Assessment of the spatio-temporal distribution of Hepatitis-a virus transmission in the state of Pará, Brazil

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Abstract

The hepatitis-A virus (HAV) is a worldwide healthcare problem, mainly affecting countries with poor sanitation and socioeconomic conditions. Spatio-temporal analyses have become an important scientific asset for identifying the clustering of disease infection, providing support for planning interventions and control strategies. This study aims to determine the spatio-temporal variability of HAV infection and related population-based demographic factors in a endemic region. The selected area of study was Pará state, Brazil. Brazilian Ministry of Health Notifiable Diseases Information System (SINAN) epidemiological report, MS vaccination coverage and Brazilian National Sanitation System (SNIS) sanitation condition datum have been analyzed. Spatial (Moran and Local Moran index) and space-time scan statistics techniques have been applied over Pará state using SINAN database for the assessment of the hepatitis-A incidence for a period of 10 years (from 2008 up to 2017). A total of 5500 cases has been reported. Gender specific incidence analysis indicated that men have higher risk of contamination than women. Sociodemographic (lack of sanitation), socioeconomic (municipality governments investments in infra-structure) presented relationship with the disease incidence. There have been evidences that extreme events of severe precipitation and severe droughs were also related to increase in hepatitis-A notification cases. Spatial statistics denoted a heterogeneous geographical structure in the disease`s incidence: isolated high and low HAV incidence clusters through the years, implying in a complex disease outbreak system that is partially controlled by public vaccination actions. Space-time scan statistics denoted that hepatitis-A incidence is highly attached to the public HAV vaccination program and to municipality specific social infrastructure. Lower incidence risk were majorly aggregated over the Nordeste Paraense and Metropolitana de Belém meso-regions. Distinct clusters of hepatitis-A incidence have been found over the studied area (Pará state), and these clusters varied over the years centered at northwest and northeast meso-regions, mainly time-located prior to the national vaccination program start (prior to 2014). National public vaccination program has not been capable of erradicating the disease in the state. Further studies are required to better assess the relationship between climate change efffects over weather events and their relation to HAV transmission outbreaks.

1. Background

Viral hepatitis is a significant worldwide healthcare problem that is caused by five morphologically and antigenically distinct viruses. Hepatitis-A, B and C (HAV, HBV, HCV) are the most commonly found antigens (Mahboobi, Porter, Karayiannis, & Alavian, 2012). Viral hepatitis are responsible for approximately 1.4 million deaths per year around the world from acute infection and hepatitis-related liver cancer and cirrhosis, with approximately 70 thousand deaths solely related to hepatitis-A (WHO, 2016). In Brazil, solely between 2000 and 2016, around 1.7% of all reported deaths have been related to HAV (MS, 2018).

HAV transmission can occur in different ways, though the fecal-oral route is the most common transmission pathway worldwide (WHO, 2011a). The contamination is done either by direct contact of a susceptible person with an infected person or by ingestion of contaminated food or water. The

transmission is intimately related to sanitary (WHO, 2016), social (Clemens et al., 2000; Jacobsen & Koopman, 2005) and environmental conditions (Parashar, Khalkar, & Arankalle, 2011; Paula, Arruda, & Gaspar, 2001). Furthermore, as climate change causes modifications in frequency and intensity of weather events, and consequently often trigger heat waves, floods, and droughts – which are expected to intensify as a result of unmitigated climate change (WHO, 2009a), hepatitis-A transmission can also be affected by it. Finally, given the tendency of severe impacts being mostly felt by children, the poor and women (WHO, 2011b), new healthcare policies and strategies should be made to encompass gender differences in the disease's transmission (Marcheggiani et al., 2010).

Hepatitis-A is age symptomatic, which compromises effective public infection rate assessments (Nunes, Malheiros, & Hepatite, 2014). It can cause debilitating symptoms and lead to acute liver failure, which is associated with high mortality (WHO, 2019). HAV infection also poses a great threat to women in gestational period. HAV infection can result in uterine contraction, potentially causing premature birth (Elinav et al., 2006).

The disease is considered endemic in Brazil, affecting most commonly children, teenagers and young adults (Clemens et al., 2000; MS, 2002). Between 2005 and 2009, HAV was considered the predominant viral hepatitis in Brazil (XIMENES et al., 2010; Zorzetto, 2011). Nowadays, HAV's endemicity is considered intermediate nationwide (Vitral et al., 2014). The Northern and Mid-Western regions can be considered as the ones with higher HAV incidence in Brazil (MS, 2018; Zago-Gomes et al., 2005). Specifically, in the northern region, mortality rate related to HAV has been increasing since 2013. Solely between 2012 and 2016, the HAV mortality coefficient has doubled, reaching 35 cases per million inhabitants (MS, 2018). Anti-HAV vaccine only became available by the private health agencies after 1992 (MS, 2013). It was only after 2014 that it became available by the public health sector. Ever since, the vaccine is present in the National Vaccination Calendar of the Unique Health System (SUS - in Portuguese) for children between 12 months and 2 years old (MS, 2014).

Hepatitis-A incidence distribution in Brazil is irregular among its regions (MS, 2018; XIMENES et al., 2010; Zorzetto, 2011). The northern region of Brazil presents a HAV incidence rate nearly 12 times higher than the national value (BRASIL, 2012; MS, 2018), mostly concentrated in the states of Pará and Amazonas, as a reflection of the regional socioeconomic impairment (Dutra, Gonçalves, Campos, Tavares, & Beltrão, 2018). HAV-related mortality rates have been increasing since 2013 in this region (MS, 2018).

Despite Brazilian improvements in sanitation conditions (Velasco, 2017), Pará's sanitation is yet virtually zero (Agência Reguladora Municipal de Água e Esgoto de Belém, 2014). Sanitation constitutes a problem that can result in high morbidity and low immunological resistance towards new aggravations (Rodrigues, Gasparetto, Monteiro, Soffiatti, & Veiga, 2010). An aggravating factor is the aging demographic profile (Campos & Gonçalves, 2018). As hepatitis-A is symptomatic with age (Hollinger, 1996) and, given Pará's aging trend (Campos & Gonçalves, 2018), more symptomatic cases of HAV can be expected in the future.

Based on the state’s sanitation condition and hepatitis-A historical records, continuous monitoring of hepatitis-A incidence is important for understanding the burden of viral infection and predicting future trends (Daw, El-bouzedi, & Group, 2014). Despite its importance, studies on the spatial and temporal distribution of the incidence of hepatitis-A in the state of Pará have not been reported in the literature.

The present study aims to evaluate HAV’s incidence in respect to Pará’s sociodemographic conditions in a cross-sectional, retrospective epidemiological approach. HAV’s spatio-temporal distribution have been analyzed considering the periods before (2008-2013) and after (2014-2017) the public vaccination program. The analyses have been conducted in two steps. First step involved a temporal analysis of the disease occurrence and sociodemographic HAV related factors over the whole Para's state. The second involved a municipality space aggregation analysis of the space-time distribution of hepatitis-A incidence.

2. Methods

2.1. Study Area

The state of Pará is located in the northern region of Brazil, encompassing a territorial area of 1.2 million km^2 with six meso-regions, 22 micro-regions and 144 municipalities (Fig. 1) (IBGE, 2017).

Pará is characterized by an equatorial climate, with annual mean temperature oscillating between 25 °C and 27 °C depending on the subregion/micro-region (Luz, Rodrigues, Ponte, & Silva, 2013), daily precipitations, and absence of dry season (FAPESPA, 2018). Mean annual accumulated precipitation oscillates between 1.8 and 13.2 meters, depending on the subregion (Lima et al., 2010).

Pará’s waterbodies possess no public management directives, state planning or even public billing policy for water use (ANA, 2013b). Only 25% of all Pará’s municipalities have 55% or more of its sewage collected and treated, and about 50% have 88% of non-treated sewage (ANA, 2013a). Pará is segmented in six Planning Hydrographic Units (PHU) (Lima et al., 2010). Each possess a specific pressure level over its water bodies. Main causal factors are climatic and land use occupation.

2.2. Data Sources

2.2.1. Cases of Hepatitis-A

The cases of hepatitis-A were obtained from the Brazil’s Ministry of Health Notifiable Diseases Information System (SINAN - in Portuguese). All data obtained had personal names and addresses omitted in order to ensure and maintain the confidentiality of the study. The study consisted of Pará’s residents with hepatitis-A virus from January 2008 to December 2017 aggregated by municipality and year.

Annual municipality specific HAV incidence was derived from the annual number of positive cases of HAV per municipality by the annual population size per municipality from Instituto Brasileiro de Geografia e Estatística (IBGE) (x 100,000).

