

Spatial dependence of malaria epidemics in municipalities of the Brazilian Amazon

Dependência espacial das epidemias de malária em municípios da Amazônia Brasileira

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ABSTRACT: *Introduction:* In 2010, there were 305 (37.8%) municipalities with malaria epidemics in the Brazilian Amazon. The epidemics spread can be explained by the spatial distribution pattern. *Objective:* To analyze the spatial dependence, autocorrelation, of the malaria epidemics in the municipalities of this region. *Methods:* An automated algorithm was used for the detection of epidemic municipalities in 2003, 2007 and 2010. Spatial dependence was analyzed by applying the global and local Moran index on the epidemic months proportion variable. The epidemic municipalities clusters were identified using the TerraView software. *Results:* The global Moran index values were 0.4 in 2003; 0.6 in 2007; and 0.5 in 2010 ($p = 0.01$), confirming the spatial dependence among the epidemic municipalities. Box Map and Moran Map identified inter-municipal, interstate and borders clusters with spatial autocorrelation ($p < 0.05$). There were 10 epidemic municipalities clusters in 2003; 9 in 2007 and 8 in 2010. *Discussion:* The epidemic municipalities clusters may be linked to the health facilities difficulties on acting together. The structural limitations of the health services can be overcome by territorial integration to support planning and control activities, strengthening the interventions. *Conclusion:* The routine analysis of the epidemic municipalities clusters with spatial and temporal persistence may provide a new indicator of planning and integrated control prioritization, contributing to malaria epidemics reducing in inter-municipal, interstate and borders areas.

Keywords: Malaria. Epidemics. Spatial analysis. Epidemiology. Planning. Amazonian Ecosystem.

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Conflict of interests: nothing to declare – **Financing source:** none.

RESUMO: *Introdução:* Em 2010, foram observados 305 (37,8%) municípios com epidemias de malária na Amazônia brasileira. A propagação dos eventos epidêmicos pode ser explicada pelo padrão da distribuição espacial. *Objetivo:* Analisar a dependência espacial, autocorrelação, das epidemias de malária nos municípios dessa região. Métodos: Foi utilizado algoritmo automatizado para detecção dos municípios epidêmicos nos anos de 2003, 2007 e 2010. A dependência espacial foi analisada por meio da variável *proporção de meses epidêmicos*, aplicando-se os índices de Moran global e local. Foram identificados os agrupamentos de municípios epidêmicos com o programa TerraView. *Resultados:* Os valores do índice global de Moran foram 0,4 em 2003; 0,6 em 2007; e 0,5 em 2010 ($p = 0,01$), confirmando a existência de dependência espacial entre os municípios epidêmicos. O Box Map e o Moran Map identificaram agrupamentos intermunicipais, interestaduais e fronteiriços com autocorrelação espacial estaticamente significativa, sendo 10 clusters em 2003; 9 em 2007; e 8 em 2010 ($p < 0,05$). *Discussão:* Agrupamentos de municípios epidêmicos podem estar vinculados às dificuldades dos serviços de saúde em atuar articuladamente. Limitações estruturais podem ser superadas buscando a integração territorial para sustentação do planejamento e ações de controle, potencializando as intervenções no contexto espacial abrangente. *Conclusão:* A análise rotineira da autocorrelação espacial entre municípios epidêmicos, identificando os agrupamentos com persistência espaço-temporal, poderá fornecer novo indicador de grande utilidade para o planejamento e priorização do controle integrado, no âmbito intermunicipal, interestadual e nas áreas de fronteiras, contribuindo para a redução das epidemias de malária.

Palavras-chave: Malária. Epidemias. Análise espacial. Epidemiologia. Planejamento. Ecossistema Amazônico.

INTRODUCTION

Malaria epidemics are usually influenced by multicausal processes, especially involving environmental (vegetation, climate and hydrology); sociodemographic (migrations, population density, socioeconomic situation and labor activity of the population); biological (species and density of mosquitoes from the *Anopheles* gender, *Plasmodium* species, and level of immunity in the population) and; political/organizational aspects (territorial division, organization and effectiveness of health services, disordered soil occupation, presence of large farming and infrastructure enterprises). Because these factors are so complex, one aspect that should be observed in the organization of planning and control actions is the spatial distribution of the disease. Patterns of morbidity and propagation of epidemics cannot be fully understood without approaching space as a category of analysis. The methods applied for spatial analysis have been mostly used to detect disease clusters, to find high risk areas, to plan for control actions and to monitor health status¹, thus providing information to subsidize the proper conduction of investigative actions and injury control.

