

Review Article

Evaluation of the malaria elimination policy in Brazil: a systematic review and epidemiological analysis study

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Abstract. After a centenary fight against malaria, Brazil has seen an opportunity for change with the proposal of the malaria elimination policy set by the Brazilian government, in line with malaria elimination policies in other Latin American countries. Brazilian malaria experts regard eliminating malaria by 2030 to be within reach. Herein we evaluated the likelihood that malaria elimination can be accomplished in Brazil through systematic review of the literature on malaria elimination in Brazil and epidemiological analysis. Fifty-two articles referring to malaria eradication/elimination in Brazil were analyzed to identify challenges and technological breakthroughs for controlling malaria. Monthly deaths (1979–2016) and monthly severe malaria cases (1998–2018) were analyzed according to age groups, geographic region and parasite species. As a result, we observed that the declining malaria burden was mostly attributable to a decline in *Plasmodium falciparum*-malaria. At the same time, the proportional increase of *Plasmodium vivax*-malaria in comparison with *P. falciparum*-malaria was notable. This niche replacement mechanism was discussed in the reviewed literature. In addition, the challenges to *P. vivax*-malaria elimination outnumbered the available technological breakthroughs. Although accumulated and basic information exists on mosquito vector biology, the lack of specific knowledge about mosquito vector taxonomy and ecology may hamper current attempts at stopping malaria in the country. An impressive reduction in malaria hospitalizations and mortality was seen in Brazil in the past 3 decades. Eliminating malaria deaths in children less than 5 years and *P. falciparum* severe cases may be achievable goals under the current malaria policy until 2030. However, eliminating *P. vivax* malaria transmission and morbidity seems unattainable with the available tools. Therefore, complete malaria elimination in Brazil in the near future is unlikely.

INTRODUCTION

Malaria eradication became the Holy Grail after the successful eradication of *Anopheles gambiae* sensu lato from northeastern Brazil between 1939 and 1941 (Kerr, 1963; Packard and Gadelha, 1997; Killeen *et al.*, 2002; Killeen, 2003). The successes and infrastructure of the Yellow Fever Service

deployed for the eradication of *Aedes aegypti* from huge areas in Brazil (Kerr, 1963) served as the basis for a new Malaria Service created by the Rockefeller Foundation and the Brazilian government. This new entity eradicated *An. gambiae* s.l. from Brazil with a vector centered approach; insecticides were applied upon all potential larval habitats in 54,000-km² of wetlands in the

Northeastern Brazil (Killeen *et al.*, 2002). The successful *An. gambiae* s.l. eradication in Brazil became the proof of concept for a wider and more ambitious malaria eradication operation, known as the Global Malaria Eradication Program (GMEP) launched in the 1950s (Packard and Gadelha, 1997). GMEP was premised on the use of chloroquine-based antimalarials and the insecticide dichloro-diphenyl-trichloroethane (DDT) for indoor spraying. GMEP actions resulted in malaria eradication from all developed countries, and a drastic reduction in malaria in tropical Asia and Latin America (Trigg and Kondrachine, 1998). GMEP also helped malaria eradication in the most populated cities and regions in the Atlantic coast of Brazil in 1960-70s (Corrêa and Alves, 1969; Mascarenhas, 1973).

The GMEP successes were hampered by: (1) insecticide resistance, (2) *Plasmodium falciparum* chloroquine-resistance, (3) anthropological factors (e.g., migration, isolation, lack of education, environmental modification), and (4) operational, administrative and financial difficulties (Palacios Fraire, 1975). After the end of GMEP, malaria re-emerged and malaria burden increased in endemic tropical countries, with the highest transmission levels in sub-Saharan areas of Africa (Trigg and Kondrachine, 1998). In Brazil, malaria was well-controlled during the GMEP.

However, after the end of GMEP, malaria emerged in the 1980s, especially in new settlements in Amazonia (Vosti, 1990) (Figure 1).

Eradication means ultimate extermination of a given species on any temporal or spatial scale. However, following multiple failures to eradicate disease, the eradication concept became controversial (Roberts and Enserink, 2007). A critic of disease eradication stated: "It is a moot question which is the more sophisticated: *Homo sapiens* or *Treponema pallidum*?" (Kerr, 1963). More recently, a second attempt for eradication, namely malaria global elimination, is proposed (Hommel, 2008). Malaria elimination means that a given species (i.e., *P. falciparum*) can be removed from humans in a certain location and in a given period under continuous control activities and improvements (World Health Organization, 2015). Today, the global malaria community is even more confident with the recent malaria burden decline and the compliance of the governments of endemic countries with the policy of malaria elimination (Rabinovich *et al.*, 2017). They advocate, for instance, if all endemic countries eliminate malaria globally, the ultimate outcome will be malaria eradication.

The governments of countries in Latin America have complied with the WHO Global Technical Strategy for malaria control and

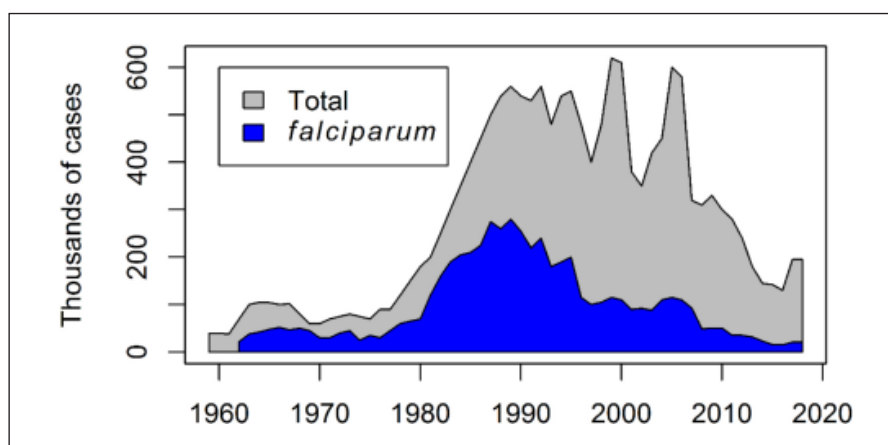


Figure 1. Annual number of laboratory-confirmed malaria cases reported in Brazil from 1959 to 2018. The total number of cases, and those due to *Plasmodium falciparum*, are shown. Data Sources: National Malaria Prevention and Control Programme, Ministry of Health of Brazil; partially adapted from (Ferreira and Castro, 2016).

elimination 2016–2030 (World Health Organization, 2015). Because of the research agenda for malaria elimination and eradication (Rabinovich *et al.*, 2017), aligned with the reduction of extreme poverty (United Nations, 2015), Latin American scientists are now more optimistic about the possibility of drastic reductions in *P. falciparum* malaria mortality (Arevalo-Herrera *et al.*, 2012; Chaccour *et al.*, 2015; Pacheco *et al.*, 2015; van Eer *et al.*, 2018). On the one hand, looking at the malaria trends in the Americas, the incidence of this disease has been reduced drastically in the last decade (Castellanos *et al.*, 2015). On the other hand, malaria elimination has encountered several challenges in Brazil (Silva-Nunes *et al.*, 2012; Ferreira and Castro, 2016) and in Venezuela (Grillet *et al.*, 2019).