Age, gender, race/ethnicity and literacy characteristics have been related to the hepatitis-A frequency, in order to evaluate potential relationship between the disease's incidence. Population age has been aggregated in five groups (Child 0–11, Teenager 12–18, Young 19–29, Adult 30–59, Elder + 60), following the classification proposed elsewhere (K. D. S. Santos, Guimarães, Sarmento, & Morales, 2019). The literacy classes derived from the SINAN literacy classification have been aggregated in 11 groups (Illiterate, Elementarcy School - incomplete, Elementary School – complete, Middle School – incomplete, Middle School – complete, High School – incomplete, High School – complete, Undergraduation – Incomplete, Undergraduation – complete, Non-Applicable (N/A)).

All geographical political division limits and shapes were obtained from IBGE (IBGE, 2019a): municipalities, micro-regions, meso-regions and state.

2.2.2. Sociodemographic Data

Annual HAV vaccination population coverage and annual number of live born people per municipality data were obtained from the Information Technology Department of the Public Health Care System (DATASUS) platform (MS, 2019). Data encompassed the annual vaccination per municipality for the period between 2014 and 2017. Prior to that period, Brazilian government would provide hepatitis-A vaccine only for vulnerable individuals and individuals with high risk of severe chronic disease, as patients co-infected with HIV, with chronic hepatitis-B and hepatitis-C, cirrhotic patients of all etiologies (Paraná & Schinoni, 2013). As a consequence, Brazil possessed a very low vaccination coverage with less than 1% of children of one to four years old receiving vaccination to hepatitis-A during that time according to those authors. HAV vaccination population coverage represents the relative amount of vaccinated people from newly born up to lower than 2 years old by its total amount.

Annual municipality sanitation data were obtained from the Brazilian National Sanitation System (SNIS). Data encompasses sewage and treated water data. Sewage data is in respect to the sewage percentual treatment relative to the consumed water per year per municipality (SNIS variable code: IN046). The index is estimated based on the assumption that the sewage generated volume is the same as the volume of consumed water (SNIS, 2014). The treated water percentage available to the population as a function to the estimated total water consumed (TWPA-ETWC) was evaluated as the fraction of the municipality's water volume that is consumed by the population divided by the total volume of the treated water available to that same population.

Brazilian Federal Government annual financial resource destinated to Pará's state government development of socioeconomic plans, policies and respective managements were obtained for the available period, between 2014 and 2017 (Brasil, 2019). This dataset is used to evaluate the temporal

trend of the Federal Government investment over Pará in respect to public health-related investments over the years. Data is discriminated per type of investment, year, month and municipality.

Since 2013, as a result of the municipality Mojuí dos Campos emancipation from Santarém's, the total number of municipalities in Pará is 144. Prior to that date, the total number was 143. Therefore, all sociodemographic data prior to 2013 have been gathered for 143 municipalities, and after that period, for all the 144 municipalities. All Brazilian political administrative subunits (i.e.: meso-regions, micro-regions, municipalities) geospatial data have been obtained from IBGE (IBGE, 2019b).

2.3. Spatio-temporal Analyses

2.3.1. Temporal Analysis

The time-series incidence analysis allows to assess the trend and seasonality of HAV transmission across the state of Pará and also in each municipality. Box plots of each year are used to visualize the temporal trend of HAV incidence, and also to identify outliers (Zhu et al., 2018). Box-plots whiskers were evaluated using the standard equation of 1.5 times the interquartile range (IQR). IQR was evaluated as being the difference between the 3° and 1° quartiles of the data's distribution. The range between maximum and minimum values represent 99.7% of the data distribution, once considered as gaussian distributed (Krzywinski & Altman, 2014).

Cross correlation statistics has been applied over the state mean vaccination coverage and the state total hepatitis-A incidence, in order to evaluate potential lagged effects from HAV outbreak on the vaccination program for Pará state. Both time-series analyses were conducted using Python.

Temporal multi-plot figures had their color-ramp and respective colorbar scaled for common minimum and maximum thresholds towards the whole period studied (2008–2017) for better assessment of temporal variation over the area studied. The minimum threshold (MinT) adopted was the minimum value of the given parameter evaluated (i.e.: incidence) of the whole time series data. The maximum threshold (MaxT) adopted was the median value of all municipalities' specific annual maximums. Therefore, for the evaluation of MaxT, two steps were required: first, obtain an annual time-series of all maximum values for a given variable (i) from all municipality specific data; second, extract the median of that maximum time-series. This algorithm allowed to easily assess potential areas of interest for a given variable (i) without excessively squeezing or extending the data's colorimetric color-ramp.

2.3.2. Spatial Autocorrelation Analysis

The Global Moran Index (GMI) and Local Indicators of Spatial Association (LISA) indicators have been applied to assess Pará's annual specific HAV incidence spatial distribution. GMI allows the assessment of the overall spatial autocorrelation in the whole study area, while LISA focuses on each municipality unit

and respective surroundings. LISA maps allow the description of spatial relationships for a given measurable attribute (i.e.

) over space dimension according to four spatial dependency cluster types (Anselin, Syabri, & Kho, 2006): (i) High-High (HH), spatial units with high values surrounded by ones with high values; (ii) High-Low (HL), spatial units with high values surrounded by ones with low values; (iii) Low-Low (LL): spatial units with low values surrounded by ones with low values; (iv) Low-High (LH): spatial units with low values surrounded by ones with high values.

Once the spatial dependency can play an important role in disease transmission (AVANZI, FONZAR, SILVA, TEIXEIRA, & BERTOLINI, 2018; Van Effelterre, Marano, & Jacobsen, 2016; Zhu, Liu, Fu, Zhang, & Mao, 2018), the definition of the neighborhood connectivity matrix (W) for the GMI and LISA tests play an important role in the spatial analyses. In the present study, the K-Nearest Neighborhood (KNN) connectivity matrix algorithm has been applied for the construction of W matrix. The KNN algorithm was selected in order to overcome the problem of retrieving W matrixes over sparse spatial structures whose geometries (i.e., municipalities) present areas that are several orders of magnitude apart from each other (i.e., municipalities with areas in km^2 vs. m^2) (Anselin, 1995; Asfar, Kurnia, & Sadik, 2016).

An optimizer KNN connectivity matrix algorithm was applied for the construction of W matrices in order to achieve the most probable spatial dependency (also called as the most robust W matrix) for each given time analyzed (i.e., year) (Furtado & Van Oort, 2010). In a sequence, for each year (or any other desirable time aggregation unit) of the dataset, the algorithm applies a grid-search over all possible KNN possibilities, verifies the KNN with highest GMI value, and defines the specific maximum KNN for the LISA test evaluation. As a result, spatial dependency is allowed to vary over time (Koenig, 1999), which in turn can encompass potential spatio-temporal variability in the HAV transmission system over time.

For both GMI and LISA, Monte Carlo randomization (99,999 permutations) was applied in order to assess the significance of Moran's Index, with the null hypothesis being that the infected cases of viral hepatitis in Pará state is completely random distributed (Anselin et al., 2006). The GMI and LISA were conducted using the PYSAL library in Python (Rey & Anselin, 2009).

2.3.3. Space-time Scan Statistics

Space-time scan statistics has been used to identify the most likely clusters, the windows with largest Log Likelihood Ratios (LLR) (Kulldorff, 1997; Pellegrini & Kulldorff, 2016). LLR is evaluated according to Eq. 1, where C denotes the total number of cases; c is the number of observed cases inside the window; n is the number of expected cases inside the window.

Equation 1

Statistical significance was evaluated with the Monte Carlo simulation method (replications set to 999 and significance level set at 0.05). Regarding the other parameters, the maximum radius of circular base

was set at 50% of the total population at risk and the maximum height of the cylinder was set at 50% of the total study period. For this statistics, a discrete Poisson based model was used, where the number of HAV incidence cases in an area is Poisson distributed according to a known underlying population at risk (Kulldorff, 2001; Kulldorff, Athas, Feuer, Miller, & Key, 1998). The null hypothesis assumed that the relative risk (RR) of the incidence was the same within space and time domains. The spatial-scan statistics were calculated with the SatScan software (Kulldorf, Rand, Gherman, Williams, & DeFrancesco, 1998) over the municipalities centroid coordinates, in accordance with other works (Pellegrini & Kulldorff, 2016).

3. Results And Discussion

3.1. Temporal Analysis

Pará's HAV positive notified new cases (PNC) and incidence values oscillated between 2008 and 2014, but followed negative trends afterwards (Table 1). PNC ranged from 717 (9.79) cases, in 2008, and 52 (0.62) cases, in 2017. A total of 5500 PNCs has been reported between 2008 and 2017, with an annual mean of 550 (7.09) cases. Annual median and mean HAV PNC oscillated around five and one cases per year respectively during the studied period (Fig. 2). PNC outliers have been observed over the period studied. Highest annual PNC reached 809 (10.38) cases in 2012, a time prior to the public vaccination program (MS, 2014).

