FACULDADE DE MEDICINA DO ABC

MEYRECLER AGLAIR DE OLIVEIRA PADILHA

PROCESSOS ASSOCIADOS AO DECLÍNIO DO FARDO DA MALÁRIA: O PARADOXO DA PERDA DE FLORESTA AMAZÔNICA

SANTO ANDRÉ

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Dissertação elaborada no Setor de Pós-Graduação Pesquisa e Inovação apresentada ao Programa de Pós Graduação em Ciências da Saúde da Faculdade de Medicina do ABC, (recomendado pelo Conselho Técnico-Científico CAPES – Portaria MEC Nº 1225 de 05/10/2010).

Área de Concentração: Saúde Coletiva

Orientador: Prof. Dr. Gabriel Zorello Laporta

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P123p Padilha, Meyrecler Aglair de Oliveira
Processos associados ao declínio do fardo da Malária: o paradoxo da perda de floresta Amazônica. / Meyrecler Aglair de Oliveira Padilha -- Santo André, SP, 2018.
43 f.: il.color. 31 cm.

Dissertação (Mestrado em Ciências da Saúde) – Comissão de Pós-Graduação, Faculdade de Medicina do ABC.
Area de concentração: Saúde Coletiva
Orientador: Prof. Dr. Gabriel Zorello Laporta

1. Malária. 2. Conservação dos recursos naturais.
3. Ecossistema amazônico.

CDD: 614
NLM: WA100

DEDICATÓRIA

A meu esposo Luiz Padilha e minhas filhas Ana Vitória e Júlia Ludimili, por proporcionarem que alcançasse essa conquista, por suportarem as ausências e por estarem ao meu lado nas horas que mais precisei, o meu amor, respeito e sincera gratidão a vocês. Os amarei eternamente.

AGRADECIMENTOS

Ao professor Dr. Gabriel Zorello Laporta pela grandiosa orientação, sempre atencioso com palavras positivas e pela confiança depositada a mim.

Ao professor Dr. Luiz Carlos de Abreu pelas colaborações e incentivos à pesquisa.

Ao professor Dr. Rodrigo Medeiros pelas conversas enriquecedoras com aquisição de novos aprendizados.

Ao Dr. Josimar Freitas pelas horas de estudos e dicas significantes para o aperfeiçoamento deste trabalho.

Ao Dr. Wladimir J. Alonso, Guilherme Romano, Marcos V. M. Lima e Janille O. Mello pela parceria e colaboração no artigo científico.

Aos meus pais e irmãos pelo apoio e carinho nesta conquista.

A minha família na pessoa do meu amado, amigo, parceiro e esposo Luiz Padilha pela compreensão, incentivo e muito apoio nesta caminhada.

A minha amiga Leonor que ficou muitas vezes com minhas filhas enquanto viajava.

A Joneide Correia pela amizade, respeito e parceria nas viagens e estudos.

As gestoras Sernízia Correia e Darci Nicácio pela compreensão e apoio nas ausências do trabalho para viagens na realização dos estudos.

A parceria da FMABC, SESACRE e UFAC para a execução do mestrado.

A todos que direta e indiretamente colaboraram para a concretização dessa pesquisa.

RESUMO

Introdução: A malária persiste como um dos grandes problemas de saúde pública do mundo. No Brasil os casos de malária concentram-se principalmente na Região Amazônica. Objetivo: O estudo teve como objetivo descrever o paradoxo da correlação entre o atual padrão de eliminação da malária e a redução das florestas amazônicas no Brasil. Método: A investigação começou com a exploração das taxas mensais de incidência de óbitos 1979-2013 e hospitalizações de 1998-2013 atribuíveis à malária por estados brasileiros. Embora tenha sido observado um declínio acentuado da carga de malária (ou seja, mortes e hospitalizações), os estados da Amazônia Ocidental, Acre e Rondônia, mostraram focos endêmicos estabilizados. Assim, investigamos por meio de séries temporais os índices mensais de parasitas de 2009-2015 para cada município nos estados do Acre e Rondônia. Observamos que os municípios de Rondônia vêm diminuíndo o índice mensal de parasitas, enquanto no estado do Acre vem ocorrendo uma transmissão estacionária da malária. Em seguida, selecionamos o município mais endêmico do Acre (Cruzeiro do Sul) para modelar as variações mensais do coeficiente dos casos de malária 2009-2015 em função de quatro conjuntos de variáveis explicativas: 1) Clima, 2) Paisagem, 3) Socioeconômico e 4) Programa de Controle da Malária. Resultados: Após a aplicação de modelos de regressão dinâmica, os parâmetros climáticos e paisagísticos tiveram contribuições importantes: a precipitação foi fortemente correlacionada com o aumento da malária, enquanto o desmatamento foi correlacionado com o declínio da malária. Ambos os resultados podem ser esperados porque representam parâmetros importantes (água e floresta) associados à disponibilidade de hábitat para os mosquitos principalmente o *Anopheles darlingi*. Para validar esse resultado, estimamos o desmatamento no mesmo período para os municípios de Acre e Rondônia com maior incidência de malária. Descobrimos que os municípios do Acre preservaram sua cobertura vegetal, enquanto os municípios de Rondônia aceleraram a perda da cobertura florestal. O estado do Acre tem uma política de preservação da floresta como uma assinatura digital. No entanto, o estado de Rondônia tem utilizado o desmatamento florestal e a pecuária extensiva como meta de desenvolvimento econômico para ocupar terras. Conclusão: Esses resultados indicam caminhos na agenda de eliminação da malária e pode definir o rumo das florestas amazônicas. Todavia, como essas florestas são importantes para a sobrevivência humana, diante desse cenário, investir em políticas públicas eficientes de controle a málaria por meio da melhoria da dimensão socioeconômica, seria essencial.

Palavras-chave: Malária. Conservação dos recursos naturais. Ecossistema amazônico.

ABSTRACT

Introduction: Malaria still is one of the biggest public health problems around the world. In Brazil, malaria cases are concentrated mainly in the Amazon Region. Objective: This study aimed to describe the paradox of the correlation between the current strategies of malaria elimination and the reduction of Amazonian forests in Brazil. Method: The investigation began with the analysis of the monthly mortality rate, 1979-2013, and hospitalizations, 1998-2013, attributable to malaria in Brazilian states. Although an accentuated decline in malaria burden (deaths and hospitalizations) was detected, the states of Western Amazonia, Acre and Rondônia, showed stabilized endemic foci. Thus, we investigated by means of time series the monthly parasite rate, 2009-2015, for each county in the states of Acre and Rondônia. We observed that the counties of Rondônia have been decreasing the monthly parasite rate, while in the state of Acre there has been a stable endemic focus of malaria. Thereafter, we selected the most endemic county in Acre (Cruzeiro do Sul) to model the monthly alterations of the coefficient of malaria cases, 2009-2015, according to four sets of explanatory variables: 1) Climate, 2) Landscape, 3) Socioeconomic and 4) Malaria Control National Program. Results: After the application of dynamic regression models, the climatic and landscape parameters had important contributions: precipitation was strongly linked to the emergence of malaria, while deforestation was linked to the decline of malaria incidence. Both results are expected because they represent important parameters (water and forest) associated with the availability of habitat for mosquitoes, especially *Anopheles darlingi*. To validate this result, we assessed the deforestation in the counties of Acre and Rondônia during the same period of elevated malaria incidence. We found that the counties of Acre preserved their forest cover, while the counties of Rondônia sped up the loss of forest cover. The state of Acre has a forest preservation policy as a digital signature. However, the state of Rondônia has used forest deforestation and extensive cattle ranching as a goal of economic development to occupy land. Conclusion: These results indicate paths to the malaria eradication agenda and may define the fate of the Amazonian rainforests. However, as these forests are important for human survival, in this case, investing in efficient public policies to control malaria by improving the socioeconomic dimension would be essential.

Keywords: Malaria. Conservation of natural resources. Amazonian ecosystem.

SUMÁRIO

1 INTRODUÇÃO

A malária é uma doença parasitária que afeta muitos seres humanos há muitos anos. No Brasil no início da década de 1940 cerca de seis milhões de casos de malária eram registrados a cada ano. Com campanhas e intervenções intensivas, tais como: borrifação residual, pulverização de casas, eliminação de criadouros, drogas antimaláricas, diagnóstico e tratamento precoce, foi possível estabilizar a doença. Todavia, a partir de meados da década de 1960 o paludismo se espalhou para lugares mais favoráveis ao seu desenvolvimento, como a região amazônica que é responsável, por mais de 99,8% da incidência dos casos de malária no país [(1)].

Dessa forma, esta região é palco de muitos estudos relacionados aos fatores que contribuem para a permanência constante do paludismo. Assim, este trabalho teve como objeto de pesquisa a malária e buscou responder a seguinte hipótese: A malária vem em processo de eliminação no Brasil e o desmatamento da floresta amazônica contribui para esta redução?

