverage rates (in 2014) of nearly 0% up to 80% (in 2017) depending on the municipality (Figure 11). Nevertheless, this temporal positive trend was not constant between the years. Higher vaccination coverage percentages were only seen in 2015 and 2017, while the year 2016 denoted a deterioration in the public vaccination coverage from that of 2015.

Space-time scan analysis

This statistical analysis was only applied for two temporal periods: before and after 2015 (Figure 12). Four HAV incidence clusters were found between 1 January and 31 December 2014, and solely two after 1 January 2015. All detected clusters were statistically significant at the P-value permutation test of 999 random replicates. Regarding the clusters of the first period, three presented a high RR for HAV infection and one (in the Northeast around the state capital Belém) with RR<1. This latter cluster remained spatially stable for the second period. Meanwhile, an RR increase (up to 18.32 times) was detected at the municipalities situated in central-northern part of the state covering 2015, the first year of the second period.

Discussion

Temporal analysis

The temporal variation in the sociodemographic profile of HAV cases detected in this study was characterized by a noticeable decrease after 2015, after which the level of new infections remained stable. Due to the dearth of effective changes in sanitary conditions in the study area (Paungartten *et al*., 2015; Magno, 2017), this initial reduction was deemed to be related to the national public vaccination efforts (Brito and Souto, 2020). The latter stability in hepatitis incidence was with all probability associated with a decrease in the vaccination efforts as the effect was found to be countrywide and not only noted for HAV, but also seen in other vaccination programmes, *e.g*., triple viral (measles, mumps, rubella) and poliomyelitis (Brito and Souto, 2020). Previous studies verified a decrease in notification reports of HAV for children and teenagers in Brazil (MS, 2018a; Souto *et al*., 2019). The present study also evidenced a similar pattern in Pará's notification reports, where there was a shift in reported cases from mostly children towards mostly young people and adults after the national public vaccination programme had started. These findings reinforce that the study area may yet be considered endemic for HAV, in which children, teenagers and young adults are deemed the ones mostly affected by the disease (Clemens *et al*., 2000; MS, 2002).

The variation of HAV in relation to residence, where we discovered a predominance for urban zones, is in agreement with previous studies (O'Brien and Xagoraraki, 2019). It could be associated with different factors: the density distribution of populations (IBGE, 2008; SNIS, 2019), the average total income per household (Stoitsova *et al*., 2015), the problem of waste disposal (Gracie *et al*., 2007), the lack of proper sanitation conditions (Paungartten *et al*., 2015), the high birth-rate (Stoitsova *et al*., 2015), and the con-

Table 5. Municipalities in Pará State, Brazil with maximum hepatitis-A incidence.

Year	Municipality	Mesoregion*	Max incidence (×100,000)
2008	Muaná	Marajó	89.65
2009	Porto de Moz	Baixo Amazonas	89.00
2010	Pau D'Arco	Sudeste do Pará	99.55
2011	Alenquer	Baixo Amazonas	447.14
2012	Alenquer	Baixo Amazonas	151.77
2013	Garrafão do Norte	Nordeste do Pará	90.96
2014	Prainha	Baixo Amazonas	324.56
2015	Belterra	Baixo Amazonas	117.40
2016	Palestina do Pará	Sudeste do Pará	67.53
2017	Pau D'Arco	Sudeste do Pará	37.45

*Mesoregions are also shown for reference. The municipality spatial locations are presented in Figure 9.