Table 1
Annual hepatitis-A positive notified new cases (PNC) and respective incidence for Pará state.

Year	PNC	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

During 2014, inundation emergency situations were reported over Pará (BRASIL, 2015). This factor may have increased HAV's transmission rates in populous municipalities, resulting in higher HAV transmission, which could explain the higher PNC values for that given year. The 2015 incidence peak can be related to the emancipation of Mojuí dos Campos municipality. Its emancipation caused in the diminishment of Santarém population size, which, in return, resulted in a higher incidence for Santarém. This higher incidence acted as an outlier for the given year. Also, during 2015, several Pará's municipalities faced severe drought (Clésio, 2015). As a consequence, several resources and ecosystem services have been affected (Alpino, Sena, & Freitas, 2016), possibly altering the HAV transmission intensity for the given year (CANN, THOMAS, SALMON, P. WYN-JONES, & KAY, 2013; Gullón, Varela, Martínez, & Gómez-Barroso, 2017). Finally, the diminishment in the HAV annual state mean PNC of the last years can be explained by the Pará's overall sanitation conditions improvement, especially on the urban regions as Belém municipality (K. D. S. Santos et al., 2019).

Annual hepatitis-A incidence also varied per gender. Male's incidence was higher than females by a ratio varying between 1.05 (in 2008) and 1.73 (in 2010), and with a mean of 1.29 times higher for the period of 2008 and 2017. Gender HAV's endemicity ratio can vary between studies, being specific for population groups, time, and even for spatial aggregation (states, country), as already observed by other works (MS, 2018; WHO, 2009b). The differences in hepatitis-A incidence per gender for Pará state can be explained by regional differences in labor and social behavioral patterns (FAPESPA, 2015; Vieira, Siqueira, Ever, & Gomes, 2013), which imply that male people tend to have higher risk of contamination than female for hepatitis-A.

The annual hepatitis-A incidence per gender and literacy groups denoted three major clusters (Fig. 3). Sorted by incidence intensity, the first group was the Non-Applicable (N/A) literacy group. It presented the highest incidence rates despite gender. Incidence has been ubiquitous for all years, except for 2017, in which both gender N/A classes presented an incidence decay. The second literacy group was the incomplete Elementary School. It was also independent of gender, though male presented an accumulated incidence (between 2008 and 2017) higher than females by 9%. The third literacy group was the incomplete Middle School, and it was also independent of gender. This third group presented higher differences between genders, with male incidences higher than females.

Year	PNC	Incidence
Hepatitis-A PNC has been majorly reported over urban areas 3,718 (69.37%) cases. This is majorly due to population density and healthcare accessibility which are both higher in those places once compared with other types of zones of residence (IBGE, 2008; SNIS, 2019).		
Reported cases between race/ethnicity in Pará denoted that the number of cases is majorly aggregated over brown with 4,322 (79.73%) cases, then white people with 638 cases (11.77%) and black people with 190 cases (3.5%). This PNC's behavior is a reflection of the population distribution for the given state (IBGE, 2019c). Based on the IBGE's Pesquisa Nacional por Amostra de Domicílios Contínua trimestral (PNAD) data, the race/ethnicity specific incidence for Pará state has been verified. Its results indicated a segregation in the population into two clusters: a first group (group A), containing white and brown people, whose specific incidence varied between $2*10^{-3}$ and $1.6*10^{-2}$; and a second group (group B), containing black people, whose specific incidence varied between $2.2*10^{-05}$ and $6*10^{-5}$. The annual variation is presented in Fig. 4.		
The distribution of the specific incidence of hepatitis-A per age group and year (Fig. 5) denoted that children are the main age group compromised by the disease. Teenager and young people are in second most compromised, and elder people presented the lowest incidence values. The results also denote that the incidence age-class specific is changing between the period studied. Initially children had incidence values of nearly 0.7, which perdured up to 2016. In 2017, this group incidence decayed to virtually zero (no registered cases). Nonetheless, for the same year (2017), the number of cases for adults changed from 0.04 up to 0.06, an increase of nearly 1.5 times. All other age classes denoted decrease in incidence between 2016 and 2017. As a consequence, the hepatitis-A incidence in the state is a main public health issue, especially for school-age children (K. D. S. Santos et al., 2019).		
Pará's annual incidence varied in intensity among the municipalities (Table 2). Its spatial distribution is presented in Fig. 6. Higher intensities were found aggregated at Marajó (2008), Sudeste Paraense (2009, 2010, 2016, 2017), Baixo Amazonas (2011, 2012, 2014, 2015), and Nordeste Paraense (2013) meso-regions. These meso-regions possess deprecated sanitation conditions, facilitating the disease transmission (IBGE, 2008; SNIS, 2019). Pará meso-regions Gross Domestic Products (GDP) capacities are heterogeneous among themselves and among their respective municipalities. Such socioeconomic reality results in social disparities (Gomes & Andrade, 2011), which, in turn, can be related to the HAV incidence spatial heterogeneity, as previously described in other works (Jacobsen & Koopman, 2005; Mantovani et al., 2015).		

Table 2
Municipalities with maximum hepatitis-A incidence per year (incidence x 100,000). Micro and meso-regions are also shown for respective reference.

Year	Municipality	Micro-Region	Meso-Region	Max Incidence
2008	Muaná	Arari	Marajó	92.97
2009	Redenção	Redenção	Sudeste Paraense	105.87
2010	Pau D´Arco	Redenção	Sudeste Paraense	99.55
2011	Alenquer	Santarém	Baixo Amazonas	537.70
2012	Alenquer	Santarém	Baixo Amazonas	151.77
2013	Augusto Corrêa	Bragantina	Nordeste Paraense	103.31
2014	Prainha	Santarém	Baixo Amazonas	437.31
2015	Belterra	Santarém	Baixo Amazonas	117.40
2016	Palestina do Pará	Marabá	Sudeste Paraense	67.53
2017	Pau D´Arco	Redenção	Sudeste Paraense	37.45

The municipality’s sewage percentual treatment relative to the consumed water index (IN046) showed little spatial variation between 2008 and 2017 (Fig. 7), with municipality changes no higher than 10% between years. Sudeste and Sudoeste Paraense meso-regions of Pará denoted better sanitation conditions, though the IN046 did not surpass 10% for any of the years analyzed. Therefore, even for these meso-regions, Pará state as a whole still presents high risk to hepatitis-A due to lack of effective sanitation conditions.

Finally, for the years of 2016 and 2017, maximum IN046 values were found in Altamira municipality with a constant value of 80%. Altamira is located in the Sudoeste Paraense meso-region, with 111,435 inhabitants (Institute Brasileiro de Geografia e Estatísticas, 2017). The public water supply system also varied over the study period. Based on SNIS dataset, the annual treated water percentage available to the population as a function of the estimated total water consumed (TWPA-ETWC) was evaluated. TWPA-ETWC varied between practically non-existent (in 2008) up to higher than 400% (in 2015). TWPA-ETWC denoted a stability (mean and median) over the studied period (2008–2017). Outliers were detected all over the time-series. Those outliers surpassed the 100% quote. Such behavior denotes that the people of Pará have different sources of water for their daily use, resulting in a higher level of sewer discharge once compared with the provided treated water. The given results have a large toll on the society from an epidemiological perspective (Deilami, Goonetilleke, McGree, & Hayes, 2017; Gentry-Shields & Bartram, 2014) which is in agreement with previous findings for the same region (Lima et al., 2010).

Regarding hepatitis-A, TWPA-ETWC denote high potential for the virus transmission, once there is a high contact rate between local populations to non-treated water resources. This high contact rate can be a major driver for continuous endemicity and perpetuation of hepatitis-A in the given state. If no meaningful changes are set into action in order to provide minimum sanitation condition to the population, not only the disease will persist over time, but also an epidemic outburst is also prone to happen (Marcheggiani et al., 2010; WHO, 2017b).