A study conducted in Brazil used the quartile control diagram to characterize the distribution of malaria epidemics in a city from the endemic region². However, besides local approaches, it is also necessary to consider the level of spatial dependence of malaria

epidemics in all of the municipalities of the region, in order to incorporate this information in the options of decision makers.

Significant autocorrelation values show that spatial dependence and inferential models should consider space to be formulated³, pointing out to priority areas for control actions.

The method used in Brazil to prioritize cities for malaria control is based on the Annual Parasite Index⁴. The sensitivity of this index is reduced after being applied to large geographic spaces. However, it is known that malaria epidemics present patterns of spatial cluster, which often surpasses the limits and political-administrative divisions inside the municipal and state territories, thus requiring joint efforts to solve the problem. The epidemic process eventually needs international cooperation to be contained. Some studies identified groups of regions to explain disease transmission, by applying the global and local Moran's index, such as the classification of several types of cancer in Germany⁵ and the spatial analysis of dengue fever in the city of Rio de Janeiro⁶. The Moran's indexes were also used to determine priority areas for malaria control in Rondônia⁷, Mato Grosso⁸ and Roraima⁹.

The Moran's indexes are indicated for the spatial analysis of areas when events are clustered by cities or other divisions characterizing regions, and when it is not possible to establish the exact location of the occurrences, but instead, values represented by indicators such as rates, proportions, means or medians¹⁰. The spatial disease cluster may be attributed to demographic, environmental or sociocultural factors that are geographically superposed, referring to an unexpected cluster in space and/or time¹¹. Therefore, knowing the structure and spatial dynamics is important to characterize health-related situations¹². This study aimed at analyzing spatial dependence, autocorrelation, of malaria epidemics in the municipalities of the Brazilian Amazon, in 2003, 2007 and 2010, in order to create thematic maps that can contribute with the understanding about the spatial distribution of epidemic phenomena in the region.

METHODS

The Brazilian Amazon (BA) is the endemic area for malaria. It is composed of 807 cities belonging to the states of Acre (AC), Amapá (AP), Amazonas (AM), Maranhão (MA), Mato Grosso (MT), Pará (PA), Rondônia (RO), Roraima (RR), and Tocantins (TO). Out of these, 52 cities have borders with seven countries: Bolivia, Colombia, Guiana, French Guiana, Peru, Suriname and Venezuela. In order to understand disease control in this region, a flowchart was elaborated for the main procedures in each managerial department: Municipal Secretariat of Health (SMS), State Secretariat of Health (SES) and Ministry of Health (MS). Epidemic cities were identified after the elaboration of an automated algorithm¹³ that used codes from the Epi Info software¹⁴, which resulted in the Surveillance System for the Incidence of Malaria in the Brazilian Amazon (SIMAM). This system processed data from 2003 to 2010, which were provided by MS. To identify epidemics, SIMAM calculated the 3rd quartile of the control diagram used to control the series of cases in each city, according

to a study conducted in Brazil¹⁵. The duration of the epidemics was classified into: short term (1 to 4 epidemic months during the year); mid-term (5 to 8 months); and long term (9 to 12 months).