Brazil is fully expecting to become recognized as a high-income industrial country (Murphy and Mullis, 2011). In order to join the ranks of high-income industrial countries, neglected tropical diseases associated with poverty, such as malaria, must be controlled (Cashwell *et al.*, 2014; Hotez and Fujiwara, 2014). Herein, we evaluated the probability of malaria elimination in Brazil. We review the literature on malaria interventions and technological breakthroughs contributing to the decline of malaria. In addition, literature on socio-economic development, historical inter-

ventions, and challenges to malaria elimination was reviewed. We counter-balanced the available technological breakthroughs with the challenges for malaria control to evaluate the possible outcomes under the ongoing malaria elimination policy. We validate our interpretations from the systematic review with epidemiological data analysis.

MATERIALS AND METHODS

Study area

Brazil encompasses the equatorial Amazon rainforest in the Northern Hemisphere to more temperate sub-tropical regions in the Southern Hemisphere, spanning over 35 degrees of latitude in South America. It has a population of 209 million (in 2019), which lives mostly in the municipalities along the Atlantic coast (ibge.gov.br/apps/populacao/projecao/index.html). The 2017 epidemiological profile of malaria transmission is shown (Figure 2).

Systematic review

A systematic review was conducted of all available articles regarding malaria eradication or malaria elimination in Brazil. Potentially relevant articles in English, Portuguese, French or Spanish were accessed in March 14th 2018 from PUBMED

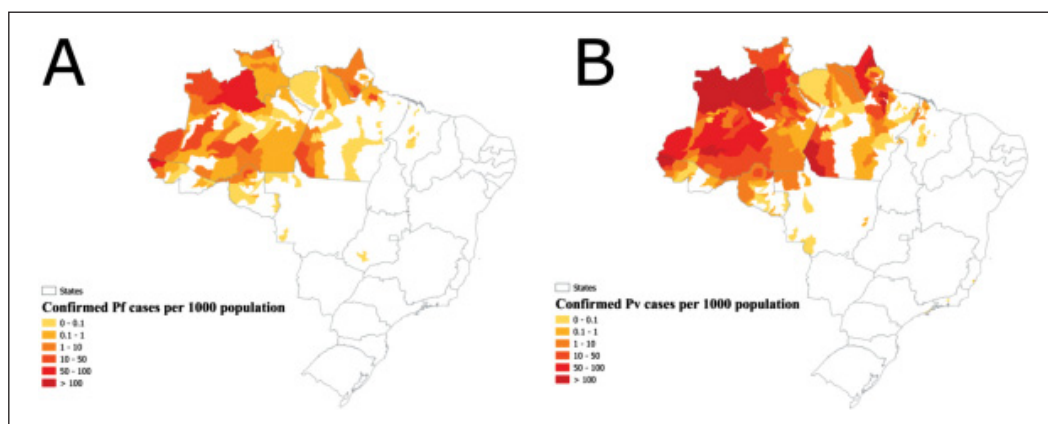


Figure 2. Confirmed cases per 1000 population in municipalities, Brazil, 2017. (A) *Plasmodium falciparum* (Pf). (B) *Plasmodium vivax* (Pv). Population at risk: 42.5 million people living in transmission zones (20% out of the Brazilian population). Data Source: (World Health Organization, 2018).

(ncbi.nlm.nih.gov/pubmed/), LILACS (lilacs.bvsalud.org/en/) and WEB OF SCIENCE (apps-whoofknowledge.ez329.periodicos.capes.gov.br) to review their full texts. We applied text search strategy using the combination of Health Sciences Descriptors (decs.bvs.br/l/homepagei.htm). Terms and keywords utilized were as follows “Brazil AND malaria AND disease eradication” or “Brazil AND malaria AND disease elimination”. We selected the following fields in text search strategy ALL FIELDS PUBMED, TOPIC/ALL YEARS WEB OF SCIENCE and ALL INDEXES LILACS. Only original and non-duplicated research studies were included. Eligibility for inclusion of articles was based

on explicit relation to either technological breakthroughs for malaria control or challenges regarding malaria (re)emergence or both. After eliminating duplicates, we identified relevant papers by screening titles and abstracts. Two independent investigators (MAOP, RTAB) performed identification and screening of articles, while a third investigator (GZL) reviewed screening and performed eligibility of the articles included herein (Figure 3). Full articles reading were achieved by applying a strategy based on PICO (P, patient, population or problem; I, intervention, C, comparison; O, outcomes; s, type of study) (Methley *et al.*, 2014).