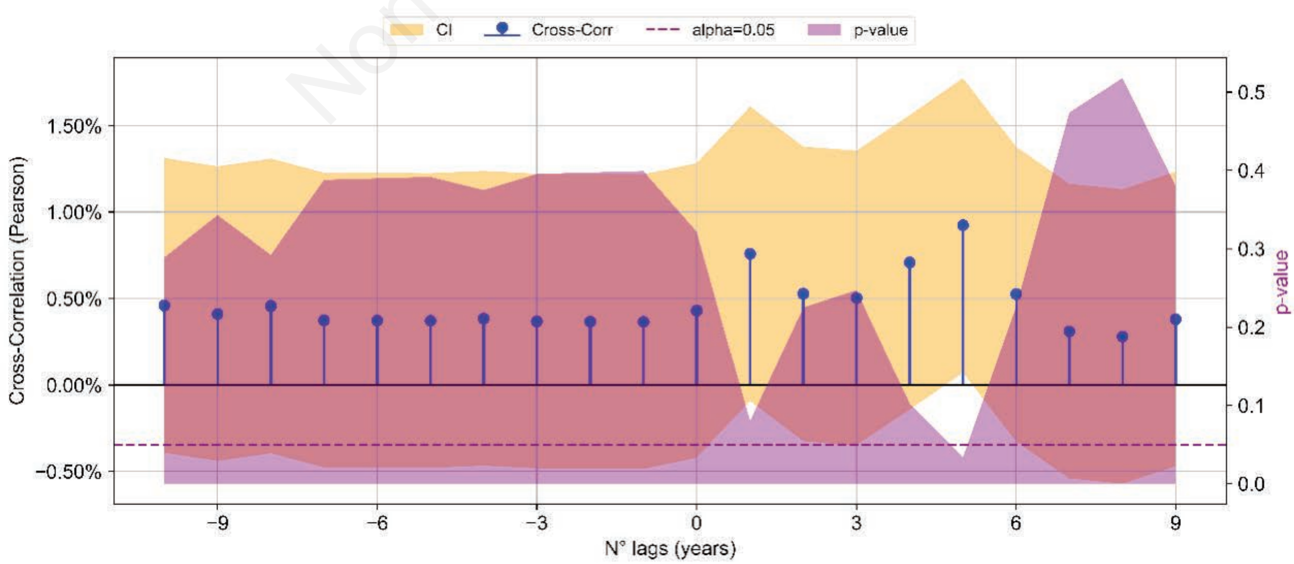

Figure 7. Pearson's cross-correlation analysis of the annual Brazilian Ministry of Health surveillance financial grant (BMH-FG) and the annual hepatitis-A incidence for Pará (values averaged for all municipalities). Figure created using Python (Version 3.8).