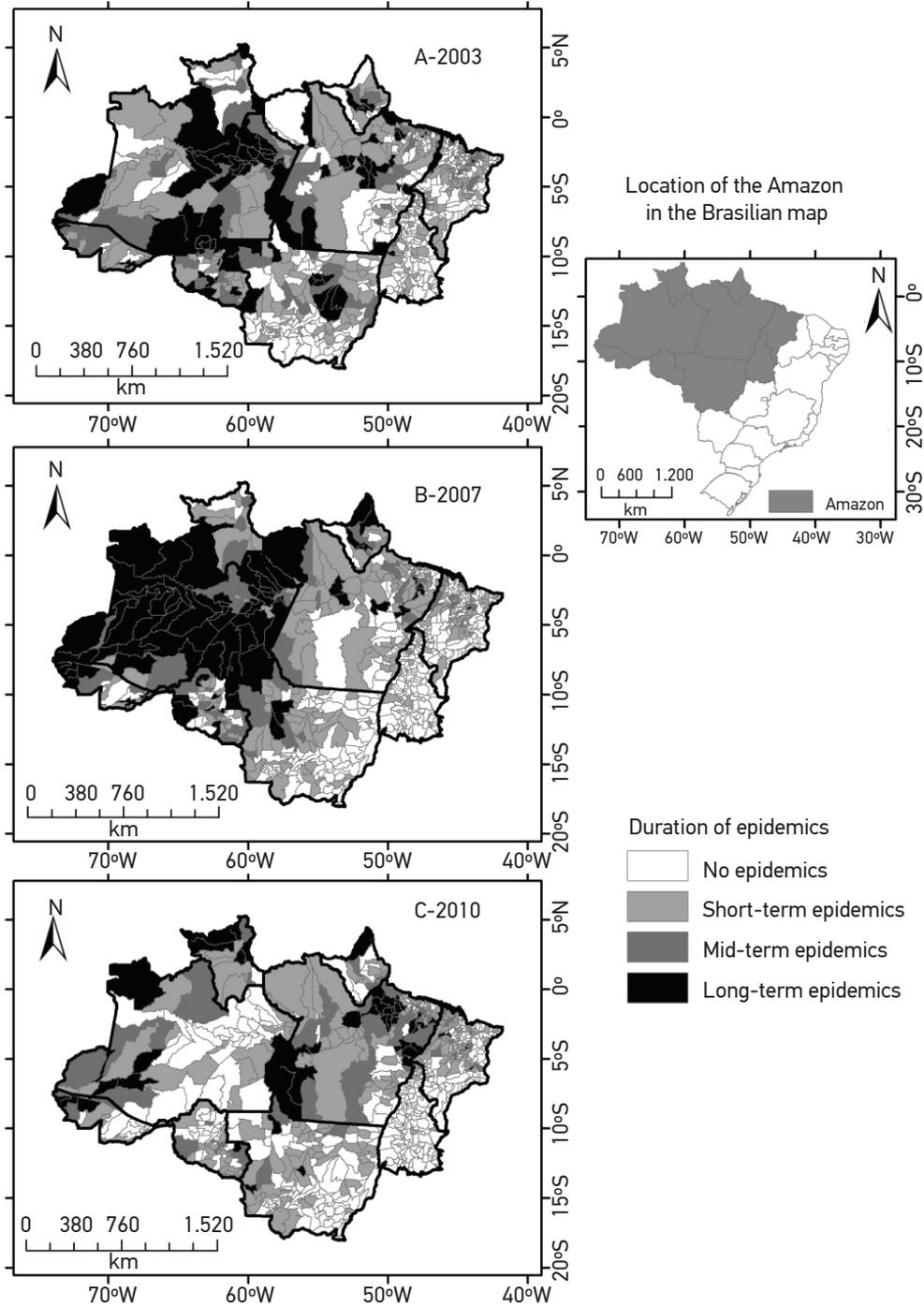
The spatial dependence of epidemics was observed by the random variable *proportion of epidemic months*, in 2003, 2007 and 2010. These years were considered to be sufficient to verify the spatial-temporal dynamics of autocorrelation. Autocorrelation derives from the statistical concept of correlation between two variables, and its formulation has been modified in spatial studies^{3,10}. This indicates that correlation is measured for the same random variable in different locations in space. Spatial analysis was conducted in three stages with the TerraView software¹⁶: (1) visualization of the distribution according to the duration of epidemics; (2) calculation of the global Moran's Index (GMI); (3) calculation of the local Moran's Index (LMI). The maps of the cities were obtained from the Computing Department of the Unified Health System (SUS)¹⁷. The null hypothesis (H_0) tested by the GMI was that of spatial independence between cities concerning the random variable. Positive values between 0 and +1 indicated direct autocorrelation, and negative values between 0 and -1 showed inverse autocorrelation, with a statistical significance test for $p \leq 0.01$. The LMI produced normalized values, Z (values for the variable proportion of epidemic months subtracted from the mean and divided by standard deviation), for each city. It also generated the weighted mean of the variable for the respective neighboring cities, Wz . These values allowed identifying city clusters with a statistically significant pattern of spatial association. The values resulting from this operation represent the quadrants in the Moran scattering diagram. Quadrant 1 (Q1 +/+) was composed of cities with positive values from the normalized variable, being the weighted mean of the neighboring cities also positive, which meant direct positive spatial autocorrelation. In quadrant 2 (Q2 -/-), there were cities with negative values from the normalized variable, with negative weighted mean for the neighboring cities, which indicated inverse positive spatial autocorrelation. Quadrant 3 (Q3 +/ -) had cities with positive values from the normalized variable, with negative weighted mean for the neighboring cities, which points to negative autocorrelation. Quadrant 4 (Q4 -/ +) had cities with negative values from the normalized variable, with positive weighted mean for the neighboring cities, which also indicated negative spatial autocorrelation.