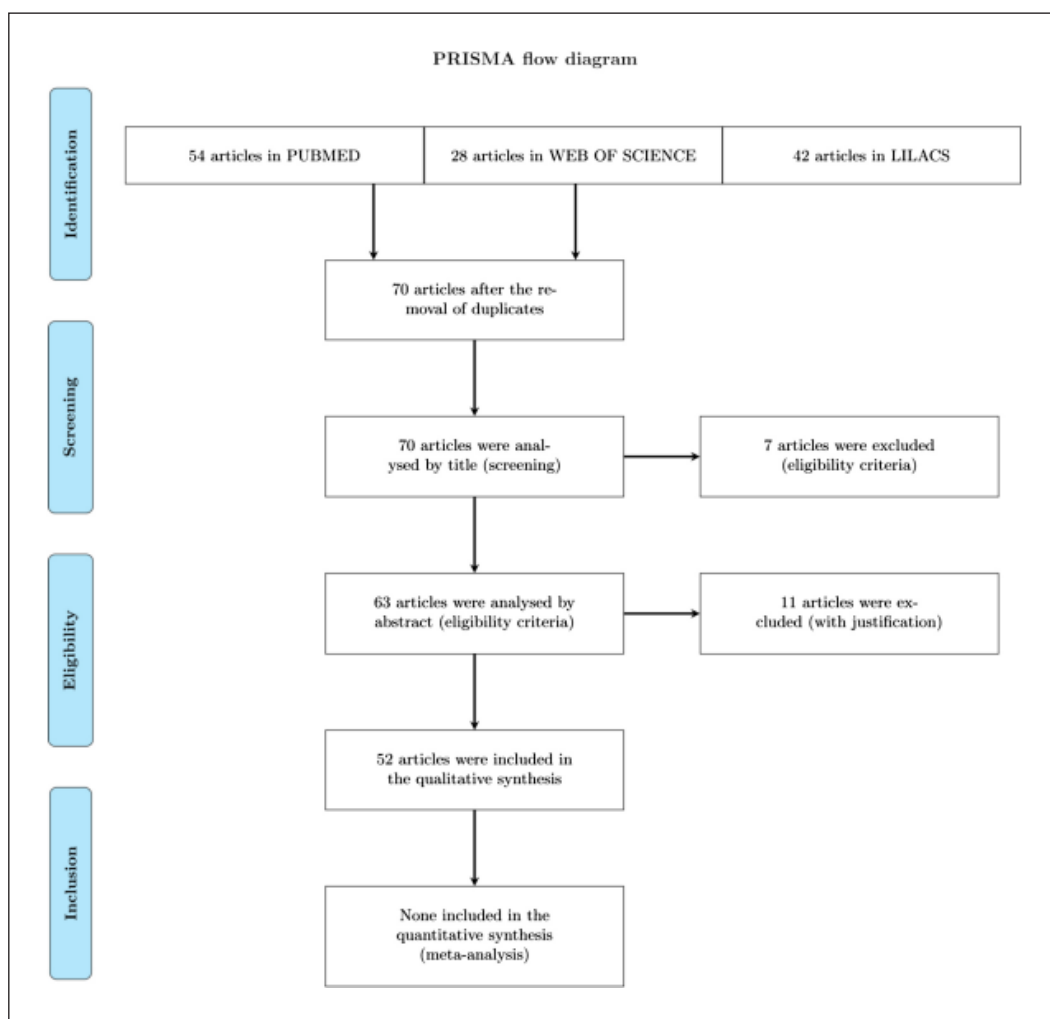


Figure 3. The PRISMA Flow Diagram. Summary of the process of systematic literature review and synthesis.

Epidemiological analysis

We performed the following analyses: (1) malaria burden in Brazil, (2) geographical differences, (3) age-dependent outcomes, and (4) *P. falciparum* vs. *P. vivax*.

We define malaria burden as the incidence rate of mortality or hospitalization attributable to malaria. Mortality data was obtained from the Ministry of Health, 1979–2016. Hospitalization data was obtained from the Unified Health System, 1998–2018. Malaria hospitalization and mortality records were extracted using the code 084 in the International Classification of Diseases (ICD) 9 for data before 1995 and the codes B50–B54 in the ICD-10 for data from 1995 onwards. Data were organized in a 4-D matrix containing the following dimensions: (1) TIME, monthly malaria mortality rate (per 100,000 ppl.) from Jan 1979 to Dec 2016 (mortality) or monthly malaria hospitalization rate (per 100,000 ppl.) from Jan 1998 to Dec 2018; (2) GEOGRAPHIC, Brazilian states (26) and a Federal District; (3) AGE, age groups (less than 1 year, 0–4, 5–9, ..., 80+); (4) PARASITE, malaria parasite species. Population data were interpolated in monthly series (epipoi.info/popweaver/). All analyses were performed using the EPIPOI software (epipoi.info/).

Ethical issues

Utilized data are of public domain according to the Brazilian Law of Information Access (12.527/2011). Patient information is not available.

RESULTS

Systematic review

Fifty-two articles in total were included in the qualitative synthesis (Figure 2). The overall number of articles referring to ‘malaria elimination’ (n = 39) was 3-fold higher than those about ‘malaria eradication’ (n = 13). The use of ‘malaria eradication’ referring to the Global Malaria Eradication Program 1955–1969 was frequently used before 2010. Out of 13 articles with the ‘malaria eradication’ term, 12 were published in-between 1963–2010. Starting in 2011 the

term ‘malaria elimination’ appearance increased exponentially in the literature. Thirty-seven out of 39 articles with reference to the ‘malaria elimination’ term were published from 2011 to 2018.

Malaria eradication era

We identified 4 technological breakthroughs for controlling malaria under the policy of malaria eradication in Brazil: (1) larval control, (2) Global Malaria Eradication Program (GMEP), (3) income and literacy increase, and (4) Global Malaria Control Strategy (GMCS). In contrast, we identified 6 challenges that prevented malaria eradication from Brazil: (1) socioeconomic deficit, (2) insecticide resistance, (3) chloroquine-resistant *P. falciparum*, (4) logistic issues, (5) simian malaria, and (6) eradication failure in specific contexts (Table 1).

The **Larval control** (Table 1) employed by the Rockefeller Foundation and the Brazilian government, under the leadership of Fred Soper, was an outstanding success through a vertically integrated programme that relied overwhelmingly on larval control. The success behind the Malaria Service of Northeast Brazil, where *An. gambiae* s.l. had invaded, was the organization of its activities. A cartographic unit mapped infested areas using aerial photographs. A field laboratory and epidemiological section allowed training, surveillance and decision-making. The entire infested area was divided into zones. All potential larval habitats were treated with Paris Green (a larvicide with established toxicity) in each zone during one week. This approach was soon repeated and suppressed malaria in Upper Egypt and Zambia, Africa, in the 1940s. These successful approaches were neglected after the advent of DDT. The policy for mosquito eradication under the **Global Malaria Eradication Program** (Table 1) shifted toward domestic adulticide methods.

A former Brazilian president Juscelino Kubitschek (1956–1961) established development policies for Brazil in the beginning of the Global Malaria Eradication Program. Brazil committed with the World Health Organization to convert its malaria control

Table 1. Technological breakthroughs and challenges for controlling malaria in the ‘eradication era’ in Brazil

Technological breakthroughs		Challenges	
Types	References	Types	References
1. Larval control	(Packard and Gadelha, 1997; Killeen <i>et al.</i> , 2002; Killeen, 2003)	1. Socioeconomic deficit	(Palacios Fraire, 1975; Vosti, 1990; Packard and Gadelha, 1997)
2. Global Malaria Eradication Program	(Corrêa and Alves, 1969; Mascarenhas, 1973; Barata, 1997; Packard and Gadelha, 1997; Trigg and Kondrachine, 1998; Bleakley, 2010; Silva and Paiva, 2015)	2. Insecticide resistance	(Palacios Fraire, 1975)
3. Income and literacy increase	(Bleakley, 2010)	3. <i>Plasmodium falciparum</i> resistance to chloroquine	(Palacios Fraire, 1975)
4. Global Malaria Control Strategy	(Trigg and Kondrachine, 1998)	4. Logistic issues	(Palacios Fraire, 1975)
		5. Simian malaria	(Deane, 1969; Palacios Fraire, 1975)
		6. Eradication is not always possible	(Kerr, 1963)

programs into eradication programs. The Malaria Eradication Group was set up in the federal government and all states complied with the new policy for malaria eradication in Brazil. Vector control was based on three annual spraying cycles of DDT in endemic regions. Malaria cases in humans were diagnosed by microscopy and treated with chloroquine. As a result, the lowest number of malaria cases in the history of Brazil was seen in 1961 when ~37 thousand cases were laboratory-confirmed. The populated cities in the Atlantic coast of Brazil became malaria-free. As seen in former endemic countries, such as the United States, people born after eradication have higher income as adults than the preceding generation. The **Income and literacy increase** (Table 1) after eradication was an important driver of development in the Atlantic coast region of Brazil. The São Paulo State Malaria Eradication Program eradicated malaria, among others such as Chagas disease, in the cities and rural areas. This state is now the most developed and richest in Brazil.