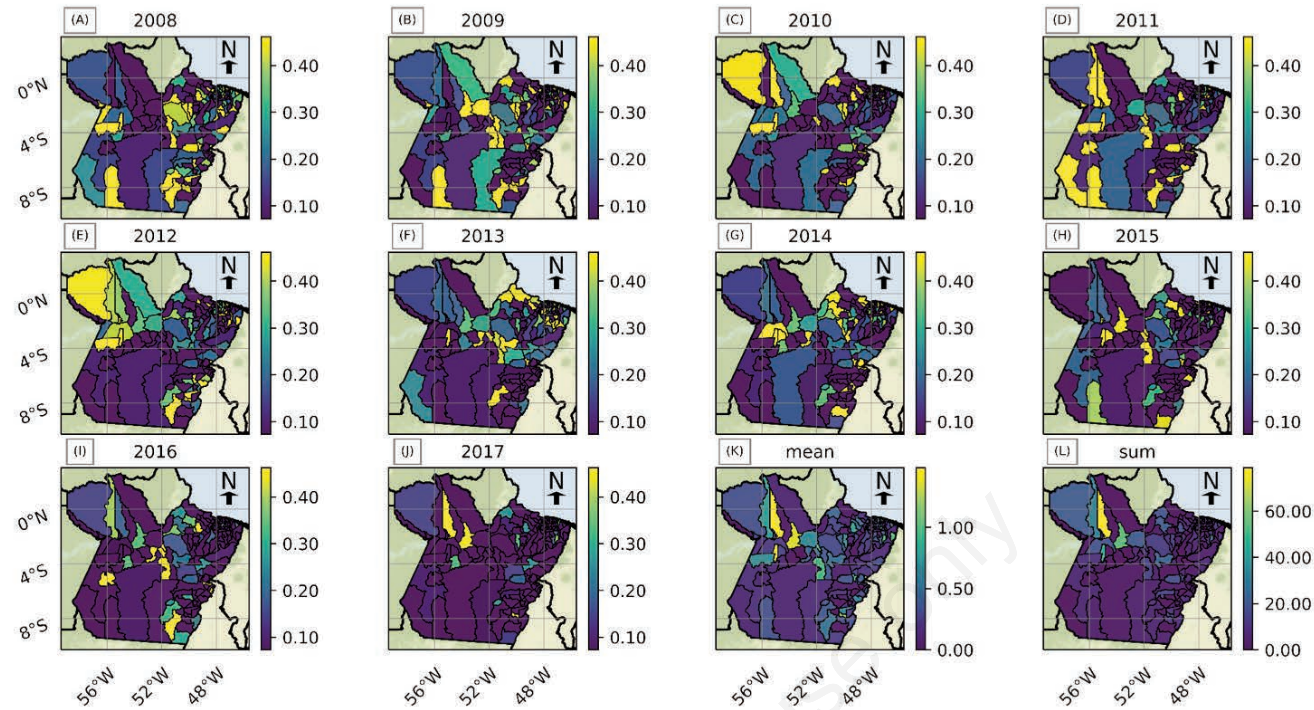

Figure 8. The calculated annual hepatitis-A incidence per municipality in Pará State, Brazil 2008-2017. The mean and accumulated incidences of the study period are also shown; incidence is per 100,000 people. Figure created suing Python version 3.8.

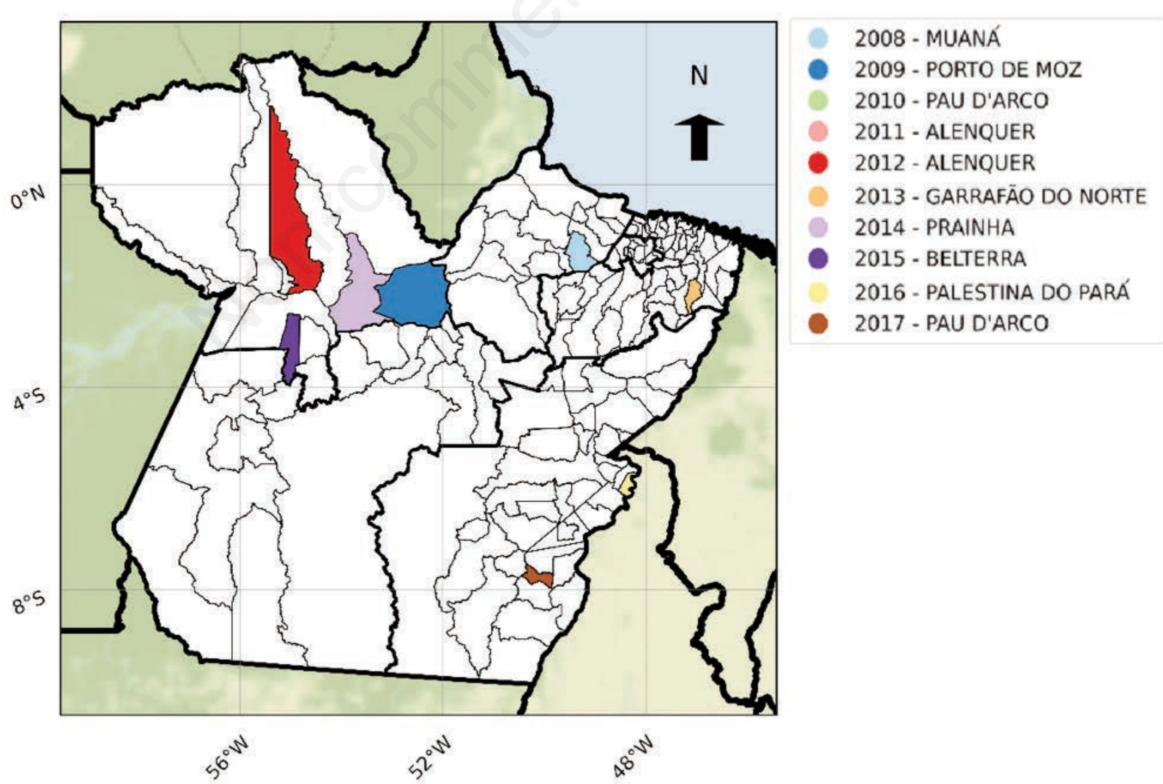

Figure 9. The maximum hepatitis-A incidence by municipality and year during the period 2008-2017 in Pará State, Brazil. Annual hepatitis-A maximum incidence details in Table 5. Figure created using Python version 3.8.