The Box Map was elaborated to identify spatial dependence, representing the LMI, in which Q1 represented cities with long term epidemics; Q2, cities with no epidemics or with shorter periods of epidemics; Q3, cities with epidemics that lasted longer, and neighboring cities without epidemics or with short term epidemics; and Q4, cities without epidemics or with short term epidemics, and neighboring cities with long term epidemics. The Moran Map was built with the same quadrants (Q1, Q2, Q3, Q4) to visualize only the areas that presented statistically significant autocorrelation ($p \leq 0.05$). However, the 0 category (zero) was added to identify cities with non-significant autocorrelation. It is worth to mention that this project was approved by the Research Ethics Committee from the Medical School at *Universidade de Brasília*.

RESULTS

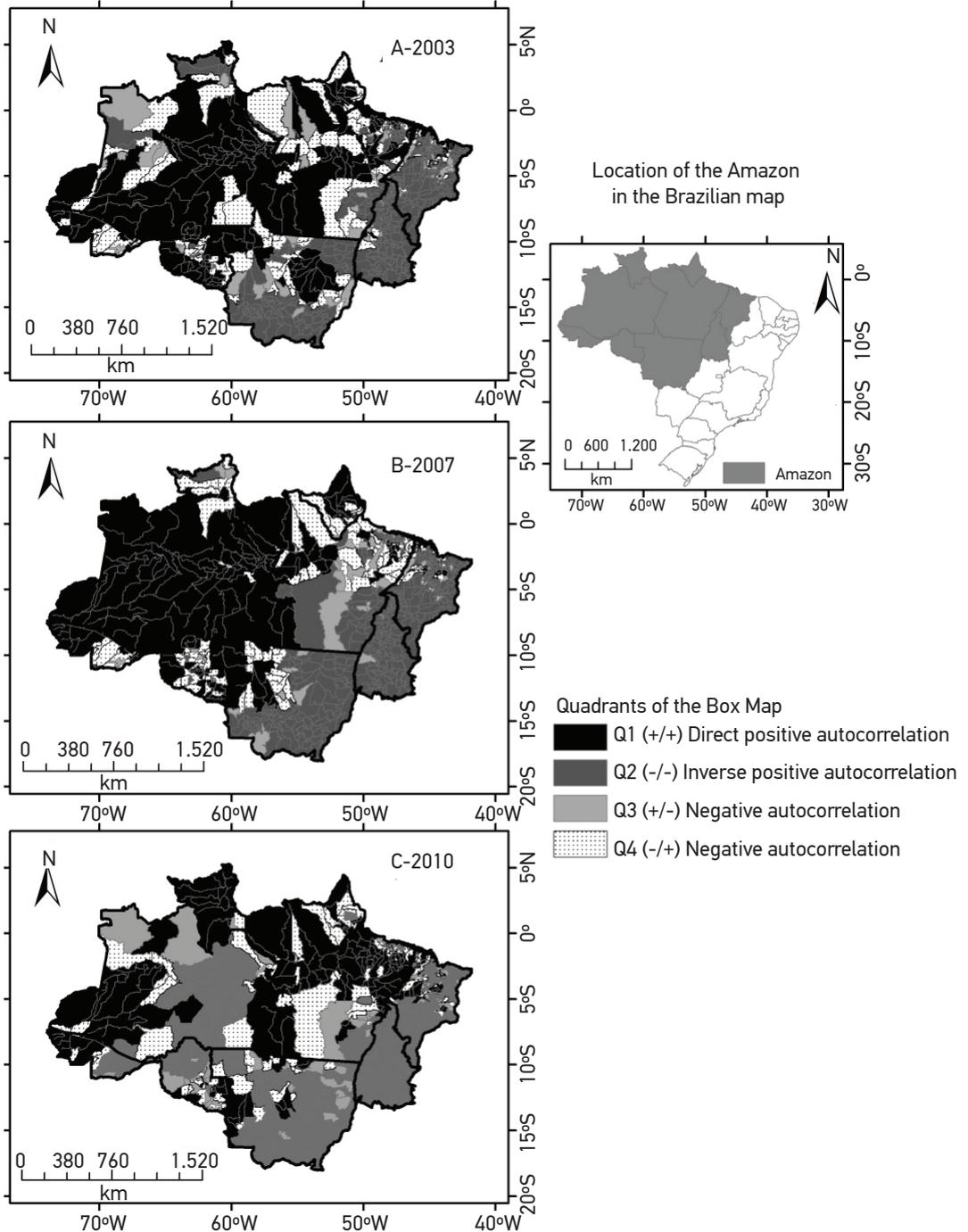
Planning and control actions for malaria in the BA are conducted by SMS, SES and MS, according to specific attributions. Most control actions are daily executed by SMS, especially those involving diagnosis and treatment of the patient, active detection of cases, investigation of risk factors, control of vectors and health education. The attributes of SMS and SES are related to their respective political-administration territories, with the possibility of carrying out joint actions when the health issue surpasses territorial limits, since both interested parties have agreed to it. In 2003, 408,832 cases of the disease were notified in BA; in 2007, 457,409 cases; and, in 2010, 333,372 cases. In 2003, there were short term epidemics in 208 cities (25.8% of the total number of municipalities in the region). This number reduced to 203 (25.2%), in 2007, and to 185 (22.9%), in 2010. Mid-term epidemics occurred in 103 cities (12.8%), in 2003; in 62 cities (7.7%), in 2007; and in 72 cities (8.9%), in 2010. Most cities