Failures to eradicate malaria in Brazil

Notwithstanding, the Global Malaria Eradication Program poorly accomplished its goals in certain regions in Latin America and Brazil, specifically in Amazonia. The phenomenon of **Insecticide resistance** (Table 1) was recognized. Particularly, endophagy and exophily (biting indoors and resting outdoors) of mosquito vectors (e.g., *Anopheles darlingi*) were recognized as challenges. Mosquito vectors did not rest on DDT-sprayed surfaces when indoors and usually rested in unsprayed areas such as clothing. The use of chloroquine in a mass treatment program involved massive and frequent exposure of the parasite to the drugs. This led to the selection of resistance to the 4-aminoquinolines and then ***Plasmodium falciparum* resistance to chloroquine** (Table 1). People mobility helped the dispersion of chloroquine-resistant strains of *P. falciparum*.

The **Socioeconomic deficit** (Table 1) unduly delayed eradication operations and proved the malaria eradication program as

unattainable in Amazonia. Human ecology was as challenging as vector ecology. Poorly built houses and shelters were found in areas where malaria transmission persisted. Demographic characteristics (e.g., human migrations or isolations) were closely related to variations in malaria transmission. Extreme examples of demographic complexity were jungle people living in nomadic and isolated societies, engaged in production of rubber, wood, nuts, gold, diamonds, and other raw materials. Such circumstances often required specific approaches, generally with an in-depth anthropological operation to define the possibilities of malaria control.

Operational, administrative and financial difficulties were **Logistic issues** (Table 1). The funds allocated to malaria eradication programs were not adequate to offset salary increases, inflation, growing needs imposed by technical problems and the tremendously increased prices of DDT (75% in 3-years) purchased by the Brazilian government in the 1970s. The three annual spraying cycles of DDT adopted in the endemic regions in the South and Eastern Brazil was impractical in many hard-to-reach communities in the Amazonia.

A further aspect that highlighted the difficulty in achieving malaria eradication was **Simian malaria** (Table 1). Monkey plasmodia added, theoretically, a new challenge to the malaria eradication campaigns. They could infect susceptible humans living in close relationship with forests harbored by mosquito vectors.

The failures from the malaria eradication campaigns in Amazonia were analyzed and the synthetic explanation for unsuccessful outcomes was **Eradication is not always possible** (Table 1). The malaria eradication campaigns were time-limited, highly prescriptive and centralized. After the end of the Global Malaria Eradication Program, malaria re-emerged in places where improvements in the malaria situation were partial. The Ministerial Conference on Malaria Control in 1992 and the World Health Assembly in 1993 created the **Global Malaria Control Strategy** (Table 1). This strategy differed from the approach used in the eradication era. It was rooted in the

primary health care approach and called for flexible, decentralized programmes, based on disease rather than parasite control. The Global Malaria Control Strategy represented the beginning of the malaria elimination era.

Malaria elimination era

In the malaria elimination era, we identified 12 technological breakthroughs. One fraction is represented by tools that have already helped controlling malaria. Health care diagnostic-and-treatment integration and artemisinin combination therapy were cited as responsible for decreasing *P. falciparum* or severe malaria (Table 2). Others are promising tools, such as novel modeling approaches, antimalarial drugs, immunization strategies, vector control intervention, or molecular tools. Notwithstanding, the number of challenges for malaria elimination were 2-fold greater than the number of technological breakthroughs, summing up to 24 in total. Out of these, at least half was related to *P. vivax* prevalence and one-third, to socio-environmental factors in Brazil (Table 2).

Decreasing *Plasmodium falciparum* and severe cases (Table 2) were accomplished by the malaria control policies set in Brazil: (1) PCMAM, Amazon Basin Malaria Control Programme, 1989; (2) PIACM, Intensification Plan of Malaria Control Activities in the Legal Amazon, 2000; and (3) NMPCP, National Malaria Prevention and Control Programme, 2003. The current first line treatment for *P. falciparum* is artemether-lumefantrine (artemisin combination therapy) plus a gametocidal dose of primaquine. A short-term challenge, however, is **Evolution of *Plasmodium falciparum* resistance** (Table 2); resistance to artemisin in *P. falciparum* has arisen in Guyana, on the border of Brazil. The resistant strains evolved independently from those previously found in Southeast Asia. The mechanism of resistance is in the propeller domain of the *kelch13* gene.

The *P. vivax* issue in the malaria elimination era

The **Decreasing *Plasmodium falciparum*** (Table 2) trend was followed by the decline

Table 2. Technological breakthroughs and challenges for eliminating malaria in Brazil

Technological breakthroughs		Challenges	
Types	References	Types	References
1. Modeling	(Laporta <i>et al.</i> , 2013; Sepúlveda <i>et al.</i> , 2015; Castellanos <i>et al.</i> , 2015; Pizzitutti <i>et al.</i> , 2015)	1. Transfusion-transmitted malaria	(Alho <i>et al.</i> , 2017)
2. <i>Plasmodium vivax</i> drugs	(Daher <i>et al.</i> , 2018)	2. <i>Plasmodium vivax</i> resistance to chloroquine	(Daniel-Ribeiro <i>et al.</i> , 2008; Silva-Nunes <i>et al.</i> , 2012; Ferreira and Castro, 2016; Siqueira <i>et al.</i> , 2016; Recht <i>et al.</i> , 2017; Daher <i>et al.</i> , 2018)
3. <i>Plasmodium vivax</i> vaccine	(Cabrera-Mora <i>et al.</i> , 2015)	3. <i>Plasmodium vivax</i> relapse	(Barbosa <i>et al.</i> , 2014; Vitor-Silva <i>et al.</i> , 2016; Siqueira <i>et al.</i> , 2016; Daher <i>et al.</i> , 2018)
4. Ivermectin vector control	(Chaccour <i>et al.</i> , 2015)	4. Asymptomatic infections	(Daniel-Ribeiro <i>et al.</i> , 2008; Chuquiayuri <i>et al.</i> , 2012; Silva-Nunes <i>et al.</i> , 2012; Barbosa <i>et al.</i> , 2014; Ferreira and Castro, 2016; Fontoura <i>et al.</i> , 2016; Siqueira <i>et al.</i> , 2016; Recht <i>et al.</i> , 2017)
5. Genomic analysis and molecular tools	(Pacheco <i>et al.</i> , 2015; Pearson <i>et al.</i> , 2016)	5. Variant immunological responses	(Costa <i>et al.</i> , 2017)
6. Hotspot identification	(Rosas-Aguirre <i>et al.</i> , 2015; Alencar <i>et al.</i> , 2017)	6. Malaria in pregnancy	(Ferreira and Castro, 2016; Bóttö-Menezes <i>et al.</i> , 2016; Bardaji <i>et al.</i> , 2017; Recht <i>et al.</i> , 2017)
7. Decreasing <i>Plasmodium falciparum</i>	(Oliveira-Ferreira <i>et al.</i> , 2010; van Eer <i>et al.</i> , 2018)	7. Bromeliad-malaria	(Lorenz <i>et al.</i> , 2015; Ferreira and Castro, 2016; Alencar <i>et al.</i> , 2017)
8. Decreasing severe cases	(Oliveira-Ferreira <i>et al.</i> , 2010)	8. Submicroscopic infections	(Barbosa <i>et al.</i> , 2014; Ferreira and Castro, 2016; Recht <i>et al.</i> , 2017)
9. Naturally acquired immunity vaccine candidate	(Daniel-Ribeiro <i>et al.</i> , 2008)	9. Evolution of <i>Plasmodium falciparum</i> resistance	(Ferreira and Castro, 2016; Recht <i>et al.</i> , 2017)
10. International Centers of Excellence for Malaria Research	(Arevalo-Herrera <i>et al.</i> , 2012; Pacheco <i>et al.</i> , 2015)	10. Vector control	(Tauli, 2011; Ferreira and Castro, 2016; Recht <i>et al.</i> , 2017)