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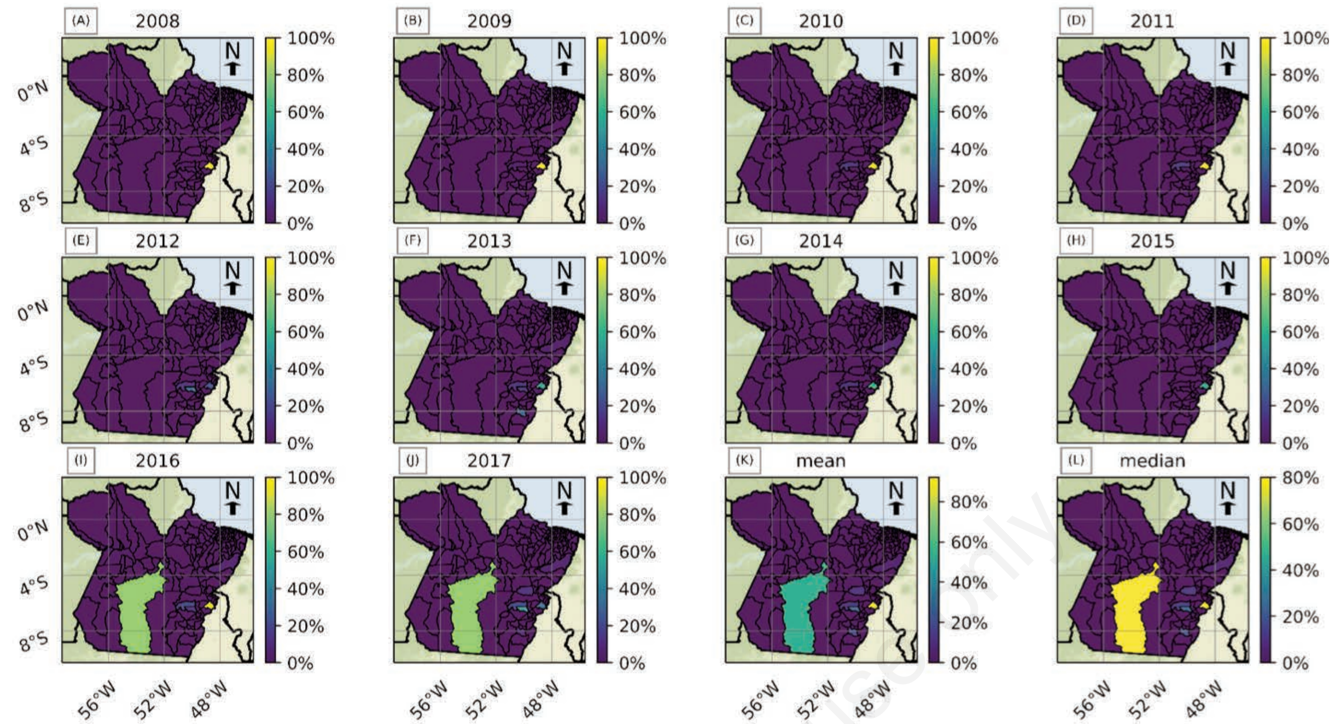


Figure 10. Spatial distribution of the annual municipality sewage treatment expressed as percentage of consumed water 2008-2017 in Pará State, Brazil. The municipalities' average and median values of the study period are also presented. Figure created using Python version 3.8.