with long term epidemics formed predominant clusters in states with higher incidence of malaria, while those with mid-term epidemics were closer to cities with long term epidemics. Cities with short term epidemics were sporadically distributed in the region. Some clusters transcended the geopolitical space of state divisions, also affecting international border areas in the states of AC, AM, AP, PA, RR and RO (Figures 1A to 1C). GMI values were: 0.4, in 2003; 0.6, in 2007; and 0.5, in 2010 ($p = 0.01$ in the three years), which confirms the existence of spatial dependence in epidemics in the cities of BA. Autocorrelation increased in 2007, in comparison to 2003, but, in 2010, numbers were similar to those of 2003. The results in the Box Map (Figure 2) enabled to verify the dynamics of the random variable in the cities, and it also identified homogeneous areas. In Q1 (+/+), 198 cities were observed in 2003 (24.6% of the region); 159 (19.7%), in 2007; and 181 (22.4%), in 2010. Q1 incorporated cities with mid and long term epidemics, suggesting that cities with long term epidemics have strong spatial influence on those with mid-term epidemics. Q2 (-/-) found most cities in the region, including those with shorter epidemics, or with no records of the epidemic phenomenon. In Q2, 403 cities were observed (50.1% of the region) in 2003; 473 (58.6%), in 2007; and 445 cities (55.1%) in 2010. In quadrant Q3 (+/-), 62 cities were detected (7.7% of the region) in 2003; 50 (6.2%), in 2007; and 59 (7.3%), in 2010. In Q4 (-/+), 142 cities were identified (17.6% of the region) in 2003; 123 (15.2%), in 2007; and 120 (14.9%), in 2010. The maps generated by Box Map showed the autocorrelation measured by the LMI, regardless of the significance level and the variation of the attribute throughout time for most cities, even in states with low transmission of malaria, such as MT, TO and MA (Figures 2A to 2C).