Table 2 continued...

Technological breakthroughs		Challenges	
Types	References	Types	References
11. Experimental assays for antimalarial drugs	(Pedroni <i>et al.</i> , 2006)	11. Detection of new foci of infection	(Chuyiyauri <i>et al.</i> , 2012; Ferreira and Castro, 2016)
12. Housing interventions	(Leandro-Reguillo <i>et al.</i> , 2015)	12. Environmental changes	(Ferreira and Castro, 2016; Siqueira <i>et al.</i> , 2016)
		13. Integrate surveillance	(Ferreira and Castro, 2016; Vitor-Silva <i>et al.</i> , 2016)
		14. G6PDd issue	(Monteiro <i>et al.</i> , 2014a, 2014b; Recht <i>et al.</i> , 2017)
		15. Reservoir-monkeys	(Araújo <i>et al.</i> , 2013; Brasil <i>et al.</i> , 2017; Figueiredo <i>et al.</i> , 2017; Alvarenga <i>et al.</i> , 2017)
		16. Gold mining	(Silva-Nunes <i>et al.</i> , 2012; Recht <i>et al.</i> , 2017)
		17. Country border malaria	(Chuyiyauri <i>et al.</i> , 2012; Recht <i>et al.</i> , 2017)
		18. Urban malaria	(Recht <i>et al.</i> , 2017)
		19. Complicated <i>Plasmodium vivax</i> malaria	(Daniel-Ribeiro <i>et al.</i> , 2008; Oliveira-Ferreira <i>et al.</i> , 2010; Lacerda <i>et al.</i> , 2012)
		20. Socioeconomic aspects	(Siqueira <i>et al.</i> , 2016)
		21. Chloroquine-induced pruritus	(Ballut <i>et al.</i> , 2013)
		22. <i>Plasmodium vivax</i> high genetic diversity	(Fontoura <i>et al.</i> , 2016)
		23. Human mobility	(Tauli, 2011)
		24. Indigenous malaria	(Leandro-Reguillo <i>et al.</i> , 2015)

of *P. vivax*. However, the *P. vivax* decline was not achieved with the same magnitude of success. Different from *P. falciparum*, asexual forms of *P. vivax* are sequestered in the liver as hypnozoites. This mechanism leads to **Plasmodium vivax relapse** (Table 2), which is a form of recurrent malaria in a previously treated person. Chloroquine alone cannot kill hypnozoites in the liver and is further related to **Plasmodium vivax resistance to chloroquine** (Table 2). Chloroquine combined with primaquine is recommendable for a radical cure of *P. vivax* malaria. However, the use of primaquine is hampered by the **G6PDd issue** (Table 2). Primaquine can induce haemolysis in glucose-6-phosphate dehydrogenase deficient (G6PDd) individuals. The prevalence of G6PDd is 10% of the Brazilian population and the frequency of haemolysis in G6PDd patients is 90%.

The use of primaquine is also not indicated in pregnant women. **Malaria in pregnancy** (Table 2) causes health problems in newborns such as iron deficiency anemia. Pregnant women are reservoirs of *P. vivax* and can infect mosquito vectors and maintain parasite transmission. Similarly, **Asymptomatic and Submicroscopic infections** (Table 2) represent a fraction of infections that remain undetected in a population and maintain low residual transmission. They can also lead to **Transfusion-transmitted malaria** (Table 2).

Human mobility (Table 2) of asymptomatic carriers of *P. vivax* living under specific **Socioeconomic aspects** (Table 2) can promote emergence of malaria associated with **Environmental changes** (Table 2). These carriers have strong epidemiologic characteristics (travelers, immigrants) and can be drivers for **Plasmodium vivax high genetic diversity** (Table 2). Examples of such a scenario are places with **Gold mining, Country border malaria, Indigenous malaria or Urban malaria** (Table 2). **Detection of new foci of infection** (Table 2) can be a challenge when a new outbreak of malaria starts with the presence of asymptomatic carriers. This situation requires **Integrate surveillance** (Table 2).

P. vivax causes a spectrum of clinical symptoms in patients, ranging from asymptomatic to severe cases. **Variant immunological responses** (Table 2) are associated with variants of toll-like receptors (TLRs) and influence an individual's susceptibility to *P. vivax* malaria and parasitemia. **Complicated Plasmodium vivax malaria** (Table 2) is becoming more frequent due to unknown reasons. Another related phenomenon is **chloroquine-induced pruritus** (Table 2) as an adverse event in patients being treated with chloroquine for *P. vivax* malaria.

Vector control in the malaria elimination era

Large-scale vector control strategies in Amazonia are unfeasible due to local environment conditions coupled with vector ecology and behavior. Malaria vector control commodities (e.g., insecticide residual spraying or insecticide treated nets) are distributed to only 5% of the Amazonian populations.

Simian malaria in the malaria elimination era

Simian malaria represents a challenge to malaria elimination. If monkey plasmodia can infect humans and cause disease, malaria elimination goals based on eliminating malaria disease can become even harder to achieve. This issue is not well understood in Amazonia. In the Atlantic forest, however, **Reservoir-monkeys** (Table 2) can play an important role as reservoirs of monkey and human plasmodia that can infect humans. Some of these infections become symptomatic and are reported by the health authorities. They recognize these autochthonous cases as belonging to the transmission cycle known as **Bromeliad-malaria** (Table 2). This term refers to the main malarial vector (*Anopheles cruzii*) in which larvae breeds in the leaves of bromeliads in Atlantic forest.