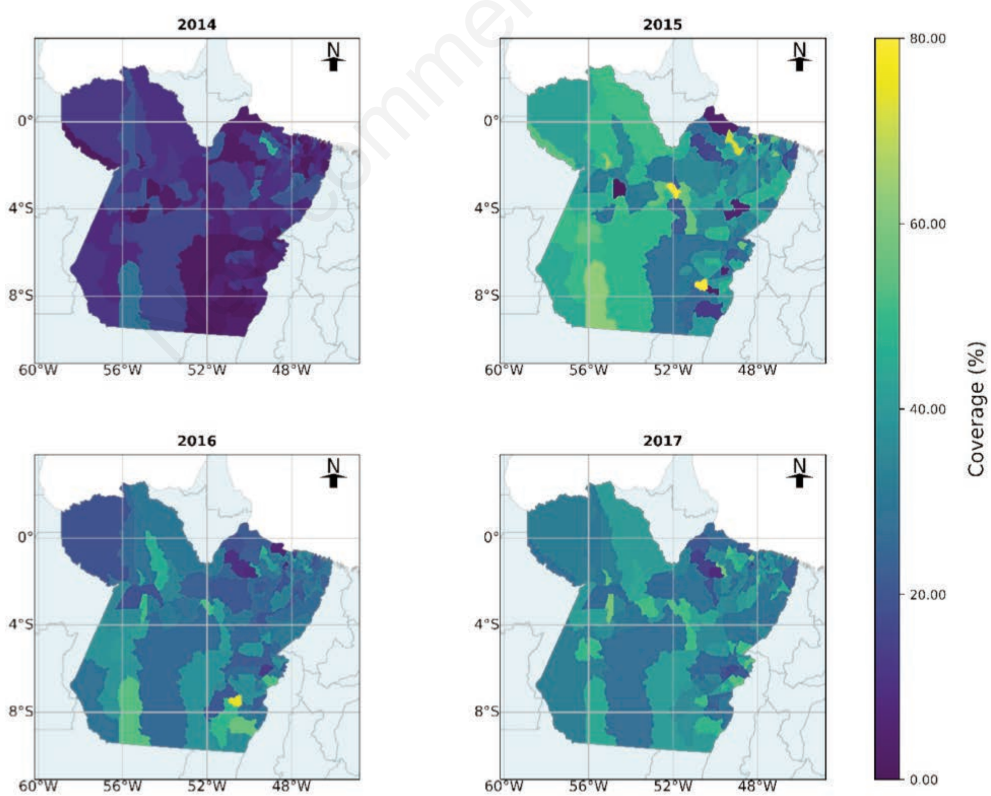


Figure 11. Annual hepatitis-A vaccination coverage by municipality in Pará State; Brazil in the period 2014-2017. Data from Information Technology Department of the Public Health Care System (DATASUS). Figure created using Python version 3.8.