O trabalho a ser apresentado foi distribuído em cinco capítulos, a seguir especificados:

1) No primeiro, tem-se a introdução, a qual contém uma breve explanação sobre o que se trata à temática e a estrutura lógica da dissertação;

2) No segundo mostramos a fundamentação teórica que nos forneceu de alicerce para o arcabouço dos paradigmas atuais. Servimo-nos desse arcabouço para desafiar o paradigma atual e propor um modelo alternativo;

3) No terceiro capítulo está o artigo científico submetido à revista Environmental Health - ISSN: 1476-069X (fator de impacto 2016=3,816). O artigo abordou principalmente o paradigma desmatamento-eliminação da malária na região amazônica, levando em consideração os aspectos climáticos e paisagísticos como fatores primordiais associados à problemática do paludismo nesta região.

4) No quarto capítulo temos a conclusão;

5) Por fim as referências do trabalho em formato Vancouver, utilizando o *Mendeley* como ferramenta para citação, especificamente as da introdução e revisão de literatura, uma vez que as do artigo estão no contidas nele no terceiro capítulo.

2 REVISÃO DE LITERATURA

2.1 Paradigma: correlação entre malária e desmatamento

Embora tenham sido feitos progressos significativos para a eliminação da malária em vários países endêmicos das Américas, esta doença ainda é uma preocupação importante para a saúde pública. Nas áreas tropicais e subtropicais da América Latina, ainda existem várias regiões endêmicas que impõem um fardo considerável às populações locais. A maioria dos casos de malária na América do Sul ocorre na região amazônica [(2)].

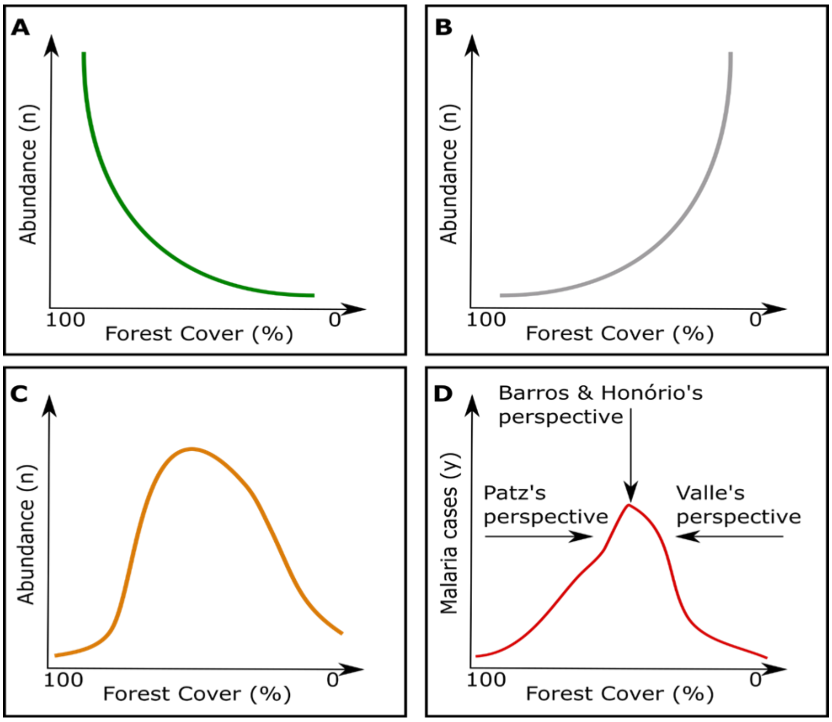
O paradigma correlação da eliminação da malária com o desmatamento vem gerando longos debates e pesquisas nesse campo científico. O aparecimento de malária e o desmatamento são associados a várias causas [(3)]. Dependendo do lugar, a relação entre eles está comumente ligada às principais características da dinâmica local de transmissão dessa doença [(4)].

Os mosquitos vetores silvestres são beneficiados naturalmente quando seus hábitats florestais estiverem em estado de conservação, os quais dependem do sombreamento da mata fechada para o desenvolvimento de suas larvas (malária florestal). Os mosquitos vetores hemi-sinantrópicos são beneficiados com sombreamento parcial ou paisagens abertas para a proliferação dos seus hábitats larvais [(4)]. Neste contexto, quando ocorre o desmatamento na área de malária florestal, os vetores dessa região sofrem redução, assim, diminuindo localmente os casos de malária, por outro lado, os vetores hemi-sinantrópicos são beneficiados com ambientes favoráveis ao desenvolvimento, exemplo o *An. darlingi* na Amazônia [(4)].

O *An. darlingi* é o maior transmissor de parasitos da malária na Amazônia [(5)]. Suas prioridades de nichos são hábitats parcialmente sombreadas e fêmeas adultas próximas, morando nas habitações humanas [(6)]. Nem uma floresta contínua ou mesmo somente uma área aberta pode beneficiar o aumento da população desse vetor. O *An. darlingi* é uma espécie de perturbação média, porque suas larvas dependem de habitats parcialmente sombreados na orla da floresta e as fêmeas adultas podem procurar seres humanos que vivem nas proximidades desses hábitats [(7)]. Essa espécie tem seu lugar nas mudanças de uso do solo e doenças vetoriais [7]. Ela é associada com a fragmentação florestal, quando a cobertura florestal é de aproximadamente 30-70%.

Alguns grupos de pesquisadores estudaram o paradigma do desmatamento-emergência da malária na Amazônia [7–9]. Cada grupo se concentrou e observou diferentes perspectivas a respeito desse paradigma. Patz e seus colaboradores estudaram a floresta contínua de acordo com a hipótese da perturbação intermediária e descobriram que o desmatamento intensifica a malária [9,10]. O grupo de Valle percebeu que a conservação também contribui para o aumento do paludismo [3,8,11]. O grupo de Barros & Honório estudou os "*hotspots*" de larvas na área de transição da floresta e descobriu que a relação entre o desmatamento e a malária é unimodal [5,7].

Figura 1 - Modelo conceitual do paradigma do desmatamento- aumento da malária



A) abundância de vetores florestais no gradiente de floresta. **B)** abundância de vetores não florestais no gradiente de perturbação de floresta. **C)** abundância de vetores em meio a perturbação de gradiente de floresta. **D)** três perspectivas acerca do paradigma do desmatamento e o aumento da malária.

Fonte:

Uma revisão sistemática recente da literatura sobre a ligação entre desmatamento e doenças vetoriais em escala global concluiu que a maioria dos mosquitos vetores de patógenos humanos é favorecida pela conversão florestal, nos quais patógenos e vetores convergem em ambientes antrópicos [12].

O debate a respeito do paradigma do desmatamento-aumento da malária na Amazônia começou com o trabalho de Vittor e seus colaboradores, juntamente com Olson e colegas [9,10] . Estes pesquisadores levaram a hipótese que o desmatamento aumenta a malária. A hipótese foi então desafiada com o trabalho de Valle e Clark [8]. Os autores observaram maior incidência de malária em habitações humanas nas proximidades de áreas de conservação, em comparação com cidades distantes. As descobertas de Valle e Clark geraram discussão na comunidade científica.

Ficou claro que a relação entre desmatamento e emergência da malária na Amazônia não era uniforme nem linear. Então, o grupo de Barros e Honório forneceu outra visão para este debate [5,7]. Eles apresentaram um modelo de transmissão de franja de floresta. Isto está de acordo com a nossa suposição de que *An. darlingi* é uma espécie de perturbação média e, portanto, o desmatamento pode beneficiar ou ser prejudicial à sua população, dependendo da quantidade remanescente da cobertura florestal.

O fenômeno do aumento da malária na Amazônia pode ser descrito da seguinte forma: uma floresta contínua foi perturbada [13]. Depois, o *An. darlingi* se multiplica abundantemente e então o desmatamento se torna o principal motivador da incidência dessa doença [9,10,14]. Se o ecótono da floresta for mantido, a endemia de malária permanecerá em um ciclo infinito [7], a não ser que o desmatamento continue e a área de transição se transforme em um ecossistema não-florestal, no qual a malária transmitida pelo *An. darlingi* terá baixa possibilidade de propagação [8].

Partindo deste ponto, pode-se perceber que a contínua perda de floresta por pecuária, exploração madeireira, incêndio, estradas ou qualquer atividade econômica humana, pode promover uma diminuição na adequação do hábitat para as larvas do *An. darlingi* e, consequentemente, diminuir o risco de malária.

3 ARTIGO

Original research article

Underlying mechanisms in declining malaria burden: a time-series modeling study

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Abstract

Background: The Centenary Brazilian fight against malaria has been benefitted from national programs of malaria control and technological innovations in the last decades. To further move forward to achieving the goal of malaria elimination, this study aimed at studying the underlying mechanisms in the malaria burden decline in Brazil.