Tools for controlling P. vivax in the malaria elimination era

Because *P. vivax* malaria is spatially and temporally clustered, sensitive tools for

better stratifying the risk of infection and targeting control interventions are needed. **Genomic analysis and molecular tools** (Table 2) and **Modeling** (Table 2) methods are being utilized toward **Hotspot identification** (Table 2). Molecular epidemiology investigations are currently being performed by the network of the **International Centers of Excellence for Malaria Research** (Table 2; ICEMR). The prevalence of multi-clone infections of *P. vivax*, which indicate high genetic diversity, is estimated by parasite genotyping methods. Declines in this prevalence are coupled with declining parasite transmission. **Modeling** (Table 2) methods are applied for predictions under hypothetical scenarios in simulated interventions. Agent-based-models can reproduce the spatiotemporal variations of malaria transmission in an Amazonian environment dominated by river floodings. The invasion of *P. vivax* in an Atlantic forest island is modeled in circumstances of low or higher biodiversity. **Housing interventions** (Table 2) are being proposed in indigenous populations suffering from highly endemic malaria transmission.

Specific tools for parasite suppression are also on development. **Plasmodium vivax drugs** (Table 2) were tested in an open label randomized clinical trial. Artemisinin-based combinations or chloroquine in combination with a short course of primaquine were effective and safe for *P. vivax* control. The main drawbacks were the adverse events; a new drug, Tafenoquine, is promising in its potential for radical cure of *P. vivax*. **Experimental assays for antimalarial drugs** (Table 2) with Wistar rats and *Plasmodium berghei* was developed as an experimental model. This model can be used for testing new antimalarial drugs at preclinical stages. **Naturally acquired immunity vaccine candidate** (Table 2) is a promising strategy based on immune responses specific to *P. vivax* antigens generated in natural infections. Whether their immunogenic potential can be applied to vaccine candidates is yet to be determined in field trials under natural conditions of parasite exposure. **Plasmodium vivax**

vaccine (Table 2) that is considered the most promising candidate is the circumsporozoite protein. This candidate can, in theory, prevent the entry of sporozoites into hepatocytes or inhibit the liver stage development of hypnozoites. A *P. vivax* circumsporozoite protein recombinant chimera (PvRMC-CSP) was proposed as a promising vaccine candidate for further development. Interestingly, the PvRMC-CSP was recognized by naturally acquired antibodies from individuals living in areas where malaria is endemic.

New tools for vector control are also needed. **Ivermectin vector control** (Table 2) is an additional vector control tool that is receiving increased attention from the malaria elimination community. Ivermectin is an endectocide drug; ivermectin treated-cattle can be bitten by mosquito vectors, which will die afterwards. The increased importance of ivermectin relies on its application in outdoor/residual malaria transmission and in places where insecticide resistance is prevalent.

Epidemiological analysis integrated with the systematic review

Resurgent malaria on the frontier of Amazonia was observed after national integration starting from 1970 (Figure 4A). Waves of migrants from the malaria-free (South and East) regions of Brazil settled in the Amazonian states of Pará, Rondônia, Amazonas, Mato Grosso, Amapá, Acre, and Roraima to engage in new economic activities (mining, logging, cattle ranching, farming). This massive human influx caused local deforestation, increases in vector (*An. darlingi*) abundance and a dramatic increase in malaria incidence in the 1980s. The monthly malaria mortality rate of 0.035 (per 100,000 ppl.; an average of 50 malaria deaths per month) in 1979 increased by 300%, and peaked to 0.11 (per 100,000 ppl.) with 150 malaria deaths per month in 1988 (Figure 4A).

All states in the Amazon Region and two in the Brazilian Savannah ('Cerrado') Region (Mato Grosso do Sul and Goiás) concentrated the majority of malaria deaths. Specifically,