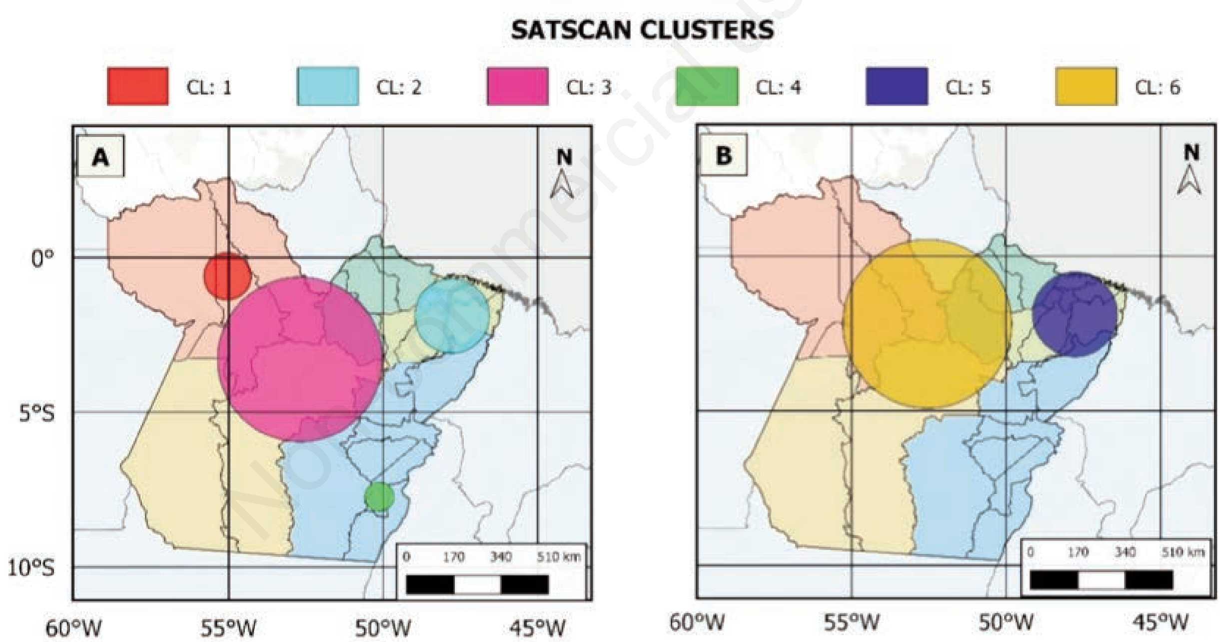
strains accessibility to healthcare centres (Fernandes and Fernandes, 2013; Affonso *et al*., 2016). The lack of proper sanitation contributes to the risk of HAV transmission by faecal-oral route (Gracie *et al*., 2007), while problems associated with manhole and storm drain clogging also play an important role in the disease transmission (UN, 2007; IBGE, 2011; Freitas *et al*., 2015). Limited availability and accessibility to healthcare centres also play an important role for the urban dominance in the disease notification reports (Fernandes and Fernandes, 2013; Affonso *et al*., 2016) as leads to underreporting, severely impacting the disease infection rate assessment (Da Silva and Boing, 2007; Santos *et al*., 2018).

Regardless of the different times in the study period, most of the PNCs were males. The situation was similar for race/ethnicity and literacy levels, where brown and illiterate people were those, most affected by the disease. While the dominance by race/ethnicity is associated with the inherent sociodemographic characteristics in Pará State, whose population is predominantly brown (IBGE, 2011), the gender and literacy inequalities should be searched in the division of labour and social behavioural activities (Vieira *et al*., 2013; FAPESPA, 2015; MS, 2017; IBGE, 2019c).

The Brazilian Federal Government financial grant to SUS was stable for the study period, with an annual uptake of nearly R$ 510 million (around US$ 100 million at the current exchange rate (Brasil, 2019). However, in light of currency exchange, inflation and currency devaluation, the Federal Government financial grant has been deteriorating over time (Tesser and Serapioni, 2020), and constraining its ability to provide essential clinical services and pharmaceutical supplies (Piola *et al*., 2013). Furthermore, issues related to availability and accessibility to healthcare centres as well as SUS internal communication and management systems (Menicucci, 2014) add to this problem.

Cluster analysis

Some of the six clusters discovered had time-windows and spatial locations concomitant with public reported emergency situations (Brasil, 2015). In 2014, the municipality of Prainha, in the Baixo Amazonas mesoregion (Figure 9), reported an emergency situation due to severe flooding, affecting its social and public services resources. As literature points out, HAV has a direct relation-



CLUSTER	RADIUS (km)	START DATE	END DATE	LLR	P-VALUE	OBSERVED	EXPECTED	O/E	RR
1	85.6	2011/1/1	2012/12/31	1257.62	0	519	18.48	28.09	31.37
2	133.33	2009/1/1	2011/12/31	292.17	0	344	937.68	0.37	0.32
3	296.05	2014/1/1	2014/12/31	277.55	0	333	66.51	5.01	5.31
4	50.73	2008/1/1	2009/12/31	113.7	0	108	16.25	6.65	6.78
5	152.07	2017/1/1	2017/12/31	99.83	0	7	116.76	0.06	0.05
6	303.75	2015/1/1	2015/12/31	517.52	0	307	28.69	10.7	18.32

Figure 12. Cluster (CL) formation with respect to hepatitis-A incidence in Pará in the periods before (in A) and after (in B) the start of the national public vaccination programme. Periods: A) 2008-2014; B) 2015-2017. Figure created using QGIS version 3.18.

ship with flood disaster events (Pal *et al*., 2016; Yavarian *et al*., 2019). Our findings reinforce this relationship though future studies are required for a thorough analysis.