Year	Municipality	Micro-Region	Meso-Region	Max Incidence
The annual HAV vaccination percentage per municipality for Pará state is presented in Fig. 8. The vaccination hotspots denote no temporal trend between municipalities. This later pattern could be due to hepatitis-A outbreaks that pushes local communities and public health agencies towards local punctual heavier vaccination actions. Such political approach is in conformity with the World Health Organization Universal Immunization Program for intermediate endemic areas, in which periods outbreaks are prone to happen (WHO, 2017a). Other factors as intra-state human migrations could also be in action (Carballo, Cody, Kelly, & Hatzakis, 2013; Castelli & Sulis, 2017). Even though pre-travel HAV vaccination and basic immunization schedule are essential for those travelling to remote rural areas where hygiene conditions may be even more challenging (Castelli & Sulis, 2017), healthcare services/centers should focus on migrant populations, and provide accessible treatment (WHO, 2017a). Nevertheless, in Brazil, the political approach is to promote immunization only to vector-borne diseases (MS, 2010). Finally, one can observe from Fig. 8 that the coverage percentage scale surpasses 100%. This later can be due to heterogeneous healthcare center spatial distribution across the state, forcing migrations and other social maneuvers, i.e. declaration of childbirth location (Nascimento, Flauzino, Cunha, Silva, & Rocha, 2015; Noordoven, 2016), to support the public vaccination program in each municipality.				
The cross-correlation between the state mean vaccination coverage and the state total hepatitis-A incidence denoted low (≤ 3%) temporal dependency between both series. Therefore, it was inferred that HAV outbreaks do not tend to push vaccination programs towards a better state public coverage. Instead, results indicate towards another scenario in which vaccination program could be majorly controlled by other factors other than the disease control, as vaccination distribution, population distance to healthcare centers, beside the own vaccination campaign and government investment and financial support. Also, another factor affecting the Brazilian vaccination program is that the vaccination is mainly induced by the disease outbreak, instead of the opposite policy, by acting as a prevention action. Therefore, the vaccination comes after or at most during a disease's outbreak in Brazil, and not prior to the outbreak, as a mitigation and prevention vaccination control should be. These findings follow along with Costa and Melo (1998) that rises the questioning of whether the Brazilian Federal Government seeks an enhancement in the State related functions and services provisioning, or if it only seeks capital expenses containment, without regarding the quality of those services supposedly offered.				
The above findings are further reinforced by Brazilian Federal Government annual financial resource destinated to Pará's state government for development of socioeconomic plans, policies and respective managements funding. According to this Federal financial support, SUS structural development is majorly stable since 2014 with annual investment of nearly R$ 510 million (around US$ 127.5 million, at current exchange rates) (BRASIL, 2019). Nevertheless, its funding is recognized as being badly managed, with several Issues regarding communication and management between the different government political spheres (Menicucci, 2014). Its reality is further aggravated once other Federal investment plans are evaluated. Based on the health specialized attention and the development of urban structures for average and small nuclei program development Federal financial fundings are facing continuous financial support downgrade. As a consequence, Pará state still lacks effective public investment and policy measures towards public healthcare programs.				

3.2. Spatial Clustering Analysis

Spatial dependency of the hepatitis-A incidence was evaluated by GMI and LISA. Results from the optimizer KNN algorithm are expressed in Fig. 9. The spatial structure of the hepatitis-A incidence varied over the years. Its W matrix had a neighboring structure varying between one (2008, 2009, 2011, 2012 and 2014) up to four nearest neighbors (in 2013 and 2015). Highest GMIs were mostly obtained through W matrixes of one neighbor (KNN = 1). Non-significant global neighborhood structures were also observed

for 2011 and 2012. The W matrices patterns imply that HAV transmission had lower spatial dependency in for this period; while after that 2012, the disease transmission became more endemic, which in turn denoted a stronger spatial dependency. In China, Zhu et al. (2018) found GMI values higher than 0.4 for most years for hepatitis-A. In our case, GMI values only reached 0.1 or higher (in module) in 2008, indicating a weak spatial cluster tendency of the reported cases in Pará.

LISA statistics denoted heterogeneous spatial structures over the years (Fig. 10), with clusters varying over the years. They were specific for given years and temporal ranges. For 2008, spatial clusters showed a random spatial distribution between LISA classes. In the following years up to 2010, a progressive increase in hepatitis-A incidence could be observed for the meso-region of Baixo Amazonas. In 2011 and 2012, given the increase continuous increase in the disease's incidence, Baixo Amazonas meso-region denoted a High-High (HH) spatial dependency. Nordeste and Metropolitana de Belém meso-regions denoted Low-Low (LL) spatial dependency for hepatitis-A incidence for the period after the national vaccination started (after 2014). This later pattern can be explained by the higher accessibility of the local population to the healthcare centers and vaccination services once compared to the other sectors (meso/micro-regions) of the state. Specific municipalities denoted scattered random LISA patterns, with exception of municipality of Belém, which presented a HH pattern between 2012 up to 2014.

3.3. Space-time Scan Analysis

Space-time scan statistics depicted two main clusters (C1 and C2) in the Pará state for HAV incidence (Fig. 11). They are statistically significant for the p-value permutation test of 999 times. C1 encompassing the Baixo Amazonas meso-region and part of Marajó and Sudoeste Paraense meso-regions. C2 encompassing Nordeste Paraense and Metropolitana de Belém meso-regions and part of Sudeste Paraense meso-region. The groups presented different time windows: C1 was evaluated between 2011 and 2015; while C2, between 2015 and 2017. C1 presented nearly 7 times higher relative risk for the disease transmission relative to the random Poisson distribution; while C2 presented 13 times lower relative risk. These results are in agreement with the Brazilian national public vaccination program (MS, 2014), explainable by the time windows of cluster C1 and C2. C1 had its time window set to years prior to the national vaccination program up to one year after its start (with a buffering of one year for public vaccination effective results). C2, with an opposite time window, which started one year right after the vaccination program started. These findings reinforce the importance of vaccination over the control of HAV transmission over Pará. Furthermore, they allow the assessment of the time lag required for the public vaccination program to take place (become effective), and its results get reflected in the PNC dataset.

Since sub-notification is a common problem in Brazil public health sector (Da Silva & Boing, 2007; M. L. Santos, Coeli, Batista, Braga, & Albuquerque, 2018), it plays an important role in our epidemiological analyses. As a consequence, potential other non-detectable clustering structures could be in action over

Pará for the period studied. Other reports have evidenced an increase in sub-notification cases over the northern states of Brazil (MS, 2015).

Several factors are responsible for sub-notification in Brazil. The decentralized SINAN's structure (MS, 2007) has been documented as one important factor in the sub-notification problem (Da Silva & Boing, 2007; M. L. Santos et al., 2018). Despite its structural development had been implemented to contribute to SINAN's democratization of health-related data, allowing all and any health professional to get access to crucial information, and allowing public availability to the society, its decentralized structure increases difficulty in data's exchange between the Brazilian political sphere units: the municipalities, the states and the Union.

Other factors associated with sub-notification in SINAN are the health attention network coverage, in which capital cities tend to possess higher coverage rates than rural areas, resulting in lower hepatitis-A transmission rates in less accessible urban centers once compared with ones that possesses higher infrastructure (i.e.: municipalities that encompasses state capital cities) (Barcellos, Lammerhirt, de Almeida, & dos Santos, 2003). Poor accessibility by the local population to healthcare centers (Romero, Ribeiro, Sá, Villa, & Nogueira, 2016), associated with Public transportation cost (MS, 2013) and lack of specialized human resources in those centers (M. L. Santos et al., 2018) are three main factors responsible for sub-notification in the SINAN.

4. Conclusion

Despite government investment in health, education and family income in Pará state, hepatitis-A is still a present healthcare issue over the state. Further investment is required for effective control and prevent of diseases' outbreak for places with deprecated sanitation and infra-structural conditions as Pará.

Hepatitis-A incidence showed to be gender, race /ethnically and age group specific, with higher rates over male groups, brown people, and over children and teenagers. Incidence varied over the years, with no evident temporal trend or seasonality, except after the national vaccination started (in 2014). Higher HAV incidence intensities were found aggregated on the meso-region of Baixo Amazonas. This pattern can be associated with disparities in gender social behavior patterns (i.e.: labor, family care, etc.). Densely populated municipalities with deprecated sanitation conditions have proven to be major areas of HAV transmission. Hepatitis-A incidence has been related to lack of basic local infrastructure. Public infrastructure investments with induced upgrade by the private sector have been related to better sanitation and lower hepatitis-A PNCs solely in Parauapebas municipality (Sudeste Paraense meso-region). In general, Pará's sanitation conditions showed a deprecated scenario for the period studied. Despite political efforts, Pará's local public reality is still prone to waterborne diseases, and further investment is required for a better sanitation control over the region.

Vaccination coverage presented spatial distribution over the state. Probably a result of several factors, including local communities' accessibility to healthcare public representants, vaccination preservation and political management and financial support. Overall, the national public vaccination program had a

negative effect over the hepatitis-A incidence (by reducing the HAV transmission) for the time and period studied, reinforcing the vaccination public policy as an important HAV transmission control agent. Nevertheless, the vaccination proved to be uncapable of erasing the disease transmission in the state. This later implies that the vaccination program must be a continued effort from the government agencies in order to prevent HAV outbreak in the future, and whenever possible, the vaccination program should be expanded to cover all population regardless of age or local of residence.