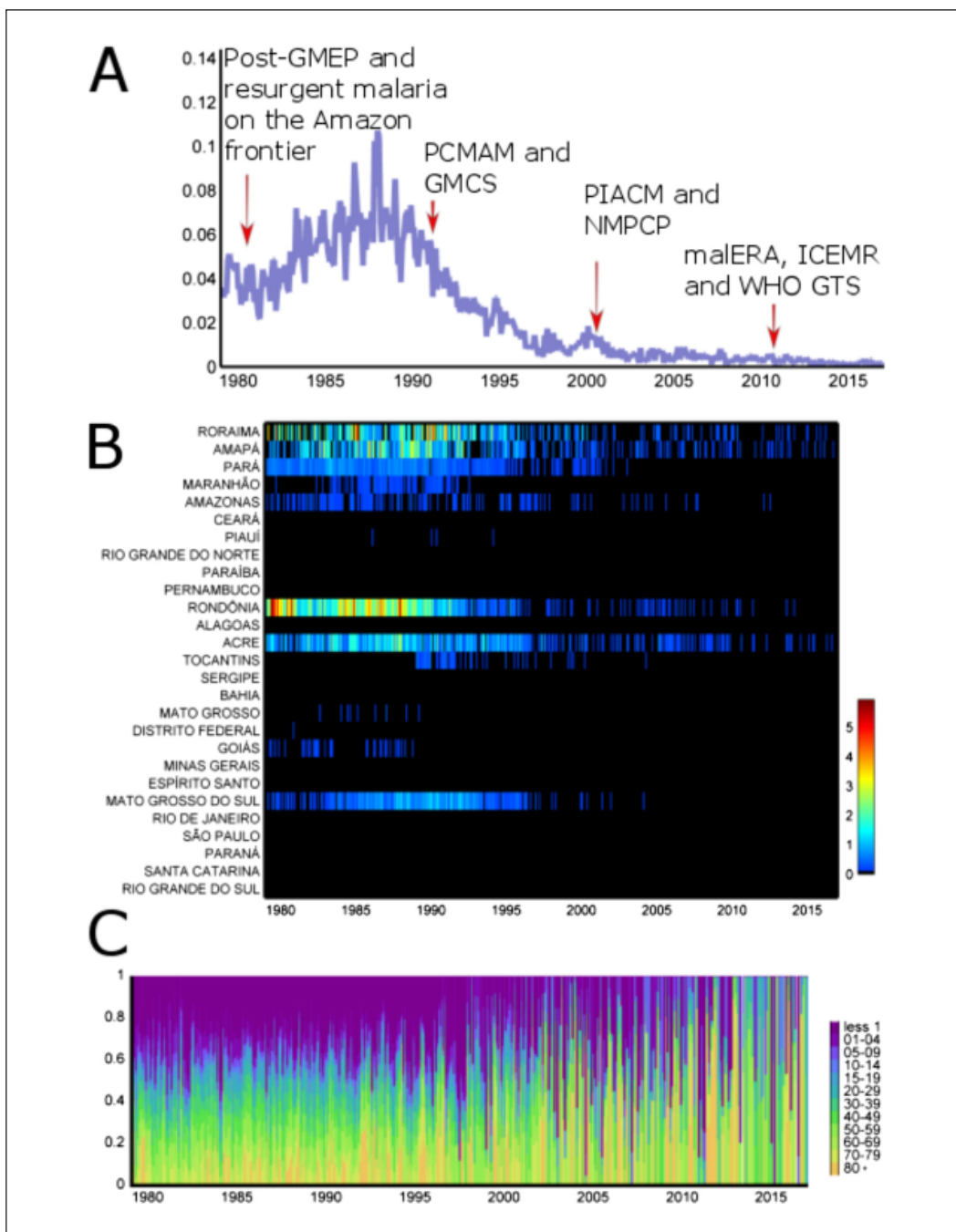


Figure 4. (A) Malaria monthly mortality rate (per 100,000 ppl.), 1979-2016, in Brazil. Red arrows show a given period of malaria policy depicted from the systematic review. GMEP, Global Malaria Eradication Program; PCMAM, Amazon Basin Malaria Control Programme; GMCS, Global Malaria Control Strategy; PIACM, Intensification Plan of Malaria Control Activities in the Legal Amazon; NMPCP, National Malaria Prevention and Control Programme; malERA, Malaria Eradication Research Agenda; ICEMR, International Centers of Excellence for Malaria Research; WHO GTS, World Health Organization Global Technical Strategy. (B) Malaria monthly mortality rate (per 100,000 ppl.), 1979-2016, per 26 states and a federal district. (C) Malaria monthly mortality rate (proportion, 0 - 1) per age-groups (less 1 year, —, 80 and plus). Data source: Ministry of Health.

one-third of monthly malaria deaths in Brazil occurred in Rondônia state in 1985 (Figure 4B).

In 1989, the Ministry of Health Amazon Basin Malaria Control Programme (PCMAM) started earlier treatment of malaria cases to reduce transmission and mortality. The network of malaria diagnosis and treatment outposts was greatly expanded throughout Amazonia. The overall malaria incidence decreased by 60% from 1989 to 1996. The proportion of *P. falciparum* infections decreased from 47 to 29% in the same period. As a result, the total number of deaths from malaria was 39 in 2016 and the monthly malaria mortality rate approaches 0 (Figure 4A).

Deaths due to malaria were proportionally more frequent in children (< 5 years), particularly in those less than 1 year of age in the 1980s and 1990s. Starting in the 2000s, there was a decrease in the proportional mortality in children under five years of age, and a concomitant increase in proportional mortality in older adults (Figure 4C).

The gains associated with PCMAM, however, were lost during the last quarter of the 1990s. More than 600 thousand microscopically confirmed malaria cases were recorded in 1999. This culminated with 2,500 monthly cases of severe malaria, and a monthly malaria hospitalization rate of ~1.1 per 100,000 ppl. in the late 1990s (Figure 5A).

As a consequence, the Ministry of Health implemented a comprehensive plan to reduce overall malaria, severe morbidity and mortality, to eliminate malaria transmission in the urban area of state capitals in Amazonia, and to prevent resurgence in malaria-free areas. In 2000, the Intensification Plan of Malaria Control Activities in the Legal Amazon (PIACM) targeted 254 municipalities (32.1% of the total number of municipalities in the Amazon), which gathered 93.6% of the malaria cases. Control measures were tailored to each specific epidemiological setting. A strong reduction in morbidity (40%) was seen in the following years (Figure 5A).

Notwithstanding, all states in Northern Brazil (e.g., Mato Grosso and those in the Amazon region) continued contributing to hospitalizations from malaria after 2001 (Figure 5B). Specifically, states in Western Amazonia (Rondônia and Acre) had high rates of hospitalizations (up to 60 per month per 100,000 ppl.) in the beginning of the 2000s (Figure 5B).

In 2003, the Ministry of Health launched the National Malaria Prevention and Control Programme (NMPCP) to reinforce the goals established in the PIACM. Following the decentralization of the health system during the 1990s each municipality could adopt different control strategies. Mass distribution of long lasting insecticide-treated nets (LLINs) started in Acre state in 2006, and was later expanded to all high-risk areas in Amazonia, from 2008 on. The network of malaria outposts increased to nearly 3,500 with ~ 4,500 microscopists and 7,600 health agents up to 2013. Malaria hospitalization rates approached 0, with a total of 500 severe malaria cases in 2013 (Figure 5A).

During the period of 1990-2008, severe cases were mostly due to *P. falciparum* (80–100%; Figure 5C). The successful use of artemisin combination therapy (artemether-lumefantrine) in the aforementioned network of malaria outposts reduced the *P. falciparum* malaria burden. In recent years, however, the monthly proportion of severe cases due to *P. vivax* has increased to 50% (Figure 5C). This is related to **The *P. vivax* issue in the malaria elimination era.**

Based on the achievements on the decreasing burden of malaria in Brazil (Figures 4A, 5A) and worldwide, many globally based initiatives were launched for malaria elimination and eradication, such as the International Centers of Excellence for Malaria Research (ICEMR) and the Malaria Eradication Research Agenda (malERA), starting in 2010. In 2015, Brazil was awarded by the Pan American Health Organization (PAHO) the Malaria Champions of the Americas Award. In the same year the NMPCP of the Ministry of Health launched the Plan for Elimination of Malaria in