Methods: The investigation started with the exploration of malaria attributable deaths 1979-2013 and hospitalizations 1998-2013 among Brazilian states. Next, a time-series analyses of monthly parasite indices 2009-2015 for each municipality in the most malaria endemic states were performed. Then, we selected the most endemic municipality for modelling monthly variations of malaria cases 2009-2015 in function of 4 sets of explanatory variables: 1) Climate, 2) Landscape, 3) Socioeconomic, and 4) Malaria Control National Program. We validated main results from the dynamic regression models with spatial analyses.

Results: A steep decline of malaria burden in Brazil was observed, with significant declines of mortality and hospitalization. However, the Western Amazonian states of Acre and Rondônia showed stabilized endemic foci. Even though municipalities in Rondônia state showed a decline in monthly parasite index, we observed a stationary malaria transmission in Westernmost Acre. After the application of dynamic regression models, all parameters had important contributions: higher precipitation was strongly correlated with the increase of malaria, whereas elevated deforestation, socioeconomic dimension, and malaria control were correlated to malaria decline. The only unexpected result was the paradoxical link between deforestation and malaria decline. To validate this result, we estimated deforestation in the same period for all municipalities of Acre and Rondônia states. We found that Acre municipalities have preserved their vegetation cover, whereas Rondônia municipalities accelerated forest cover loss.

Conclusions: The decreasing trend of malaria burden in Brazil seems to be negatively correlated to parameters (water and forest) associated with habitat availability to the mosquito vectors and positively correlated to parameters (social structure and medicines) that avoid pathogen persistence among hosts and vectors. Notwithstanding, we find a paradox or dilemma: correlation between deforestation and malaria decline. We discuss rationale and consequences of forest cover loss as a predictor to the declining malaria burden.

Keywords: Brazil; Climate; Communicable Disease Control; Ecological and Environmental Processes; Forest; Malaria; Socioeconomic Factor.

Introduction

Malaria elimination has become the Holy Grail of malariologists worldwide since the mid of the last century [1-3]. Failures of the earlier Global Malaria Eradication Program, launched in the 1950s, occurred because of the interruption of DDT use - justified on its side effects on human health and on the environment -, the increase of people living in risk-areas, and malaria parasite drug-resistance in Africa, until the end of the program in 1969 [4]. Recently, however, good news has arrived and the community is now more optimistic with the ongoing malaria elimination programs [5-7]. Indeed, looking at the malaria trends in Brazil, the incidence of this disease is dropping widely in the last decades [8, 9]. Although there may be a sense of last crusade against malarial parasites, new challenges regarding asymptomatic reservoirs and resistant strains to antimalarial drugs can change the directions of strategies for malaria elimination in the next decades [10-12].

Humans have finally reached a context in which malaria elimination is becoming more tangible every day. For instance, Bhatt et al. [13] state that current malaria interventions (e.g., insecticide-treated mosquito net, Artemisinin-based combination therapy, and indoor residual spraying) are responsible for the decline of malaria burden in the sub-Saharan Africa with an estimated number of prevented 700 million cases in 2000-2015, approximately. Specifically, Bhatt and colleagues estimated that malaria burden decline achieved was 68% attributable to insecticide-treated mosquito net. This intervention has been used in Brazil since 2007, as well as indoor residual spraying, 1945, and Artemisinin-based combination therapy, 2006 [14]. It may be possible that insecticide-treated mosquito net, which now covers 20% of Brazilian population [14], is responsible for a significant fraction of declining malaria burden in Brazil. However, some other factors specifically related to the socio-economic context were also important in Brazil, and maybe they are so in Africa, although they were not enlightened in Bhatt et al. [13].

The reduction of the disease incidence is not occurring only in Brazil, yet this is a global trend, which has been accompanied with optimism regarding elimination prospects. In Bangladesh, for instance, a reduction of 64% of malaria incidence 2008-2012 was enough evidence to Haque et al. [5] discuss the possibilities of having a free malaria country, under the circumstance of maintained economic efforts in the agenda of government priorities. In the Americas, situation is likely as optimistic as in Bangladesh. Both studies by Carter et al. [9] and Bardach et al. [8]

have showed that malaria trends are declining in the Latin America. This can be further evidenced by the malaria elimination target in 2020 in regions of Central America set from important groups of malaria research and elimination advocating [7]. However, this view is not unanimous, as argued by Boncy et al. [15] that, in the case of Haiti, the 2020 malaria elimination goal seems not realistic, given the lack of basic infrastructure for surveillance and tools for malaria control.

Herein, we studied the underlying mechanisms of the phenomenon of declining malaria burden in Brazil. Coefficients of mortality and hospitalization attributable to malaria have sharply declined since 1979 (Fig. 1A) and 1998 (Fig. 2A), respectively. These declining trends were not homogeneous among Brazilian states (Fig. 1B, Fig. 2B). Overlapping the results of these coefficients per each Brazilian state, it can be concluded that malaria foci are mostly endemic in the westernmost states of Brazil (Fig. 1C, Fig. 2C). Then, the objective of the current study was to modelling the time-series of malaria cases in function of climate, landscape, socioeconomic, and malaria-control explanatory variables in Acre and Rondônia states.

Our hypotheses were that 1) optimum climate and landscape conditions can favor *Anopheles darlingi* (main malarial vector) abundance and thus malaria emergence [16,17]; 2) better socioeconomic conditions can make local populations less vulnerable to malaria exposition [18]; and 3) malaria control parameters are correlated to malaria declining trends [19].

As may long have been recognized, Brazil as a country is fully expecting to become part of the world-first class group of developed nations [20]. Along with other developed world essential characteristics, which goes from a sizeable gross domestic product to a fair human development index, is the need for having controlled neglected tropical diseases associated with poverty such as malaria [21,22]. Within this context is important to analyze spatially and temporally the malaria burden in Brazil and evaluate the effects of the program of malaria control and forecast future trends for the possibility of malaria elimination. We suggest that, given the pace of malaria decline in this country, its elimination is possible in the next decade, maybe until 2030. Notwithstanding, the other facet of the present work points to a win-lose scenario for planetary health. Humans may be facing a so-wanted malaria elimination era in Brazil and at the same time ruining with the last remnants of tropical rainforests in the Amazon.

Materials and Methods

This section was divided into five subsections: 1) availability of datasets; 2) exploratory data analysis; 3) time-series modelling; 4) validation of modelling results; and 5) ethical issues.

Availability of datasets

All data underlying the findings herein reported were provided as supporting information of the present work: 1) attributable-deaths to malaria, Brazil, 1979-2013 (S1 Dataset; S1 Text); 2) attributable-hospitalizations to malaria, Brazil, 1998-2013 (S2 Dataset; S1 Text); 3) monthly malaria cases per municipality, Acre and Rondônia states, 2009-2015 (S3 Dataset); 4) time-series modelling (S4 Dataset); and 5) validation of modelling results (S5 Dataset).

Exploratory data analysis

We explored monthly-based data on number of malaria cases reported by resident population in each municipality in Acre and Rondônia states, 2009-2015.

<u>Malaria data</u>

Malaria data per month and municipality were available in the following SIVEP-Malaria website [23]. This data is systematically collected by the integrated network of hospitals and health units in the Malaria Control National Program throughout the Brazilian Amazon. We considered and summed up all the positive slides (*P*. *vivax*, *P*. *falciparum*, *mixed*) diagnosed and reported in each municipality as the studied parameter named 'malaria cases'. Malaria cases were herein assumed as a consequence of parasite transmission among mosquito vectors and humans [24] within a hotspot of transmission in each municipality.

<u>Population data</u>

Population data per year and municipality were also available in the SIVEP-Malaria website [23]. Population data represented the total number of resident people living and thus exposed to malaria parasites in a given municipality. Each municipality has an annual estimation of its population size and is in charge to input the annually-based number of resident people in the SIVEP-Malaria system. However, because monthly-based data were needed, then we performed linear interpolation between subsequent years, using the following equation:

$$\frac{y - y_0}{x - x_0} = \frac{y_1 - y_0}{x_1 - x_0}$$

In where, y_0 and y_1 were the available population data in given months x_0 and x_1. The coordinate (x, y) was estimated thereby; population data (y) was linearly interpolated in each month (x).

Software for exploratory analysis

We utilized the analytical software for epidemiological time-series, EPIPOI v. 15 [25]. Malaria and population data spreadsheets were firstly imported. Following, we performed two exploratory analyses: 1) a line plot, monthly parasite index (number of positive slides for malaria divided per 1000 resident persons) for a given state (Acre or Rondônia), 2) a grid-map plot, monthly malaria cases per municipality, 2009-2015.