The spatio-temporal analyses applied have shown to be effective in detecting spatial clusters over the region and period studied. Global Moran and LISA analyses depicted that hepatitis-A incidence presented a heterogeneous spatial dependency over the years, which were mostly related to near adjacent municipalities, with municipalities clusters in the Baixo Amazonas meso-region. Spatial dependency proved to be weak for most of the years studied, except for 2012 and 2013. Space-time scan statistics segmented the state in two main zones for HAV incidence, HAV incidence segments presented distinct time windows, well correlated with the Brazilian national public HAV vaccination program: one with high relative risk for HAV transmission, between 2011 and 2015 over the Baixo Amazonas meso-region; and another with low relative risk, between 2015 and 2017, over the Marajó and Metropolitana de Belém meso-regions.

Among the limitation in this study, sub-notification cases are an important factor in depicting main areas of healthcare need. Nevertheless, the present work demonstrates the epidemiological spatio-temporal behavior of Hepatitis-A over the state of Pará for the period between 2008 and 2017. Our findings can help in the assessment of effective implementation of surveillance guidelines for public health policies towards prevention strategies and disease's infection control over Pará state.

List Of Abbreviations

CAPES COORDENAÇÃO DE APERFEIÇOAMENTO DE PESSOAL DE NÍVEL SUPERIOR

CNPQ Conselho Nacional de Desenvolvimento Científico e Tecnológico

DATASUS Technology Department of the Public Health Care System - SUS

GMI GLOBAL MORAN INDEX

HAV HEPATITIS-A VIRUS

HBV Hepatitis-B virus

HCV Hepatitis-C virus

HH HIGH-HIGH LISA CLUSTER

HL HIGH-LOW LISA CLUSTER

IBGE INSTITUTO BRASILEIRO DE GEOGRAFIA E ESTATÍSTICA

IN046 Municipality's sewage percentual treatment relative to the consumed water index

INPE INSTITUTO NACIONAL DE PESQUISAS ESPACIAIS

IQR Interquartile range

KNN K-NEAREST NEIGHBOR

LH LOW-HIGH LISA CLUSTER

LISA LOCAL INDICATORS OF SPATIAL ASSOCIATION

LL LOW-LOW LISA CLUSTER

LLR LOG LIKELIHOOD RATION

MaxT Maximum threshold

Mint Minimum threshold

MS BRASIL MINISTRY OF HEALTH

PHU Planning Hydrographic Units

PNAD Pesquisa Nacional por Amostra de Domicílios Contínua trimestral

PNC POSITIVE NOTIFIED NEW CASES

SESPA SECRETARIA DE SAÚDE DO PARÁ

SINAN SISTEMA NACIONAL DE AGRAVOS E NOTIFICAÇÕES

SNIS Brazilian National Sanitation System

TWPA-ETWC The treated water percentage available to the population as a function to the estimated total water consumed

W CONNECTIVITY MATRIX

Declarations

Ethics approval and consent to participate

All manuscript's data has been acquired from the national public institutes of Brazil, follows the Brazilian Law N° 12.527/2011 (BRASIL, 2011) of data access rights. The manuscript ensures the confidentiality of

personal information of any involved person.

Consent for publication

Not applicable. The manuscript does not contain any individual person’s data in any form.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The author(s) declare(s) that they have no competing interests.

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[1] <http://www.inpe.br/pci/arquivos/minuta_chamada_04_2019.pdf>

Authors' contributions

PL analyzed the datasets, developed the results and discussion and wrote the manuscript.

MK and RG followed the manuscripts development, auxiliating in the manuscript development.

All authors read and approved the final manuscript.

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Authors' information

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Figures

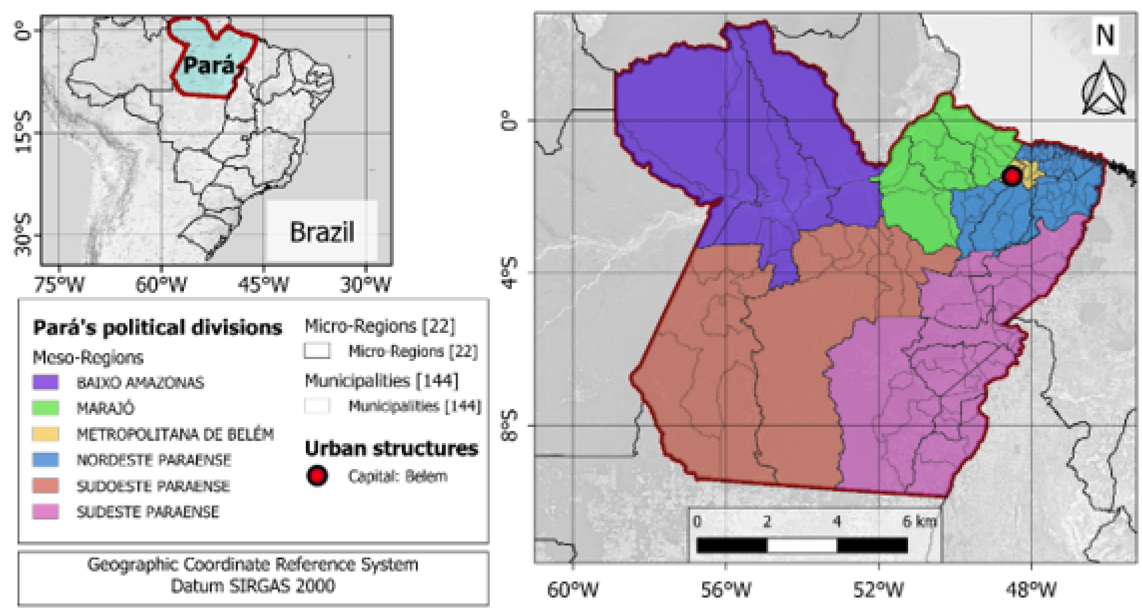

Figure 1

Map showing the location of the state of Pará in the northern region of Brazil, the location of the capital Belém, meso and micro-regions.

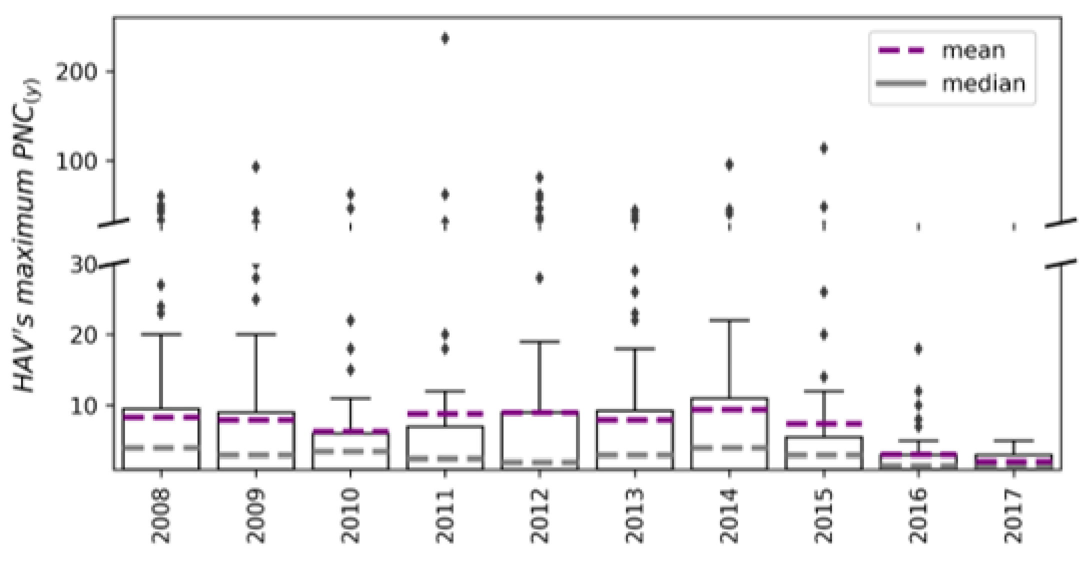

Figure 2

Box-plot distribution of the annual positive notified new cases of hepatitis-A from Pará state.