The spatial dependence of epidemics detected by the Moran Map (Figure 3) was only observed in cities with statistically significant spatial autocorrelation ($p \leq 0.05$). In Q1 (+/+) 101 cities were found in 2003 (12.5% of the total); 96 (11.9%), in 2007; and 88 (10.9%), in 2010. Seven cities remained in this quadrant in the three years. In Q2 (-/-), there were 165 cities in 2003 (20.5%); 166 (20.6%), in 2007; and 196 (24.3%), in 2010. Also, in Q2, 67 cities were present in the three years. In Q3 (+/-), there



Source: Surveillance System for the Incidence of Malaria in the Brazilian Amazon (SIMAM).

Figure 1. Distribution of cities with malaria epidemics, according to the duration of the epidemic phenomenon. Brazilian Amazon, 2003, 2007 and 2010.



Source: Surveillance System for the Incidence of Malaria in the Brazilian Amazon (SIMAM).

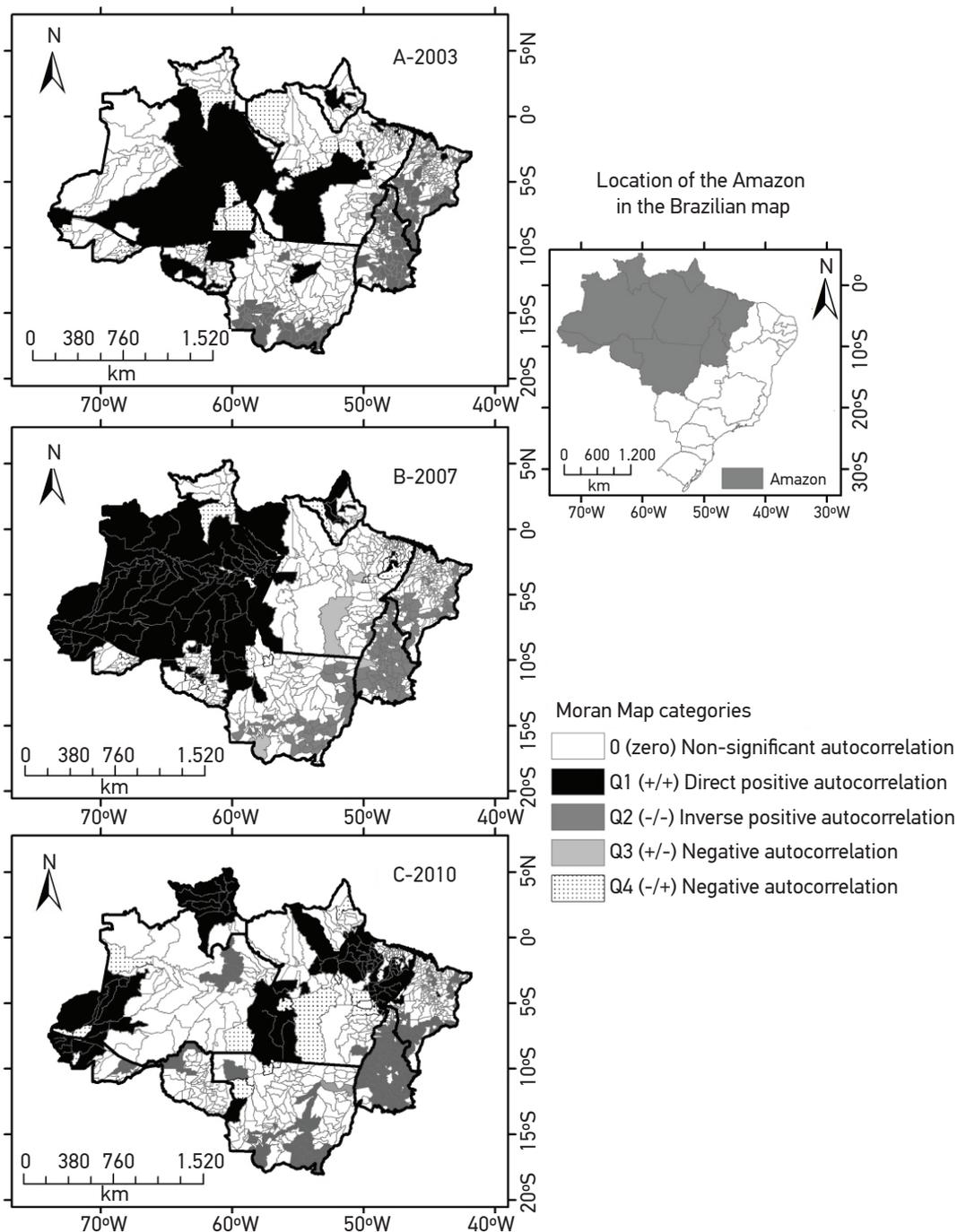
Figure 2. Box Map for the proportion of epidemic months in the cities of the endemic area. Brazilian Amazon, 2003, 2007 and 2010.

were 8 cities in 2003 (1.0%); 5 (0.6%), in 2007; and 5 (0.6%), in 2010. In Q3, no cities were present in the three years. In Q4 (-/+). 30 cities were detected in 2003 (3.7%); 21 (2.6%), in 2007; and 28 (3.5%), in 2010. No cities were present in Q4 in all of the analyzed years. The spatial dependence of epidemics in the cities was shown by the Moran Map, and clusters were located in Q1. In this quadrant, three types of clusters were observed: (1) intermunicipal cluster, in which all cities were part of the same state; (2) interstate cluster, in which cities belonged to different states; and (3) border cluster, in which cities belonged to one or more states, however, some of them were in international border areas.

In 2003, ten clusters were detected in the Q1 in the Moran Map. The first one was composed of four cities located in the borders of AM (1), AC (3) and the frontier with Peru. The second had ten cities in the borders of AM (1), RO (5) and MT (4). The third cluster was comprised of six cities: AM (4), RR (2) and the border with Venezuela. The fourth cluster was composed of four cities: AM (3) and PA (1). The fifth one had ten cities: AM (3), AC (1), RO (6) and the frontier with Bolivia. The sixth cluster had 24 cities, all of them in AM. The seventh was comprised of 8 cities, all of them in PA. The eighth cluster had 5 cities, all of them in AP. The ninth cluster had 6 cities, all of them in MT. And the tenth cluster had 10 cities located in RO and in the frontier with Bolivia (Figure 3A).