The space-time scan statistics depicted an increase of RR after the vaccination programme had started in the following mesoregions: i) Baixo Amazonas; ii) Marajó; iii) Nordeste Paraense; iv) Metropolitana de Belém (Figure 1). Given that riverine communities have geographical and mobility constraints, they usually lack proper access to healthcare services, sanitation (AMAE, 2014) as well as educational services (Fernandes and Fernandes, 2013). Indeed, these barriers also impact the public epidemiological reports (Gama *et al*., 2018). For example, municipalities in the Baixo Amazonas and Marajó mesoregions, despite having low population densities (IBGE, 2008, 2011a; SNIS, 2019), they comprise several riverine communities (Amaral *et al*., 2013; Affonso *et al*., 2016), which are known to lack proper public sanitation (AMAE, 2014; Paungartten *et al*., 2015). Municipalities from the *Nordeste Paraense and Metropolitana de* Belém mesoregions are characterized by higher population densities (IBGE, 2008, 2011a; SNIS, 2019), encompassing a set of subnormal residential conglomerates; several of which comprise households that are near storm drains, near open-air sewage discharges and/or near open-air dumpsites (IBGE, 2011b; AMAE, 2014; Paungartten *et al*., 2015); also, though in a less amount, these municipalities encompass some riverine communities (Amaral *et al*., 2013; Affonso *et al*., 2016).

In respect to the observed RRs mentioned above, one can expect an increase in the disease morbidity, mostly followed by a decrease in the population immunological resistance, increasing the likelihood towards new aggravations (Rodrigues *et al*., 2010). These findings are reinforced by the aging epidemiological profile observed in this study and by previous reports (Clemens *et al*., 2000; Campos and Gonçalves, 2018). As HAV's morbidity is age dependent (Hollinger and Ticehurst, 1996), and given Pará's aging trend (Campos and Gonçalves, 2018), more symptomatic cases of HAV can be expected in the future. Lastly, in respect to people migration and goods transportation, an effective control of the HAV is even more urgent in order to prevent outbreaks in neighbouring places close to the study area (Desbordes, 2021).

Conclusions

HAV incidence has been shown to be time-dependent, and gender, race/ethnically, age group specific. Incidence varied during the study period, with no evident temporal trend or seasonality, except after the national vaccination program started in 2014. However, after 2015, there was a shift in PNC's age group predominance towards young and adults; therefore, there is an aging trend in the notification reports of HAV, as an effect of the public vaccination programme.

Despite drops in PNC, the disease still persists in Pará State, demanding continuous investments in education, development and maintenance of healthcare centres and public vaccination efforts. With the vaccination coverage heterogeneous by time and municipality, a trend towards lower vaccination coverage rates was evidenced in the last years of the study period (after 2016); a trend which should be followed up over longer time-periods.

Riverine and subnormal residential conglomerate communities were the ones mostly affected (higher relative risk) by the disease. A pattern which implies that HAV is associated with poor sanitation condition areas. As waterborne diseases are intimately related to people migration and goods transportation, the present study reinforces the need for continuous prevention and control strategies of HAV.

Only by means of specific priority measures from all key stakeholders, involving health, environmental, sanitation and food sectors, as well as the local and neighbouring community agents, one can achieve meaningful inputs for effective controlling HAV. Particularly for Pará state, the measures to tackle the disease must be still funded by the local government in order to ensure safe and effective prevention, care and treatment services, and their affordability together with multiple health security policies, such as health insurance and medical aids.

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