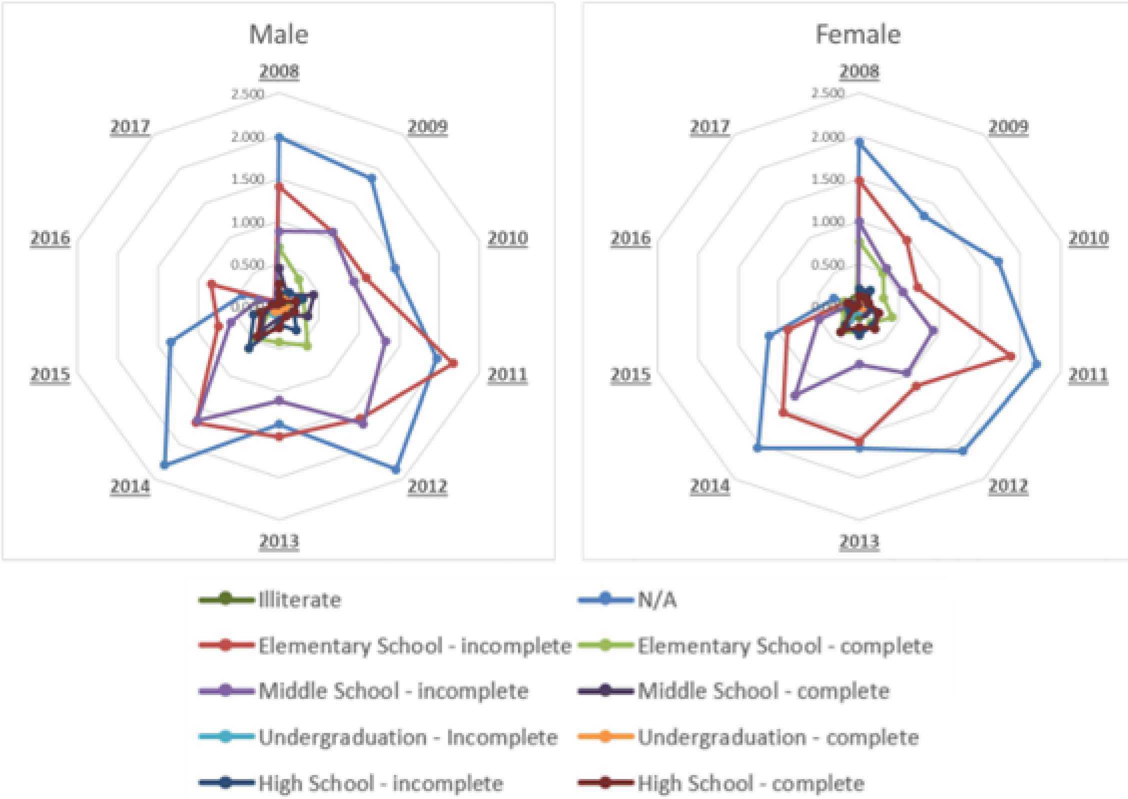

Figure 3

Annual incidence per gender and per literacy group (incidence x 10,000).

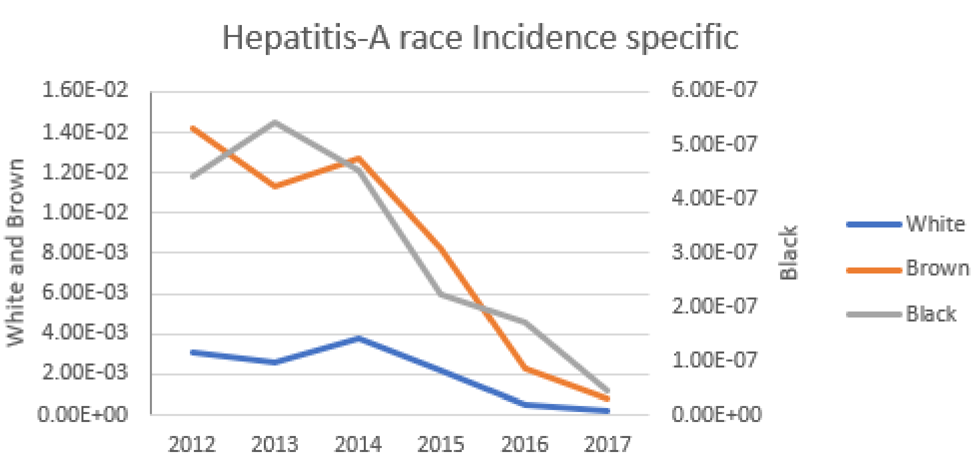

Figure 4

Race/Ethnicity hepatitis-A specific incidence for Pará state.

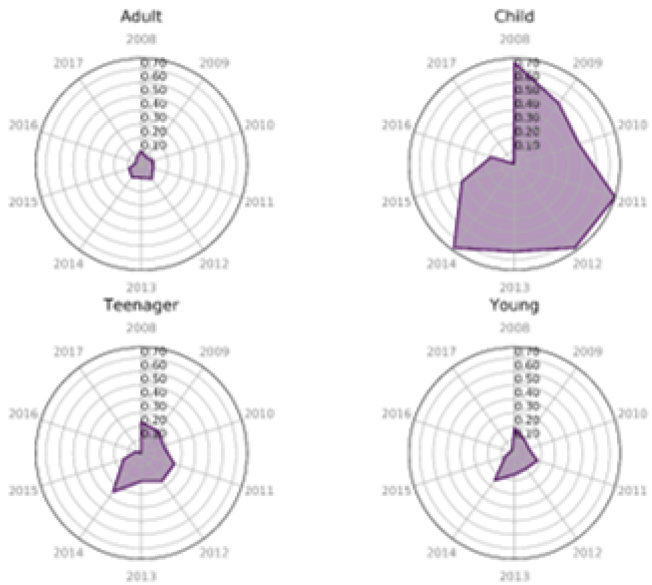

Figure 5

Distribution of the specific incidence of hepatitis-A per age group and year (incidence x 1,000).

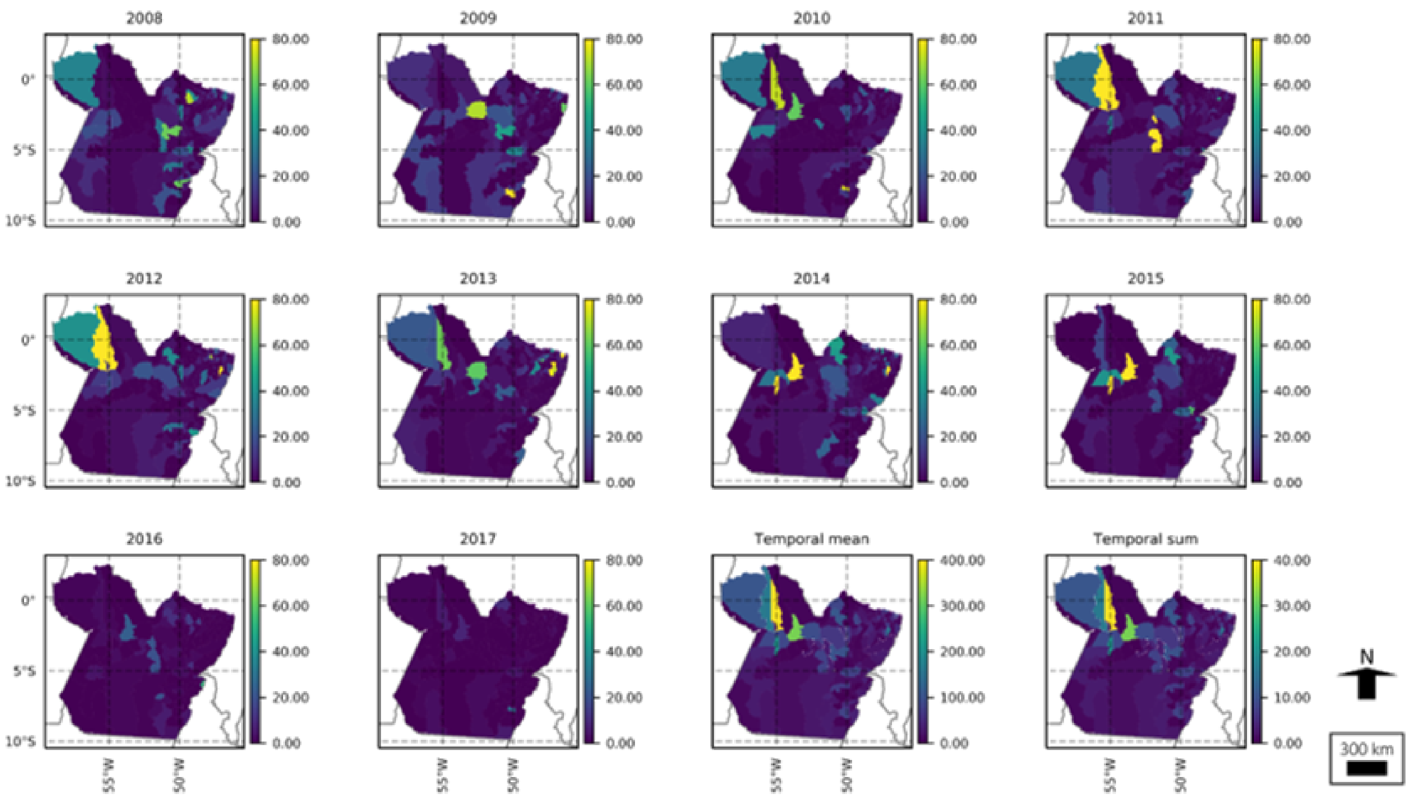

Figure 6

Annual hepatitis-A incidence per municipality in Pará state, 2008-2017. Temporal mean and sum are also shown. Incidence units: number of cases per 10000 people. Scalebars have been normalized according to

previously described method.