Time-series modelling

We performed a dynamic regression modelling to identify important explanatory variables for malaria emergence in a municipality with the following condition: highest number of malaria cases. Specifically, we utilized an autoregressive integrated moving average (ARIMA) model of the form:

$$y_t = \beta_0 + \beta_1 x_{1,t} + \cdots + \beta_k x_{k,t} + n_t$$

The number of malaria cases and the coefficient of malaria cases (number of cases / population * 100,000) per month were the response variables (y_t). The explanatory variables (x_1, x_2,…, x_k) were divided into four blocks: 1) climate (two variables); 2) landscape (three variables); 3) socioeconomic (7 variables); and 4) malaria-control (one variable). The ARIMA parameter n_t is the model error [26].

We utilized the implementation of ARIMA in the package *forecast* for the R programming environment v. 3.2.5 [27]. With this implementation, we could estimate the equation of the regression model by using a stepwise approach with backward selection of explanatory variables, adopting a level of significance of 0.05 (error type I, α). The 95% confidence interval of each intercept (β_1, …, β_k) was estimated using the Stata 10 (StataCorp™) [28]. R-scripts can be made available upon request.

Climate data

We selected two meteorological parameters: 1) total precipitation (mm), 2) average maximum temperature (˚C). Data for these parameters were available in meteorological stations throughout the Brazilian territory in the INMET website [29].

We had to interpolate these data into a raster image and then we could be able to attribute them for a given municipality. We used data in the following meteorological stations: Uruguaiana (-29.75, -57.08), Corumbá (-57.67, -19.02), Ponta Pora (-55.71, -22.55), Eirunepe (-69.86, -6.66), Labrea (-64.83, -7.25), Benjamin (-70.03, -4.38), CZS (-72.66, -7.6), RB (-70.76, -8.16), and Tarauaca (-67.8, -9.96). We summed up monthly total precipitation in dry and wet seasons of each year (2009-2015). We calculated the arithmetic mean for average maximum temperature in each season.

These data were imported into a geographic information system (QGIS v. 2.12.0) [30]. Subsequently, we created regular grids from the scattered data of precipitation and temperature using the inverse distance weighting interpolation algorithm. We could generate regular grids with pixels of 20-km^2 (spatial resolution) containing interpolated data of precipitation and temperature. Then, we applied the zonal statistics approach to calculate the mean pixel value for precipitation and temperature in each municipality.

Landscape data

Land-use and land-cover thematic maps based on satellite imagery were obtained in the INPE/PRODES Project website [31]. Forest cover (km^2) and deforestation (km^2/year) per municipality and year are regularly estimated in the INPE/PRODES Project and made available through its website [31]. Next, each thematic map per year (2009-2015) was imported in the Fragstats v. 4.2 [32]. Consequently, we estimated edge density (m/ha) of forests in each municipality per year. Edge density was calculated by summing up the perimeter (m) of forest edges divided by the total area (ha) of a given municipality.

Socioeconomic data

Socioeconomic data were obtained in the PNUD/Atlas Project website [33]: life expectancy at birth (days); infant mortality rate (per 1000 live births); mean number year of schooling for people aged 25 years and above (years); proportion of people living in extreme poverty (% of people earning less than US$ 1.25 a day); proportion of people living in poverty (% of people earning less than US$ 3.75 a day); GINI index (inequality index, 0-1, the most inequality = 1); and municipal human development index (0, minimum; 1, maximum).

Malaria-control data

The Malaria Control National Program has been very effective in controlling malaria in Brazil since 2003. It has decentralized the units of parasite diagnostic and treatment throughout Amazon. The rationale herein was to choose parameters that could represent the robustness of such a program. We then obtained the total number of exams of blood smear in slides done per month and municipality, available in the SIVEP-Malaria website [23]. The number of exams was considered a variable of malaria control because each positive diagnosis is followed by a specific antimalarial treatment.

Validation of modeling results

We made a validity check of the inference that was obtained from the results of time-series modelling. We firstly made thematic maps of deforestation (km^2/year) and annual parasite index for malaria (positive slides / 1,000 persons) per municipality. Following, we selected the municipalities with the highest annual parasite index. We correlated these values with deforestation by applying a Spearman correlation testing (α = 0.05) with the following hypotheses: H_0: maintenance of malaria endemicity is followed by the maintenance of the intensity of deforestation (business-as-usual); H_a: deforestation can increase malaria (positive correlation) or deforestation can decrease malaria (negative correlation). The null hypothesis represents a scenario in where occurs conservation of forest cover or, in other words, dynamic equilibrium of deforestation and forest recover. The alternative hypothesis represents a scenario of non-equilibrium that forest cover is disturbed, which can change the level of malaria emergence risk.

Ethical issues

Regarding Brazilian Institutional Review Board for protection of human subjects, the present study does not need any approval to access data. This is because patient confidentiality had been assured. All patient-data had been anonymized before we could access them in health information systems in the present study. Additionally, such data should be of public domain, according to the Brazilian Law of Information Access (12.527/2011).

Results

We firstly recognized the phenomenon of the declining malaria burden in Brazil, except for the westernmost states in the Amazon (Fig. 1A-C, Fig. 2A-C). Then, we investigated malaria incidence in Acre and Rondônia states in order to find explanations for the maintenance of the disease endemicity. After careful and closer observations on the epidemiological trends of monthly parasite index in Rondônia state, we also observed a malaria declining trend (Fig. 3A,B). The same was not true, however, when considering epidemiological trends of monthly parasite index and malaria cases in Acre state (Fig. 4A,B). Particularly, municipality of Cruzeiro do Sul (CZS) in the Juruá Valley showed a high level of endemicity, with a mean annual parasite index of 217 per 1,000 human residents, 2009-2015 (Fig. 4B).

Considering that CZS is an urban center in the region of Juruá Valley, likely impacting malaria spread through the mobility of malaria parasites to nearby municipalities, we focused in modelling the time-series of monthly malaria data in this municipality. Full results of the modelling process are available for Model 1 (Table 1) and Model 2 (Table 2). We performed a stepwise backward in each block: climate, landscape, socioeconomic and malaria-control. Significant variables were selected ($p < 0.05$) and maintained up to the final models:

Model 1

Monthly malaria cases (y_t) = -2188.54 **+ 0.19** x_1(precipitation) **+ 0.40** x_2(forest cover) **+ 0.015** x_3(total number of exams) + n_t; $n_t = 0.99_{t-1} – 0.25_{t-2} + e_t$; e_t ~ Normal (0, 226.96).

Model 2

Coefficient of malaria cases per 100,000 people (y_t) = -16,884.66 **+ 0.23** x_1(precipitation) **- 0.40** x_2(deforestation) **– 0.0009** x_3(forest edge density) + n_t; $n_t = 0.94_{t-1} – 0.28_{t-2} + e_t$; e_t ~ Normal (0, 291.06).

Overall, higher precipitation was important in predicting malaria emergence in both models. Landscape variables were also important, and they pointed to a paradox: correlation between deforestation and malaria decline. Socioeconomic variables were mildly important, particularly poverty, in predicting malaria emergence; however, they were less significative and were dropped before entering the final models. The correlation between the malaria-control variable, total number of exams, with malaria emergence showed the robustness of the Malaria Control National Program.

Considering that the contributions of climate, socioeconomic and malaria-control variables were expected, we focused in the paradoxical relationship between deforestation and malaria decline in the validation of modelling results. Accordingly, we extrapolated this relationship for all municipalities in Acre and Rondônia states and applied a hypothesis testing for the municipalities with higher malaria incidence (Fig. 5A,B). The relationship in municipalities in Acre state was in accordance with the null hypothesis: constant deforestation levels maintained malaria endemicity. The relationship in municipalities in Rondônia state, however, showed another pattern in accordance with the alternative hypothesis: the increase of deforestation levels has declined malaria incidence. Additionally, we observed that Acre averagely deforested 20,508.4 km^2 / 170,884 km^2 = 12%/year and Rondônia averagely deforested 84,930 km^2 / 240,374 km^2 = 35%/year. Rondônia has therefore deforested triple than Acre, 2009-2015.

Discussion

Our analyses show that the evolution of mortality and hospitalization attributable to malaria in Brazil shows some remarkable patterns. This may be due breaking-through malaria interventions like active case detection, specific treatment, including Artemisinin-based combination therapy, and insecticide-treated mosquito net that have been operating in the Brazilian Amazon, contributing substantially to the decreasing trend of malaria burden [34,35]. Perhaps this may lead to the false idea that these are the only determinants related to malaria control in Brazil. Other determinants, in fact, indirectly related with malaria control can be recognized.

The main contribution of the present study was to identify underlying mechanisms linked to malaria decline in a broad spectrum of causality. We included as determinants of malaria decline: 1) climate, 2) landscape, 3) socioeconomic dimension, and 4) malaria control. We conclude that the prospect of the hypothesis of malaria elimination as a possible future in Brazil for the next decade is promising. Notwithstanding, we also conclude there may be a correlation between forest cover loss and malaria decline in Brazil. The rationale of this correlation can be logically deducted.

In the following paragraphs, we first make opening remarks, then discuss the determinants of malaria emergence or decline in Amazon. Subsequently, we make an appraisal of the present results in the context of planetary health and end with limitations of our study and new avenues.

<u>Opening remarks</u>

Association between deforestation and mosquito-borne disease can be complex and unpredictable [36,37]. Considering Barros and Honório’s proposal [38], *An. darlingi* is a mid-disturbance species, because its larvae depends on partially-shaded habitats in the forest fringe and adult females can seek humans that live nearby these larvae habitats. The complex relationship between *An. darlingi* and deforestation has led the intense debate regarding the factors underlying malaria emergence in the Amazon. This debate will be discussed in the next paragraph.

The debate of the deforestation–malaria emergence paradigm started with the work by Vittor and colleagues [39]. They found increasing biting rate by *An. darlingi* and larval habitats in open areas within continuous forests in the Peruvian Amazon [40]. This evidence was reinforced by other publication from Mâncio Lima County, Acre state [41]. The hypothesis was then challenged by Valle and Clark [42], who observed higher malaria incidence in human settlements nearby priority areas for nature conservation. The findings by Valle and Clark [42] generated arguing in the scientific community [43,44]. Then, a third research group has provided another view. They analyzed malaria incidence and mosquito ecology data on local transmission scale in a rural settlement, Roraima state [38,45,46]. These authors proposed a forest fringe transmission model and therefore deforestation may benefit or be harmful to *An*. *darlingi* population depending on the amount left of forest cover [38].

<u>Predictors of malaria emergence or decline</u>

Precipitation was positively correlated with malaria emergence in the present study. This is related to the well-defined seasonality in Amazonian regions with two distinct stations: 1) Wet season, from November to April; 2) Dry season, from May to September. Although malaria occurs all the year round, its transmission is intensified with higher precipitation. Higher precipitation causes the increase of larval habitats availability for the females of *An. darlingi*, increasing ultimately their abundance. The link between higher precipitation and elevated malaria incidence is the core of climate change issue [16]. Climate change can alter the water cycle, which in turn can augment floods and then larval habitats for mosquito vectors [16]. On the other hand, climate change can be related to lower water availability, which can have a negative impact in populations of *An. darlingi* and malaria incidence in the future of Amazon [47].

Landscape variables herein considered were correlated to malaria incidence in disagreement with the main view that malaria emergence is linearly correlated with deforestation in Amazon. It is important to note that the ecologic niche of *An. darlingi* has an axis of forest dependence, because its larvae cannot tolerate sunlight [48].

What frequently happens is that humans coexist with forest fringe ecosystem all the time in Amazon, and forest fringe habitats are ideal for this species [38]. The phenomenon of malaria emergence in Amazon can be described as follows: a continuous forest has been disturbed and thus forest fringe ecosystems are everywhere [49]. Following, it occurs peaks of abundance of *An. darlingi* [17] and then recent deforestation is linked as the main cause of malaria incidence [39-41]. If this ecotone of forest fringe is maintained then malaria endemicity will be maintained in indefinite cycles [38] unless deforestation continues and the forest fringe ecosystem turns into a non-forest ecosystem, in where malaria associated with *An. darlingi* is less likely [42]. From this view, it can be realized that continuing with the forest loss by cattle ranching, logging, fire, roads or any human economic activity, can promote a decrease in the habitat suitability for *An. darlingi* larvae and therefore diminishing malaria risk.

Socioeconomic determinants herein studied were mildly important as predictors of malaria emergence. Specifically, poverty was positively correlated to malaria emergence. Considering the literature [22] and our experience on collecting mosquito vectors in houses with recent malaria cases in Amazon, it is expected this relationship between poverty and malaria; in fact, we believe malaria is an infectious disease of poverty. Although we recognize that malaria interventions, like active case detection, specific treatment, and insecticide-treated mosquito bednets have been contributing substantially to the decreasing trend of malaria burden [34,35], this may lead to the false idea that these are the only ways for controlling malaria. Other indirect ways, such as, developing basic infrastructure and experiencing urban growth due to the production of internationally traded commodities, and the increasing assimilation of their capital into local urban areas can have an impact on quality of life [50,51]. As basic infrastructure and urbanization increase, the overall quality of life of the whole population also augments, decreasing the chances of contracting malaria [51]. For instance, Malaria in Mississippi in US was long ago eliminated; however, malaria was attributable to deaths in the 1940s. During that time a combined effort of entomologists and public health workers had decreased malaria transmission. One important factor that is recognized for eliminating malaria in Mississippi was the increase in family income that diminished the chances for malaria rebound, due to the fact that people could afford better protection, better clothing, quality food, medical services, and therapeutic drugs [52]. Even if the southern US is exposed to human mobility from endemic malaria countries in Latin America today, malaria risk is not an issue, maybe because the regions that had malaria before in Mississippi and Florida have achieved a socioeconomic developed condition that make them not receptive for malaria.

The number of malaria exams was correlated with malaria incidence. This result meant that wherever malaria transmission is happening, there will be a health post with a diagnostic facility and specific treatment for controlling malaria in Amazon. This shows the robustness of the Malaria Control National Program, which is actively contributing with the malaria declining trend in Brazil [35]. Malaria elimination represents the reduction to zero of the incidence of infection by human malaria parasites in a defined geographical area (e.g., Amazon) as a result of deliberate efforts with continued measures to prevent re-establishment of transmission required [1-3]. To accomplish such a goal, innovative approaches have been advocated from different groups involved in the development and/or implementation of public health entomology capacities, transmission-blocking malaria vaccines, new technologies for tracking parasites and detecting infections, and new therapeutic products [2,6,35]. These novel approaches are necessary for the achievement of malaria elimination in Brazil, e.g., [1], especially because of the dynamics of changes in the land-use of new frontiers of human occupation in Amazonian forested borders, which represent an important issue to malaria control [49]. For instance, we showed that malaria burden declined in all states, possibly indicating malaria elimination locally in some states, but we also showed high incidences of hospitalizations-attributable malaria in Acre state 2004-2006.

<u>Planetary health and the fate of Amazonian rainforests</u>

According to Ostfeld [53], planetary health is a new discipline and its approach is intended for the exploration of theoretical and empirical co-benefit scenarios [53]. For instance, Castro [54] proposed environmental factors that could help prevent new malaria outbreaks. One globally important scenario currently facing a lose situation is the tropical rainforest in Amazon [55]. Amazonian biodiversity is under threat because of the widespread depletion of habitats for native species [56]. Deforestation is considered the leading cause [57] and maintaining forest cover has been the current strategy for conservation [58-61].

In our study system we observed differences on deforestation and malaria incidence among Acre and Rondônia states. Rondônia had 3 times higher rates of deforestation and a declining malaria trend. The correlation of deforestation and malaria decline in Rondônia was also observed by Angelo and colleagues [62]. The fast and prominent deforestation in this state is related to its main economic activities: logging and cattle ranching [51]. This state is one of the main exporters of wood and bovine meat to the high consumption network in the Southern and Southeastern Brazil [51]. On the other hand, we observed lower deforestation rates in Acre state and stable endemic focus of malaria in the Westernmost part of this state, particularly in the Cruzeiro do Sul municipality. Acre state has a long story of nature conservation with the leader Chico Mendes that pioneered the production of latex in the forest [63]. The production of latex is dependent of forest conservation and thus such an activity protects forest integrality [63]. For instance, this state has an extrativist reserve for latex extraction named Chico Mendes (930 thousand ha) [64]. Additionally, Acre state is the leader in the production of Amazonian fishes with economic values in fish farming [64]. Fish farming represents a win-win situation for planetary health because it provides economic gains for the landowner and at the same time protects native ichthyofauna. Also, fish farming is not associated to deforestation, such as cattle ranching or logging [59]. Notwithstanding, the introduction of fish farming have contributed to malaria emergence in the westernmost counties of this state [65]. This occurred because of widespread poorly managed fish farming ponds that were colonized by *An. darlingi* [66]. This example can be translated into a day-by-day expression: the glass of water is half empty, half full.

The trueness is that human civilizations in the Earth are subjected to the tragedy of the commons [67] and it is likely that humans are not psychologically ready for a planetary health approach [68]. For instance, we showed herein that humans may be at one step to achieving a paradoxical duet: malaria elimination in Brazil and the loss of Amazonian rainforest. This paradoxical duet or dilemma could be solved with the increase of socioeconomic dimension, as it was observed in Mississippi and Florida in the past century [52]; however, this socioeconomic dimension may not change in the Brazilian Amazon for the next years as it is not in the mainstream policy adopted by the current federal government. Moreover, when it comes to decide between environmental protection or disease prevention, it is remarkable that some people might only prefer malaria elimination [69].