The Moran Map showed that, in 2007, the 96 cities located in the Q1 formed a large cluster, which was subdivided into 9 clusters in order to facilitate geopolitical and administrative understanding. The first one was composed of 14 cities located in AM (6), AC (8) and the border with Peru. The second one was composed of six cities located in AM (3) and MT (3). The third cluster had 11 cities located in AM (5), RR (4), PA (2) and in the frontier with Venezuela. The fourth cluster had six cities located in AM (4) and PA (2). The fifth one had six cities located in AM (3), AC (1), RO (2) and the frontier with Bolivia. The sixth cluster was composed of 37 cities located in AM and in the border with Colombia. The seventh cluster had three cities located in PA. The eighth cluster had five cities located in AP and in the border with the French Guiana. The ninth cluster had four cities located in RO (Figure 3B).

In 2010, there was an expressive reduction in the number of epidemic cities in the state of AM; on the other hand, the situation became more complicated in PA. There were eight clusters in the cities located in Q1. The first one was composed of ten cities, located in AM (3), AC (7) and in the frontier with Peru. The second one was composed of ten cities, all of them in RR and in the borders with Venezuela and Guiana. The third cluster had seven cities located in AM (2) and PA (5). The fourth cluster had four cities located in PA (3) and MA (1). The fifth one had eight cities, all of them in MA and in the border with Colombia. The sixth cluster had four cities located in the region of Marajó, in PA (2) and AP (2). The seventh one had 39 cities, all of them in PA. And the eighth cluster had three cities, all of them located in MT (Figure 3C).



Source: Surveillance System for the Incidence of Malaria in the Brazilian Amazon (SIMAM).

Figure 3. Moran Map for the proportion of epidemic months in cities of the endemic area. Brazilian Amazon, 2003, 2007 and 2010.

DISCUSSION

The unacceptable load of malaria and its socioeconomic impact makes it important to improve the disease control. One of the issues is the operational limits of health services, including inadequate tools to interrupt transmissions in some locations¹⁸. In that regard, the Federal Court of Accounts declared that it is important to raise awareness among administrators so that they can provide political and managerial support for the creation of surveillance and control actions toward malaria. Therefore, it would be possible to reduce the “exportation” of cases from states and cities with poor action to others, where the action is more effective¹⁹. Some limitations can be overcome by searching for territorial integration to support control actions in the cities, by involving the states²⁰, and also the federal scope, in order to give more power to interventions in a wider spatial context. The search for territorialization in health has been adopted by several initiatives; however, usually the concept of space is reduced to administration, so the potential of this concept is neglected for the identification of sanitary problems and proposals for intervention²¹. In the case of malaria epidemics, the need for the proper management of the territory to achieve successful control became clear, due to its transcendence in the political-administrative space.

The distribution and duration of epidemics in BA may be connected to difficulties of the health services to give an articulate response with effective contention actions. The duration of the epidemics is marked by an interval, that begins and ends²², and a period of time from one to four months was adequate to interrupt the phenomenon, since most cities could control the events in this period of time. Due to the diversity of factors involved in the transmission of malaria, its effective control requires the execution of integrated planning actions to neutralize the effect of spatial dependency of epidemics in the cities.

The patterns of morbidity and propagation of epidemics cannot be explained without an approach that considers space and time. The spatial distribution that was found provided the previous notion of groups of epidemic cities that required the most attention. However, it was necessary to improve the analysis by incorporating techniques of statistical classification of the spatial structure of epidemics, examining patterns and identifying clusters, according to Moran's indexes. The values of spatial autocorrelation represented by the GMI were close to those observed for the risk of contracting malaria in the state of RR (≤ 0.5)⁹ and RO (0.5 to 0.7)⁷, however, they were higher than the values found in MT (0.3 to 0.4)⁸. This shows that the duration of epidemics and the risk of contracting malaria can go on the same direction to subsidize the priority of control actions. The results presented significance evidence of spatial dependence, both in the state and in the municipal scopes, which suggests that geographic location is important to determine epidemics. Therefore, it is necessary to consider the spatial association of the disease in the neighboring cities, based on factors that extrapolate the geographic boundaries defined by criteria that are exclusively political

and administrative. However, because this measure of autocorrelation produced a single value for the global set of the cities, it only expressed the spatial dependence of the region as a whole, and required details by the LMI.