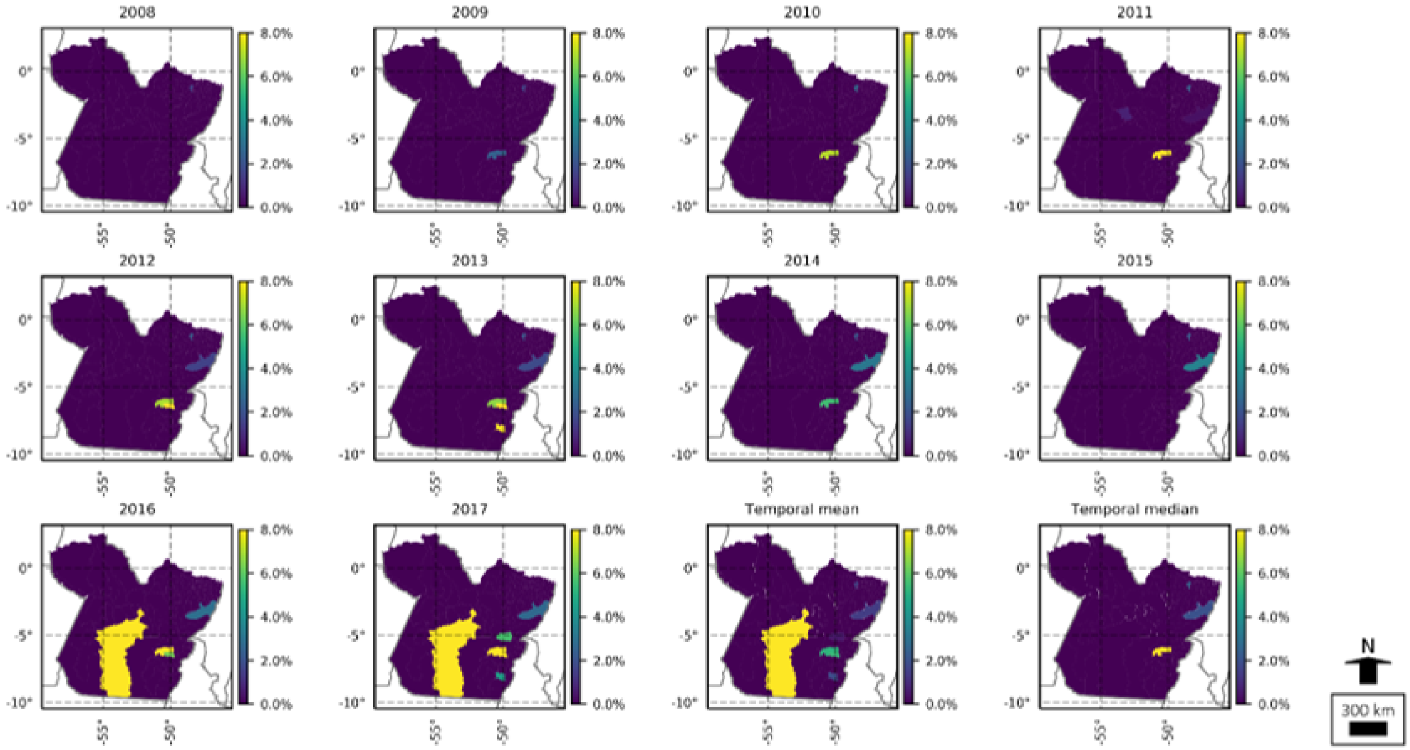

Figure 7

Spatial distribution of the annual Pará’s municipality sewage percentual treatment relative to the consumed water (incidence x 1,000).

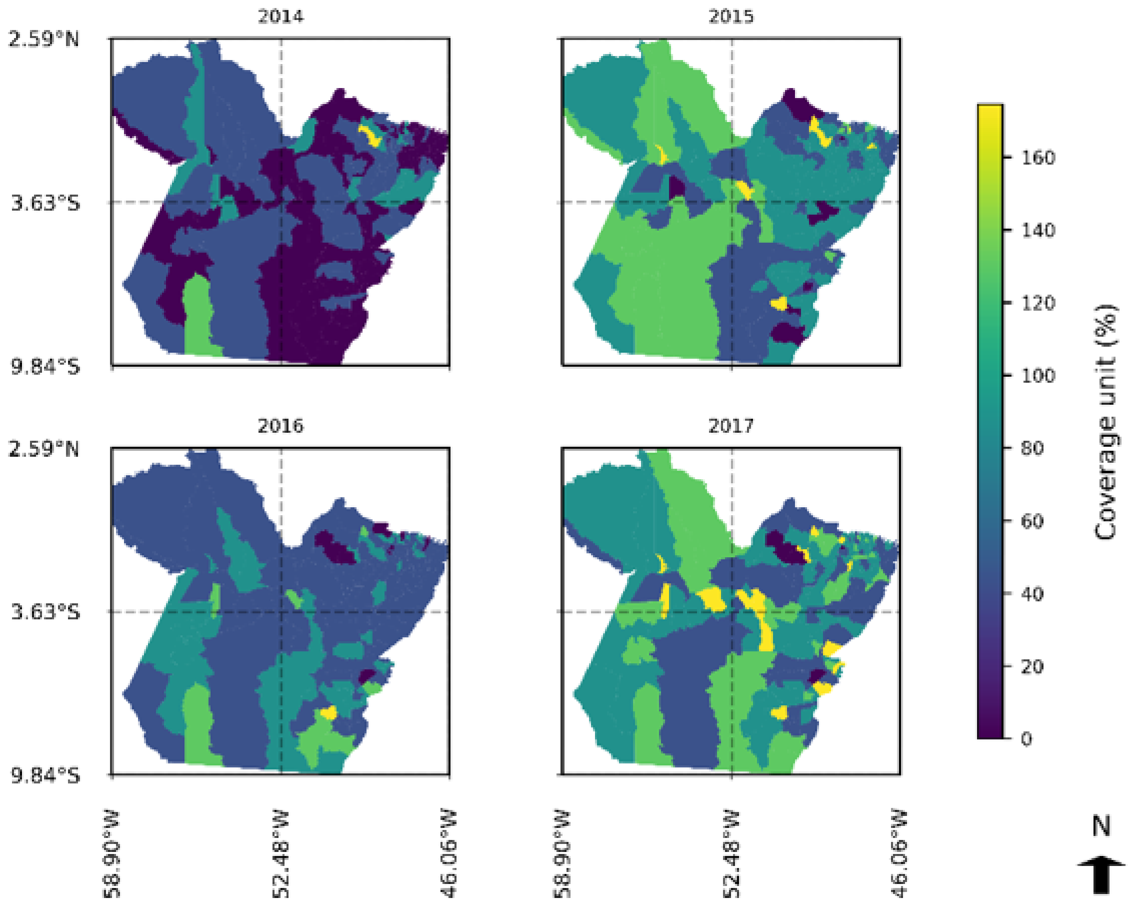

Figure 8

Annual HAV vaccination percentage per municipality for Pará state, 2014-2017.

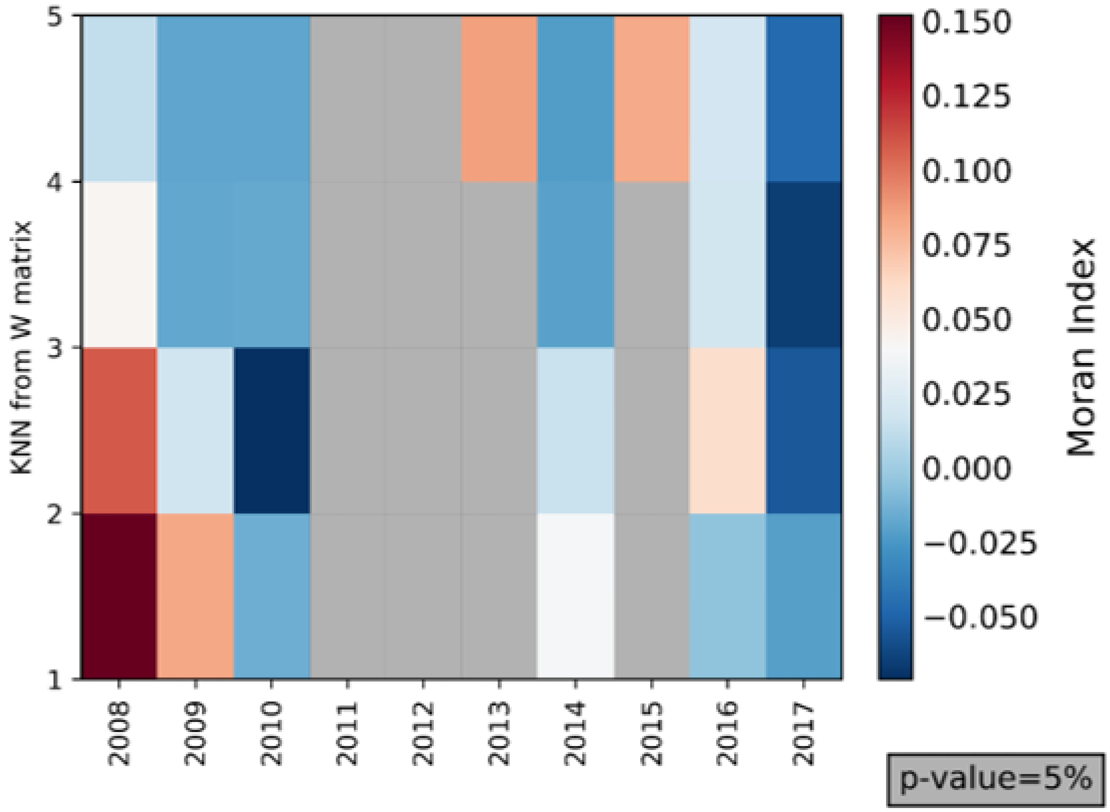

Figure 9

Annual Global Moran Index per KNN W matrix for HAV incidence in Pará state

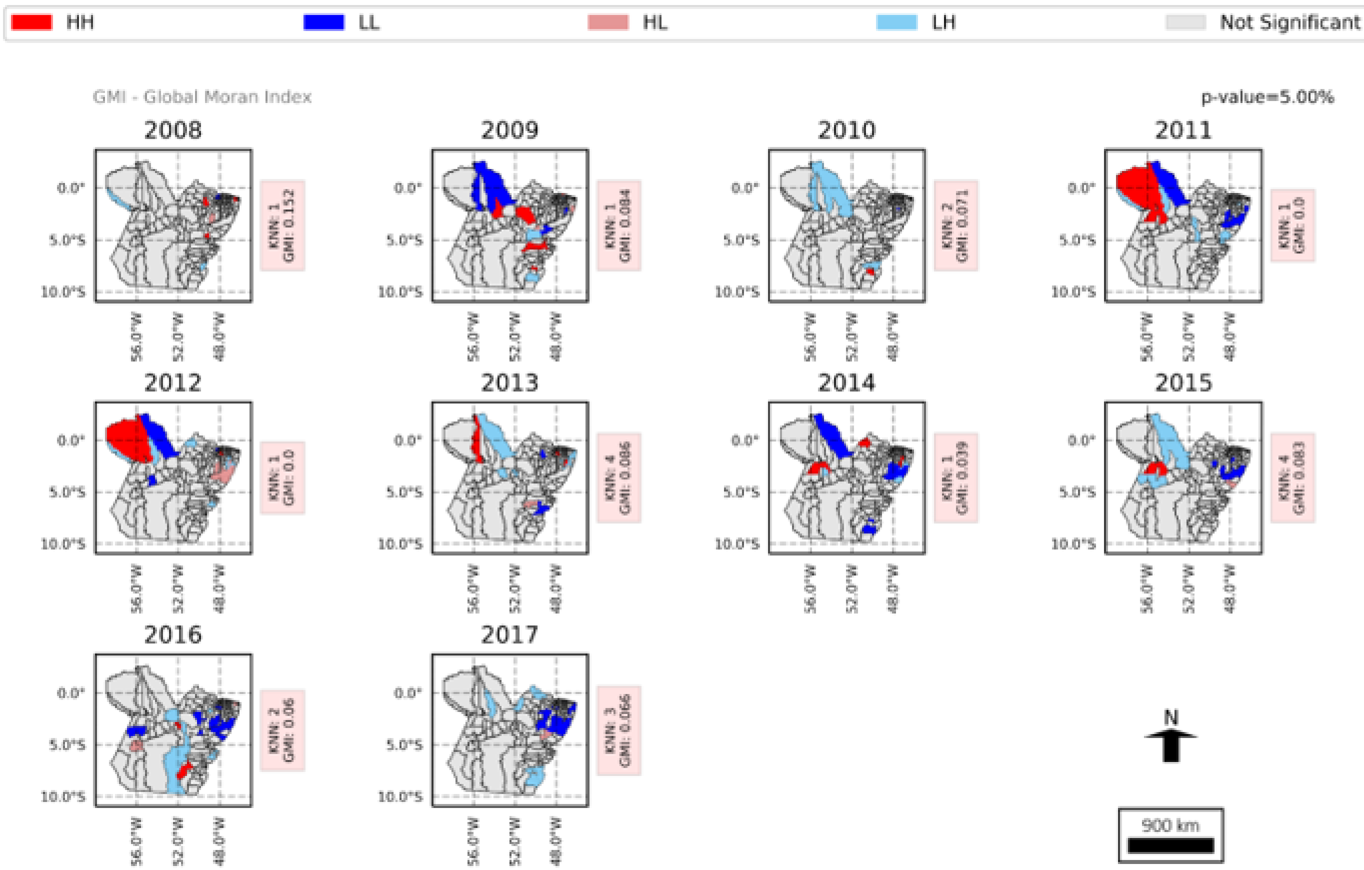

Figure 10

Local Indicators of Spatial Association (LISA) per year (2008-2017) in Pará's municipalities based on HAV incidence data, and respective annual GMI.

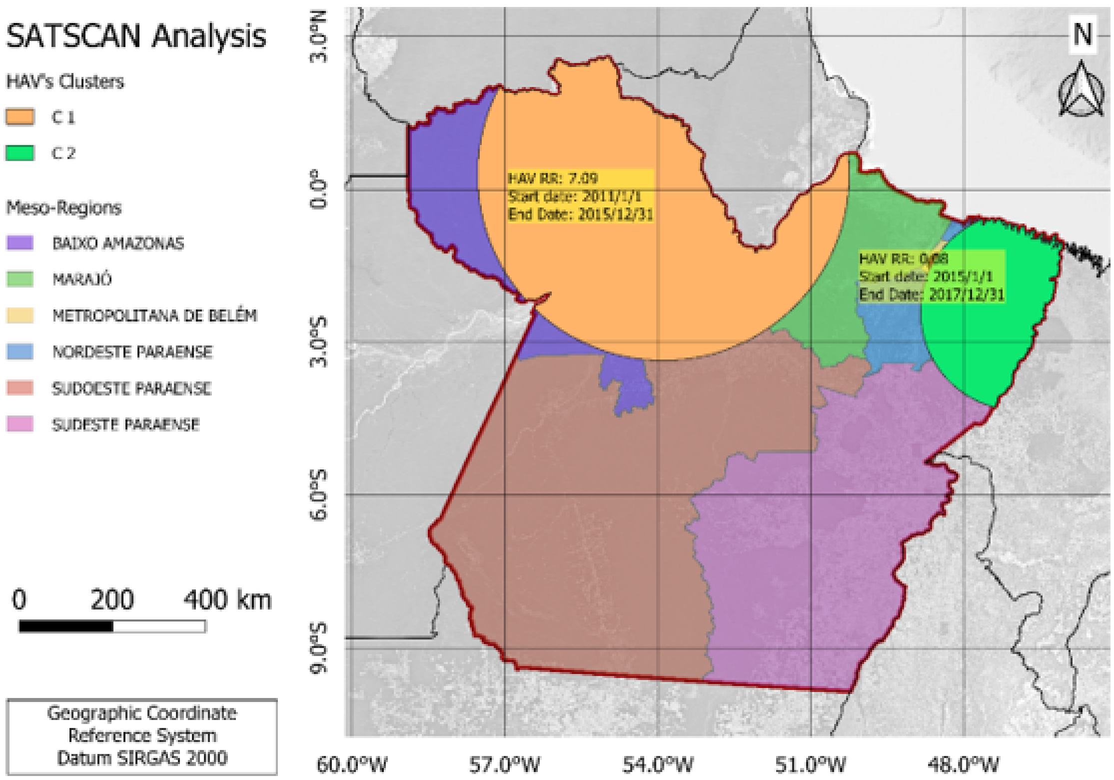

Figure 11

Space-Time Scan analysis of anti-HAV vaccination coverage in Pará state, between 2008-2015. All clusters (orange – C1 and green – C2).