Limitations and new avenues

This study provides data and evidences for country, state and municipality spatial scales; however, it fails in providing data and evidences for a landscape scale (5-km^2 as spatial resolution). The landscape scale is the scenario for the dynamics of malaria transmission; it is where hosts, vectors, and pathogen converge. This means that a landscape is the ideal scale of a study design for finding proximate causal mechanisms to malaria emergence. Our finding that deforestation is correlated to a malaria declining trend could be tested in a follow-up of landscapes under forest disturbance.

Moreover, this follow-up could be an experimental study; and the intervention could be money donation to the landscape's landowners, conditioned to forest protection. Half selected landscapes can receive the bonus (intervention group) and may be monitored for the level of forest conservation (forest cover ~ 80%). The other half shall not receive any bonus. With this experimental design we could be testing the unimodal relationship between deforestation and malaria emergence.

Conclusions

The present study shows that underlying mechanisms in the declining burden of malaria in Brazil could be related to forest cover loss, increased socioeconomic conditions, and malaria control activities.

Within the concept of the planetary health, the pathways to preserve rainforests and keep up with the malaria elimination agenda would be to maintain the current malaria elimination program that has heroic role in the declining trend of malaria burden and increase the socioeconomic dimension of local populations until sustainable economic activities are the core business plan.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

All data utilized during this study are herein included as supporting information.

Competing interests

The authors declare there are no competing interests.

Funding

MAOP, JOM, and MVML are supported by the Secretaria de Estado de Saúde do Acre (SESACRE) process n. 007/2015. GR is a recipient of a National Council for Scientific and Technological Development (CNPq) scholarship (process n. 162253/2017-6). GZL is supported by the São Paulo Research Foundation (FAPESP) and Biota-FAPESP Program, process n. 2014/09774-1.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors' contributions

Original idea: WAJ, GZL. Study design: MAOP, JOM, GZL. Organization of datasets: MAOP, JOM, GR, MVML, WAJ. Data analysis: WAJ, MVML, GR. Production of figures and tables: WAJ, GZL, GR. First manuscript draft: GZL. Contributed revisions: WJA.

Acknowledgements

The authors are grateful to the Department of Vital Statistics, a branch of the Brazilian Ministry of Health, for providing the mortality and hospitalization data, and to Alicia A. Livinski (National Institutes of Health Library) for all her valuable comments on the earlier versions of this manuscript.

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Figure legends

Figure 1. A). Mortality incidence (per 100,000 persons) attributable to malaria in Brazil, 1979-2013. **B**) Mortality incidence (per 100,000 persons) attributable to malaria according to states of Brazil, 1979-2013. **C**) States with higher mortality incidence attributable to malaria in Amazon, Brazil. Source: **S1 Text**.

Figure 2. A) Hospitalization incidence (per 100,000 persons) attributable to malaria in Brazil, 1998-2013. **B**) Hospitalization incidence (per 100,000 persons) attributable to malaria according to states of Brazil, 1998-2013. **C**) States with higher mortality incidence attributable to malaria in Amazon, Brazil. Source: **S1 Text**.

Figure 3. A) Monthly parasite index (positive slides per 1,000 residents) in Rondônia state, 2009-2015. **B**) Monthly parasite index (positive slides per 1,000 residents) according to municipalities in Rondônia, 2009-2015, ordered by increasing latitude. Data source: SIVEP-Malaria.

Figure 4. A) Monthly parasite index (positive slides per 1,000 residents) in Acre state, 2009-2015. **B**) Monthly malaria cases according to municipalities in Acre, 2009-2015, ordered by increasing latitude. Data source: SIVEP-Malaria. **CZS**: Cruzeiro do Sul.

Figure 5. A) Spatial and temporal correlation of deforestation (log km^2/year) and malaria incidence (per 1,000) in Acre state: a, Mâncio Lima; b, Rodrigues Alves; c, Cruzeiro do Sul. **B**) Spatial and temporal correlation of deforestation (log km^2/year) and malaria incidence (per 1,000) in Rondônia state: a, Cujubim; b, Candeias do Jamari; c, Machadinho d'Oeste; d, Nova Mamoré; e, Porto Velho. Data source: Ministry of Environment and Natural Resources, SIVEP-Malaria.

Figure 1.

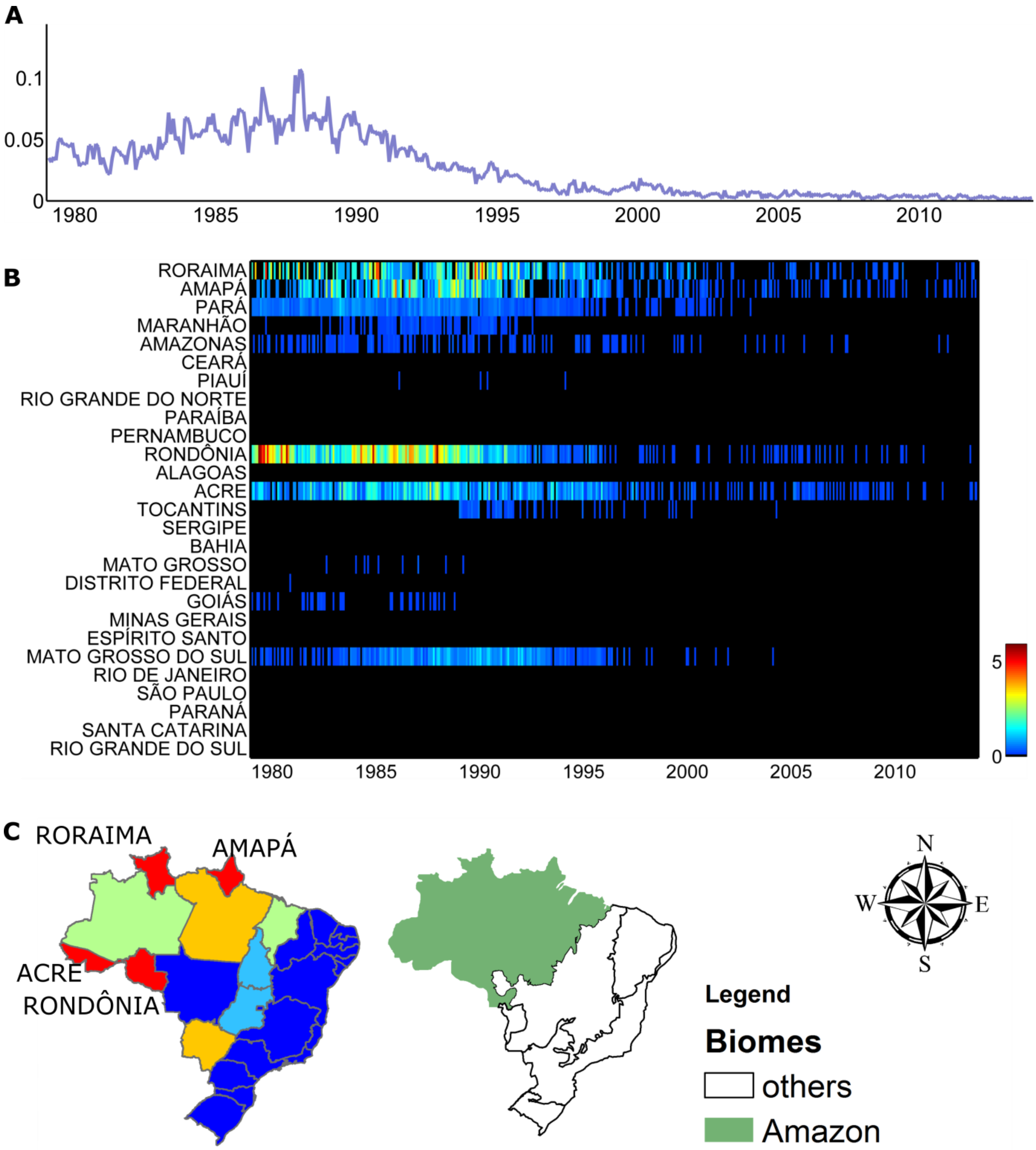

A
0.1
0.05
0
1980
1985
1990
1995
2000
2005
2010
B
RORAIMA
AMAPÁ
PARÁ
MARANHÃO
AMAZONAS
CEARÁ
PIAUÍ
RIO GRANDE DO NORTE
PARAÍBA
PERNAMBUCO
RONDÔNIA
ALAGOAS
ACRE
TOCANTINS
SERGIPE
BAHIA
MATO GROSSO
DISTRITO FEDERAL
GOIÁS
MINAS GERAIS
ESPÍRITO SANTO
MATO GROSSO DO SUL
RIO DE JANEIRO
SÃO PAULO
PARANÁ
SANTA CATARINA
RIO GRANDE DO SUL
5
0
1980
1985
1990
1995
2000
2005
2010
C
RORAIMA
AMAPÁ
ACRE
RONDÔNIA
N
W
E
S
Legend
Biomes
others
Amazon

Figure 2.

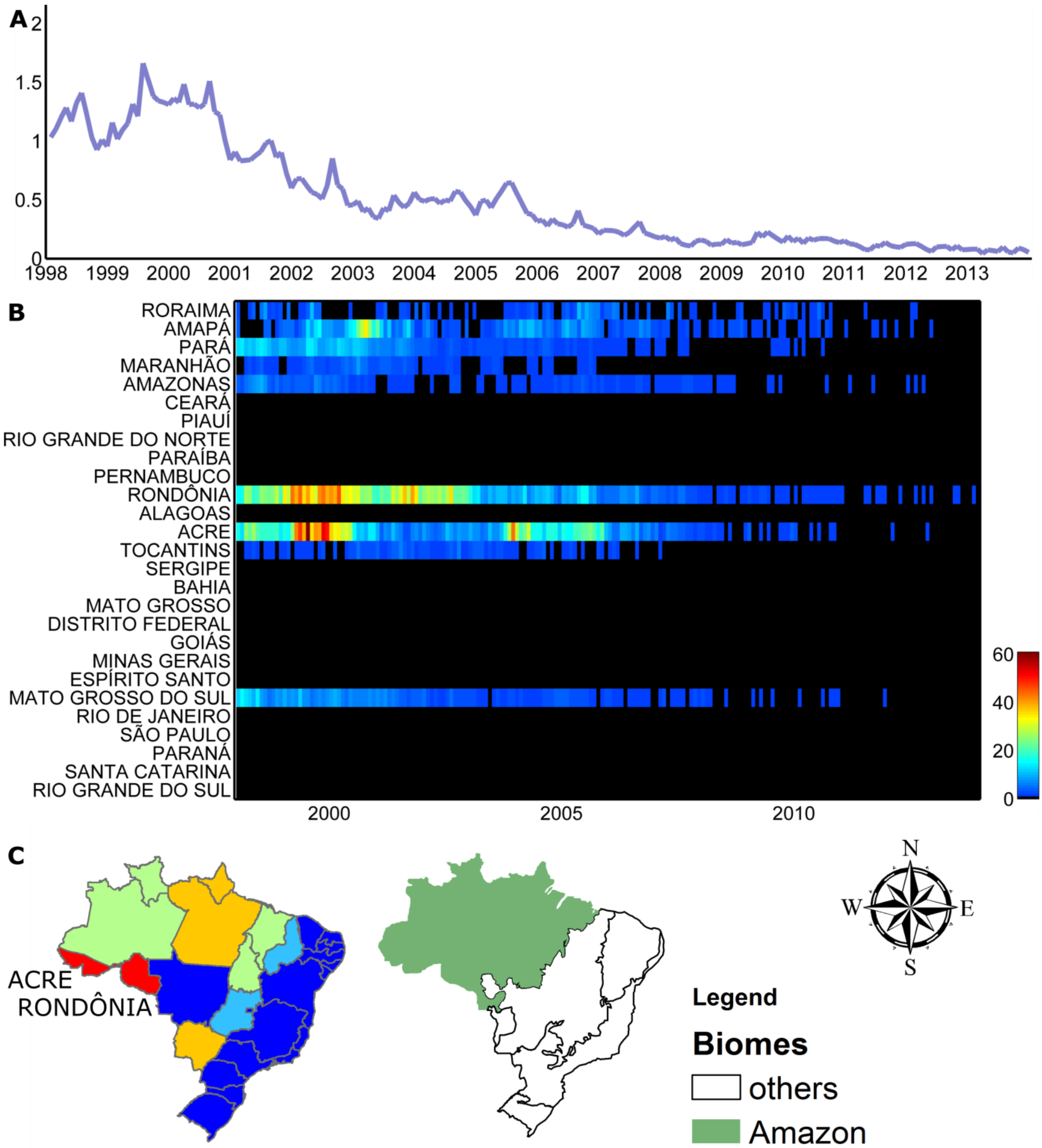

A
2
1.5
1
0.5
0
1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013
B
RORAIMA
AMAPÁ
PARÁ
MARANHÃO
AMAZONAS
CEARÁ
PIAUÍ
RIO GRANDE DO NORTE
PARAÍBA
PERNAMBUCO
RONDÔNIA
ALAGOAS
ACRE
TOCANTINS
SERGIPE
BAHIA
MATO GROSSO
DISTRITO FEDERAL
GOIÁS
MINAS GERAIS
ESPÍRITO SANTO
MATO GROSSO DO SUL
RIO DE JANEIRO
SÃO PAULO
PARANÁ
SANTA CATARINA
RIO GRANDE DO SUL
2000 2005 2010
60
40
20
0
C
ACRE
RONDÔNIA
N
W
E
S
Legend
Biomes
others
Amazon

Figure 3.

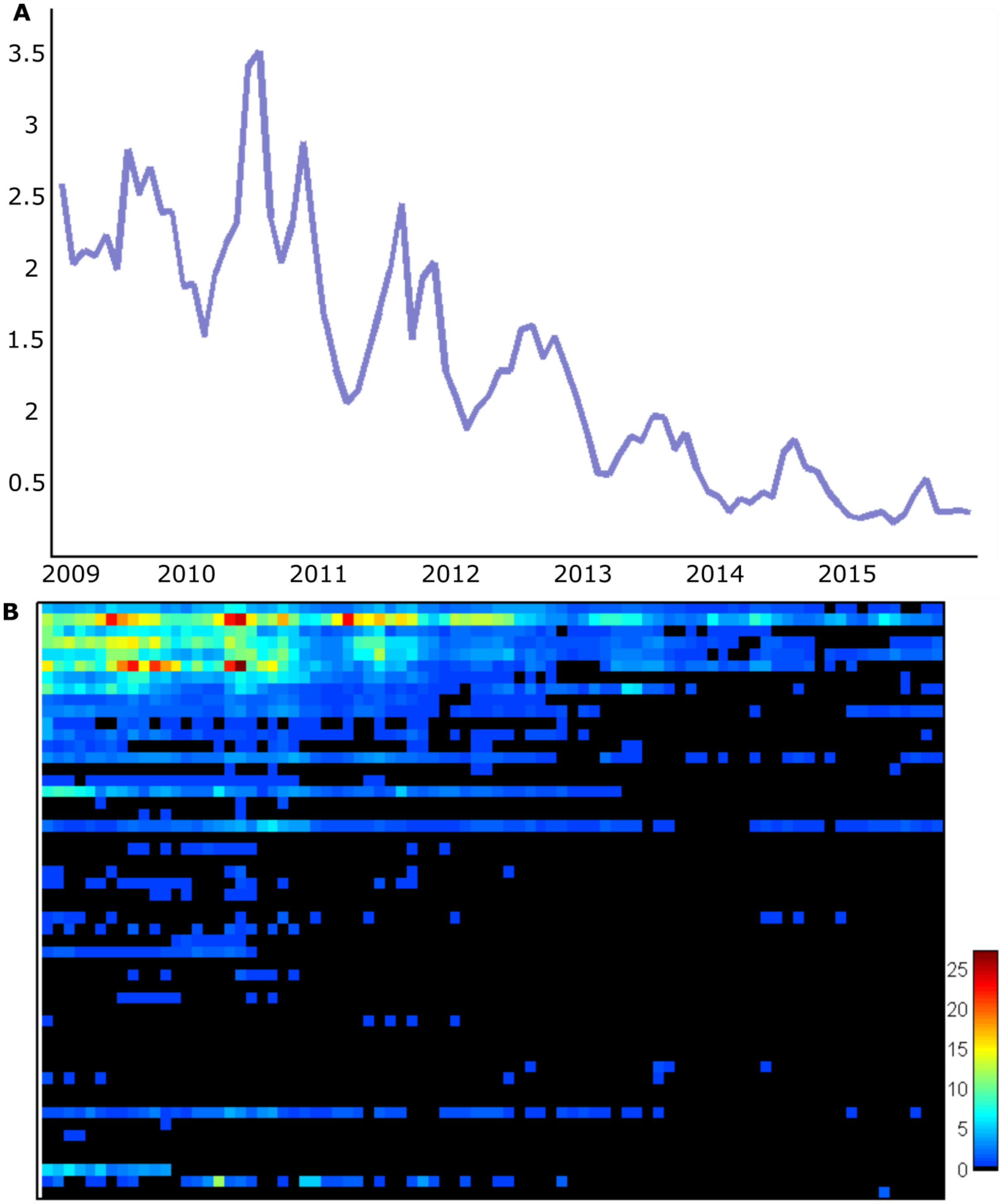

A
3.5
3
2.5
2
1.5
2
0.5
2009
2010
2011
2012
2013
2014
2015
B
25
20
15
10
5
0

Figure 4.

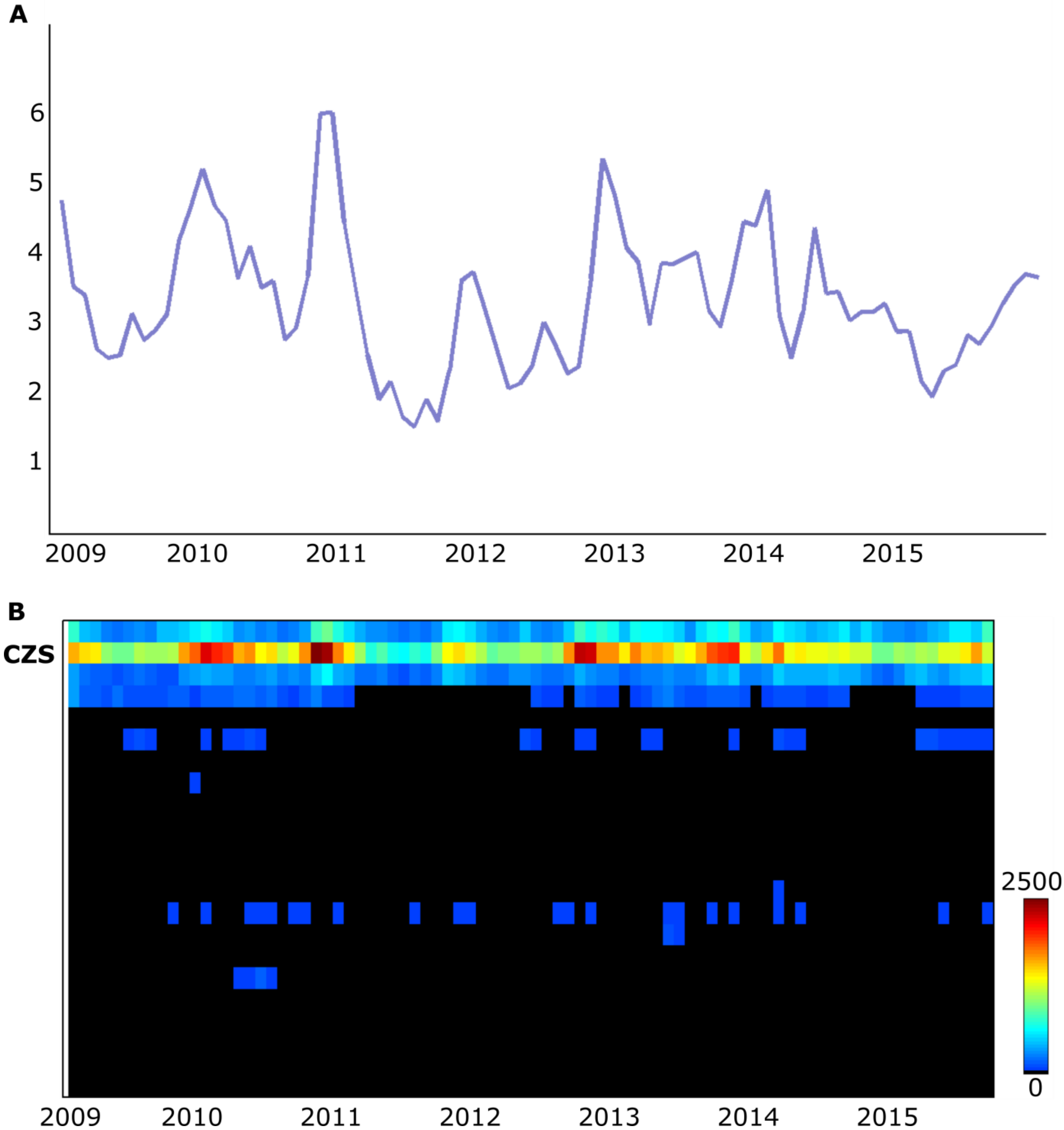
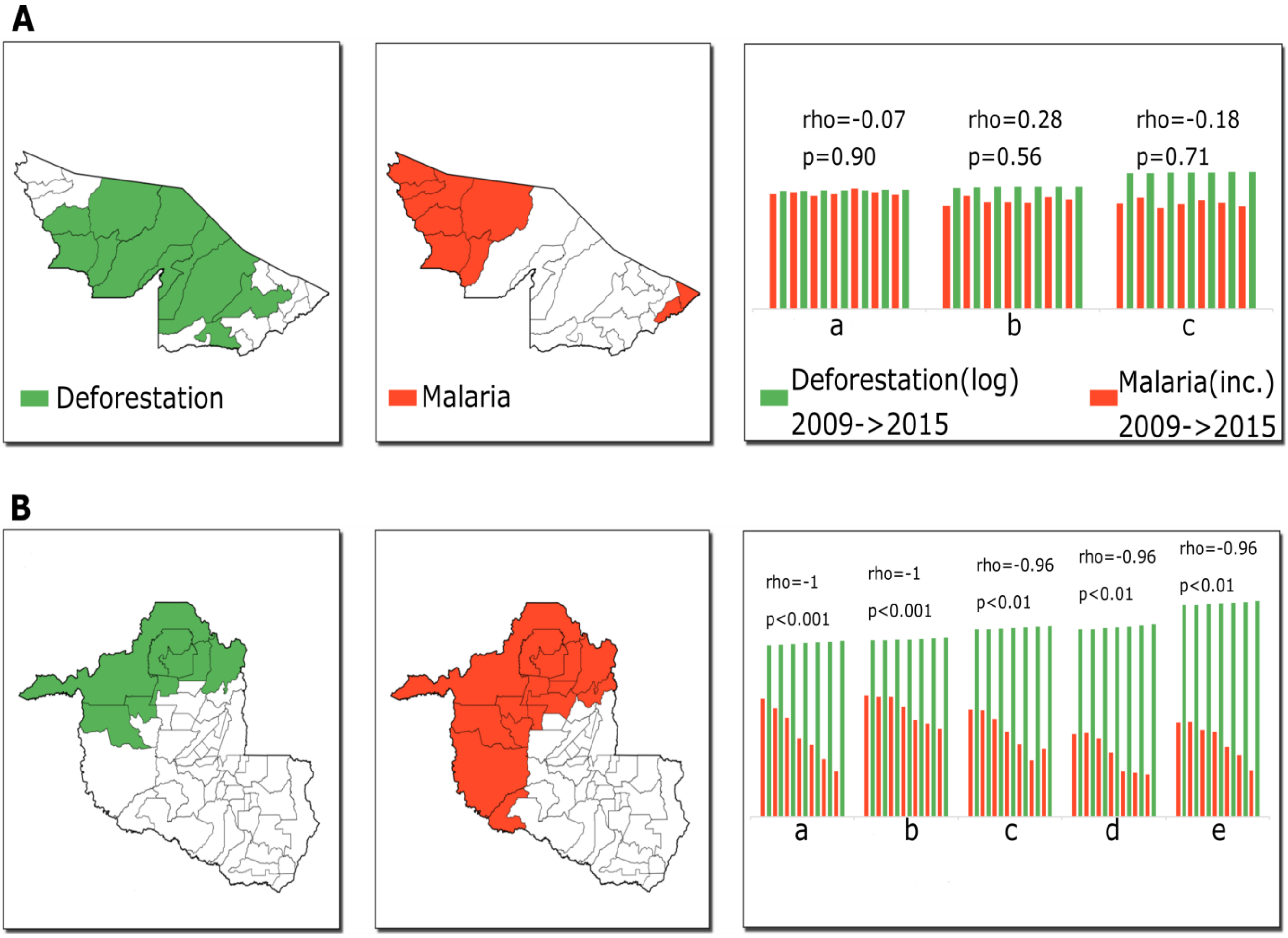

A
6
5
4
3
2
1
2009
2010
2011
2012
2013
2014
2015
B
CZS
2500
0
2009
2010
2011
2012
2013
2014
2015

Figure 5.


A
Deforestation
Malaria
rho=-0.07
p=0.90
rho=0.28
p=0.56
rho=-0.18
p=0.71
a
b
c
Deforestation(log)
2009->2015
Malaria(inc.)
2009->2015
B
rho=-1
p<0.001
rho=-1
p<0.001
rho=-0.96
p<0.01
rho=-0.96
p<0.01
rho=-0.96
p<0.01
a
b
c
d
e

4 CONCLUSÃO

O desmatamento mostrou correlação significativa com a redução dos números de casos de malária. Esta doença apesar de se mostrar em declínio a proporção de Brasil, requer atenção especial, onde políticas públicas intensivas sejam efetivadas, principalmente no estado do Acre, que apresentou o maior percentual de paludismo no país e que tem em seu eixo de gestão a proposta de conservação da floresta.

Quando se aponta possibilidades de enfretamento a malária, estas podem se tornar ferramentas importantes para que pessoas acometidas por esta doença possam usufruir mais saúde e melhor qualidade de vida. Podendo os recursos que são empenhados no paludismo serem investido em educação que é a chave para uma sociedade ter progresso e desenvolvimento contínuo.

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