By applying the referred index, it was possible to identify the homogeneous areas and to classify differentiated clusters, by ruling out the spatial randomization in the distribution of cities with longer epidemics. The clusters presenting statistically significant spatial autocorrelation, represented in Q1 of the Moran Map, were considered to be critical, since it gathered cities with more severe epidemic processes. The influence of neighboring cities in the dynamics of distributing the proportion of epidemic months caused changes, which could be seen in some clusters in the analyzed years. This occurrence was related to several factors, which contributed with the increasing incidence and the consequent production of malaria epidemics. However, it is important to emphasize that matters related to the intermunicipal organization of health services may have had strong influence on the longer duration of epidemics in homogeneous areas with positive direct autocorrelation, as demonstrated in Q1 in the Box Map and in the Moran Map. By improving the organization of the of the assistance network, it will be possible to achieve the regional integration of actions and health services with the integrated regional planning, which will be able to ensure qualified ongoing attention. This aspect is currently prioritized in SUS. The integration of health services in specific regions aims at ensuring full assistance, and counts on legal instruments that enable the financing of articulated actions between states and cities²³. The execution of integrated control actions can prevent the long duration of epidemics and reduce the high levels of incidence of the diseases. Even though the competences for control actions addressed to malaria are specifically defined for each managerial department²⁴, the planning system should work for an ongoing, articulated, integrated, solidary and harmonic activity of the three managerial departments. This type of work will lead to the consolidation of the planning culture simultaneously with the other developed actions, with established pacts and strict analysis of the role of each governmental sphere²⁵.

Concerning the clusters generated by the Moran Map, the one located to the southeast of AM and northwest of AC, also bordering Peru, stands out. Despite the varied number of cities throughout the years, it was persistent in the three analyzed years. The same was observed in the triple frontier of AM, PA and MT. An identical situation was seen in AP, where cities changes, however, an epidemic cluster was always present in that state. The border frontier the states of RO and MT also had epidemic clusters in the cities in the three studied years. Differently, the state of RR and the southeast of PA presented worse epidemic situation from 2010 on, which reinforces the need for a periodic update in this type of study to provide information addressed to integrated planning and control actions. These clusters required intermunicipal actions, which should have been coordinated by SES when the matter was still restricted to the state. However, in places where state frontiers were surpassed, MS should play an articulating role, both for the integrated planning and the development of control actions with SMS and SES. However, it is important to care

for the risks imposed by malaria in international frontiers. In these areas, twin cities are important for mobility, which favors the transmission of malaria²⁶, as it could be seen in frontiers with the states of AC, AM, AP and RR. Other factors that contribute with the progress of the disease is the deforestation of large areas and the contact between lumberjacks, miners and indigenous populations²⁷. Despite the identified difficulties, the public sector is still prevalent in the frontiers with regard to the operation of the basic health network, considering the possibility of integrating local health systems²⁸. The mitigation of the issue of malaria in frontier areas depends on the constant knowledge concerning the epidemiological situation, and also on the international cooperation between Brazil and the involved countries, which requires permanent articulation about planning and systematic execution of disease control. It is recommended that the Program for Malaria Control can ensure the analysis of the situation of the disease in frontier cities and their respective neighboring countries. Therefore, together with the Pan American Health Organization (OPAS), it is possible to articulate planning and disease control actions, using the already available mechanism from the Amazon Surveillance Network of Antimalarial Resistance (RAVREDA) and from the Initiative Against Malaria in the Amazon (AMI)²⁹.

CONCLUSION

This study showed there is spatial dependence of malaria epidemics in the cities of the BA, which is characterized by the direct and positive autocorrelation, and that the special dependence of epidemics determined the occurrence of epidemic clusters of cities with intermunicipal, interstate and inter-border characteristics. This scenario requires the permanent analysis of the spatial dependence of epidemics in the cities, by detecting clusters with space-temporal persistence and by characterizing them as important indicators for planning and priorities in terms of integrated control actions, be them intermunicipal, interstate or inter-borders, therefore contributing with the reduction in disease epidemics.

The Box Map was a more sensitive tool to detect epidemic clusters of cities, so its use provided better performance in areas of low and moderate malaria transmission. At the same time, the Moran Map was more specific, ideal to identify epidemic clusters in areas of high transmission, where epidemics lasted longer. The daily application of instruments for spatial analyses in health services, aiming at surveillance and malaria control, may have positive effects on future results. However, it is still a major challenge that can be overcome with investments in technical formation of professionals who are directly involved in the disease control in the three managerial spheres, especially if there are political priorities in relation to regional planning and control, as it has been predicted in the organic guidelines of SUS for a long time.

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Received on: 02/05/2013

Final version presented on: 01/13/2014

Accepted on: 02/14/2014

ERRATUM

Brazilian Journal of Epidemiology 2014;17(3): 615, 617, 619, 621, 623, 625 e 627
DOI: 10.1590/1809-4503201400030004

Article: Dependência espacial das epidemias de malária em municípios da Amazônia Brasileira

On pages 615, 617, 619, 621, 623, 625 e 627, where it reads:
Spatial dependence of malaria epidemics in municipalities of the Amazonian Ecosystem

It should read:
Spatial dependence of malaria epidemics in municipalities of the Brazilian Amazon