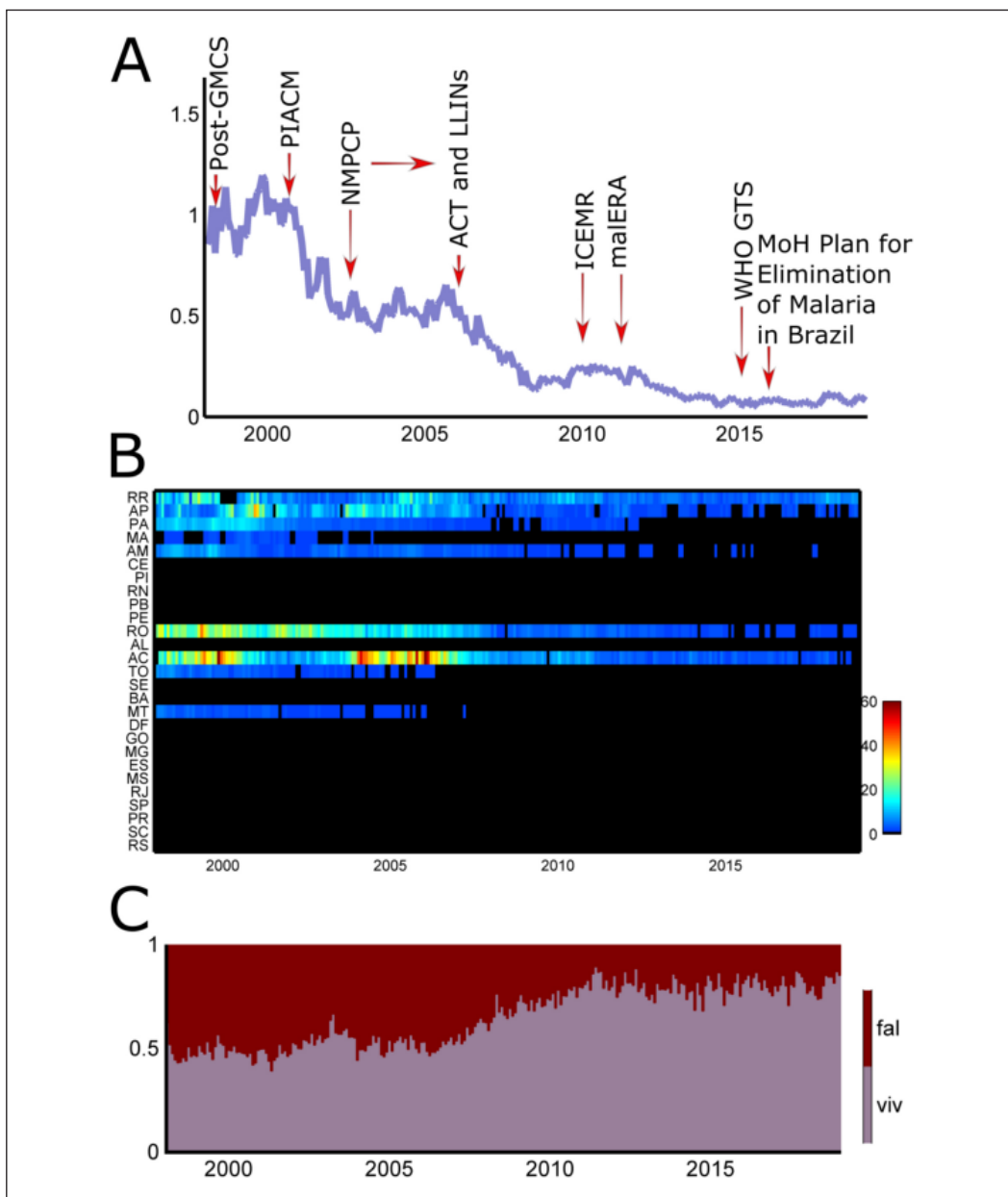


Figure 5. (A) Malaria monthly hospitalization rate (per 100,000 ppl.), 1998-2018, in Brazil. Red arrows show a given period of malaria policy depicted from the systematic review. GMCS, Global Malaria Control Strategy; PIACM, Intensification Plan of Malaria Control Activities in the Legal Amazon; NMPCP, National Malaria Prevention and Control Programme; ACT, Artemisinin Combination Therapy; LLINs, long-lasting insecticide-treated bed nets; ICEMR, International Centers of Excellence for Malaria Research; malERA, Malaria Eradication Research Agenda; WHO GTS, World Health Organization Global Technical Strategy; MoH, Ministry of Health of Brazil. (B) Malaria monthly hospitalization rate (per 100,000 ppl.), 1998-2018, per 26 states and a federal district. RR, Roraima; AP, Amapá; PA, Pará; MA, Maranhão; AM, Amazonas; CE, Ceará; PI, Piauí; RN, Rio Grande do Norte; PB, Paraíba; PE, Pernambuco; RO, Rondônia; AL, Alagoas; AC, Acre; TO, Tocantins; SE, Sergipe; BA, Bahia; MT, Mato Grosso; DF, Distrito Federal; GO, Goiás; MG, Minas Gerais; ES, Espírito Santo; MS, Mato Grosso do Sul; RJ, Rio de Janeiro; SP, São Paulo; PR, Paraná; SC, Santa Catarina; RS, Rio Grande do Sul. (C) Malaria monthly hospitalization rate (proportion, 0 - 1) per parasite species (fal = *Plasmodium falciparum*, viv = *P. vivax*). Data source: Unified Health System.

Brazil. The plan complies with the policies recommended by the World Health Organization Global Technical Strategy. The Brazilian plan focuses on eliminating *P. falciparum* malaria by 2030.

In the years 2017–2018, the number of total malaria cases (Figure 1) and severe cases (Figure 5A) have increased. The 2017 epidemiological profile of *P. falciparum* (Figure 2A) and *P. vivax* (Figure 2B) in Brazil shows widespread hotspots of malaria transmission in the Amazonian states of Amazonas, Acre, Rondônia, Pará, Amapá and Roraima. These hotspots (Figures 2A, 2B) of active and residual malaria transmission are obstacles to the plan of malaria elimination in Brazil.

DISCUSSION

The malaria elimination policy in Brazil is herein evaluated through analysis of results from systematic review and epidemiological analysis. Literature review showed (1) increasing importance of *P. vivax*-malaria in Brazil and (2) decreasing deaths and severe cases from *P. falciparum*-malaria. In concordance, epidemiological analysis indicated (1) a new burden from *P. vivax*-attributable hospitalizations and morbidity and (2) a diminished burden from *P. falciparum*-malaria.

The ‘eradication era’ was responsible for important achievements, such as the overall decline of malaria transmission in Brazil in late 1960 (Corrêa and Alves, 1969; Mascarenhas, 1973; Barata, 1997; Trigg and Kondrachine, 1998; Bleakley, 2010; Silva and Paiva, 2015). After the end of the Global Malaria Eradication Program (Palacios Fraire, 1975), malaria burden increased, particularly in the Amazon Region (Vosti, 1990). The 1992 Global Malaria Control Strategy was proposed as a flexible and cost-effective program (Trigg and Kondrachine, 1998). This was the basis for several national programs for controlling malaria globally in the 1990s and 2000s. For instance, the National Malaria Prevention and Control Program (NMPCP) was launched by the

Brazilian Ministry of Health in 2003 (Ferreira and Castro, 2016). By means of the NMPCP, malaria deaths and severe cases decreased significantly in Brazil after 2010 on.

The Malaria Elimination Research Agenda (malERA) was proposed in 2011. The malERA’s main goals are reducing the burden and eliminating malaria in the 91 countries and territories with ongoing malaria transmission in the world. Its ultimate goal is to eradicate malaria globally (Rabinovich *et al.*, 2017). Countries and territories are working under the global technical strategy for eliminating malaria. On the one hand, there are countries that are moving towards malaria elimination. Decreased endemic malaria in Suriname in South America was related to the mass-distribution of free insecticide-impregnated bednets and improved access to malaria services (van Eer *et al.*, 2018). On the other hand, there are other countries that are not succeeding; malaria elimination in Haiti in Central America seems unachievable (Boncy *et al.*, 2015). In Brazil, the general perception from the scientific community is that elimination is not on the horizon (Ferreira and Castro, 2016; Siqueira *et al.*, 2016; Recht *et al.*, 2017). Two malaria experts were cautious regarding the 2030 goal for malaria elimination (Ferreira and Castro, 2016). