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The periodicity of *Plasmodium vivax* and *Plasmodium falciparum* in Venezuela

María-Eugenia Grillet[a,*], Mayida El Souki[a], Francisco Laguna[a], José Rafael León[b]

[a] Laboratorio de Biología de Vectores y Parásitos, Instituto de Zoología y Ecología Tropical, Facultad de Ciencias, Universidad Central de Venezuela, Apartado Postal 47072, Caracas 1041-A, Venezuela
[b] Escuela de Matemáticas, Facultad de Ciencias, Universidad Central de Venezuela, Apartado Postal 47072, Caracas 1041-A, Venezuela

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ABSTRACT

We investigated the periodicity of *Plasmodium vivax* and *P. falciparum* incidence in time-series of malaria data (1990–2010) from three endemic regions in Venezuela. In particular, we determined whether disease epidemics were related to local climate variability and regional climate anomalies such as the El Niño Southern Oscillation (ENSO). Malaria periodicity was found to exhibit unique features in each studied region. Significant multi-annual cycles of 2 to about six-year periods were identified. The inter-annual variability of malaria cases was coherent with that of SSTs (ENSO), mainly at temporal scales within the 3–6 year periods. Additionally, malaria cases were intensified approximately 1 year after an El Niño event, a pattern that highlights the role of climate inter-annual variability in the epidemic patterns. Rainfall mediated the effect of ENSO on malaria locally. Particularly, rains from the last phase of the season had a critical role in the temporal dynamics of *Plasmodium*. The malaria–climate relationship was complex and transient, varying in strength with the region and species. By identifying temporal cycles of malaria we have made a first step in predicting high-risk years in Venezuela. Our findings emphasize the importance of analyzing high-resolution spatio-temporal data to better understand malaria transmission dynamics.

1. Introduction

Malaria, one of the most serious parasitic diseases of tropical ecosystems, is caused by parasites of the genus *Plasmodium* (Apicomplexa: Plasmodidae) and transmitted among human hosts by the bites of infected female *Anopheles* mosquitoes (Diptera: Culicidae). In 2010, malaria was responsible for 219 million cases, causing nearly 700,000 deaths (World Health Organization, 2012). Epidemiological patterns of malaria can be highly heterogeneous and caused by a complex set of interactions among parasites, vectors, and hosts occurring at specific locations, and at specific times. In low endemic and epidemic areas, *Plasmodium* incidence exhibits regular seasonal cycles and multiyear oscillations over time (Hay et al., 2000). Annual changes in rainfall and temperature may directly or indirectly affect *Anopheles* reproduction and mortality rates, the blood feeding frequency of the mosquito female and the extrinsic incubation period of *Plasmodium* and thereby cause seasonal variations in both vectors and parasites (Stresman, 2010). Longer-term or inter-annual cycles of the parasite might be driven by extrinsic climatic factors (Bouma and Dye, 1997; Bouma et al., 1997; Poveda et al., 2001), intrinsic mechanisms associated with epidemiological dynamics such as host immunity (Hay et al., 2000), or both factors (e.g., Pascual et al., 2008).

In the Americas, malaria is still a serious health concern, with almost 20% of the total population at some degree of risk, especially in countries such as Venezuela, where the reported morbidity has increased significantly in the last decade (World Health Organization, 2012). In Venezuela, *Plasmodium vivax* malaria accounts for 82% of all cases, followed by *P. falciparum* (16%), *P. malariae* (<1%) and *P. vivax*/*P. falciparum* mixed (1.4%) infections (Cáceres, 2011). The pattern of malaria transmission varies regionally, depending on climate, biogeography, ecology, and anthropogenic activities. Whereas *P. falciparum* malaria occurs mostly in the lowland rain forests of the Venezuelan Guayana region, *P. vivax* malaria is endemic in the coastal plains and savannas as well as the lowland Guayana forests (Rubio-Palis and Zimmerman, 1997). Before the successful malaria eradication campaign in the early 20th century in Venezuela, recurrent epidemics occurred every five years, particularly in the savannas landscapes and coastal plains where *Anopheles darlingi* was the main vector of *P. falciparum* (Gabaldon, 1949). This author observed that malaria cycles apparently coincided with periodic fluctuations of the vector population. Later, Bouma and Dye (1997) associated these epidemics of malaria with the El Niño Southern Oscillation

* Corresponding author. Tel.: +58 2126051404; fax: +58 2126051204.
E-mail address: maria.grillet@ciens.ucv.ve (M.-E. Grillet).

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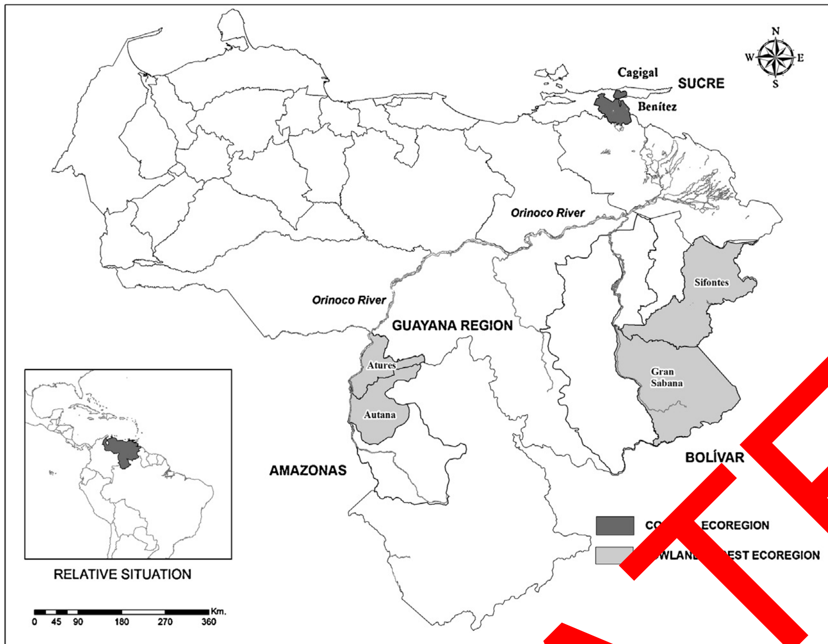

Fig. 1. Map of Venezuela showing the main malaria regions: Amazonas, Bolívar and Sucre States. Malaria cases were aggregated across the municipalities within each state. In the low-land forest eco-region, malaria is caused by *Plasmodium vivax* (84%) and *P. falciparum* (21%), and mainly transmitted by *Anopheles darlingi*. In the coastal eco-region, the infection is caused by *P. vivax* and transmitted by *An. aquasalis*.

(ENSO). This previous work analyzed malaria at the country level, yearly timescales, and overall malaria incidence (*P. vivax* + *P. falciparum*). However, no study has addressed temporal patterns in malaria infections, specially their inter-annual cycles, by resolving the species and the malaria eco-regions of Venezuela. Such downscaling in space and parasite taxonomy could reveal significant heterogeneity in malaria periodicity. Since malaria has become again a serious health problem in this country (Cáceres, 2011), year-to-year variation in the size of epidemics is of particular concern. Understanding this inter-annual variability in the population dynamics of malaria can provide useful insights for malaria elimination programs. Furthermore, a better knowledge of the malaria temporal patterns would allow the development of more effective surveillance and early warning systems to predict disease risk in response to changes in climate.

In this paper, we re-examine the question of malaria's multi-year cycles in Venezuela by using primarily a statistical method of time-series analysis well suited for transient patterns in diseases dynamics and environmental conditions over time (non-stationary patterns). We specifically address the following questions: (i) Is there evidence for particular frequencies in the temporal dynamics of malaria? (ii) Is malaria periodicity species-specific and geographically variable? (iii) Is the inter-annual pattern of malaria in Venezuela associated with climate variability? (iv) If so, does rainfall mediate the effect of ENSO on malaria locally? To do this, we analyze the monthly incidence of *P. vivax* and *P. falciparum* (1990–2010) from three endemic regions of the country. We show that ENSO has played a role in the long-term malaria dynamics during the last 20 years in Venezuela, but that the disease–climate relationship is complex, varying in characteristic periodicities and strength according to region and parasite species.

2. Materials and methods

2.1. Study area

Venezuela is located in the northern coast of South America with a surface area of contrasting landscapes including a northern Caribbean coastal plain and the Venezuelan Guayana in the south (Fig. 1). Malaria is a major public health problem in different endemic-epidemic eco-regions of the country such as the lowland rain forests and savannas of Guayana (<200 m), and the north-eastern coastal plains. Currently, the lowland Venezuelan Guayana is considered a region of high-risk of stable malaria mainly caused by *P. vivax* (~76–84% of cases) and *P. falciparum* (~21–15% of cases), and largely transmitted by *An. darlingi* and *An. marajoara* (Magris et al., 2007; Moreno et al., 2007). *An. darlingi* is mainly a riverine and forest-dwelling species, while *An. marajoara* is a mosquito species associated with wetlands, secondary forests, and human intervention (Moreno et al., 2007). The whole Guayana region covers an extensive area of the country (530,145 km^2), however, the population density is very low and heterogeneously distributed in two administrative areas (Fig. 1): the Amazonas State (0.86 inhabitants per km^2) and the Bolívar State (6.74 inhabitants per km^2). Most of the inhabitants of Amazonas live in the north-western corner of the state (in the Atures and Autana municipalities) and belong to predominantly indigenous ethnic groups (Metzger et al., 2009). Here, the savanna ecosystem is the dominant landscape of malaria transmission (Rubio-Palis and Zimmerman, 1997) and *An. darlingi* is the main species vector. In Bolívar State, the population at risk is mostly localized in the south-east (e.g., in the Sifontes Municipality), where economic activities are agriculture, gold and diamond mining, and forest exploitation. In this endemic area, the lowland forest ecosystem is the dominant malaria landscape, with *An. darlingi* and *An. marajoara* as the main species vectors (Moreno et al., 2007). In the malaria coastal eco-region (Sucre State), along the Caribbean Sea (Fig. 1), the infection is caused by *P. vivax* and transmitted by *Anopheles aquasalis*. This area is largely composed of mangroves, herbaceous and woody swamps. *An. aquasalis* is mainly associated with brackish and freshwater wetlands (Grillet, 2000). Economic activities of the population are mainly fishing, subsistence agriculture, and tourism.

Semi-annual, annual and inter-annual cycles strongly characterize weather and climate variability in Venezuela (Pulwarty et al., 1992). The large-scale spatial features of rainfall are primarily influenced by the annual location of the Atlantic Inter-tropical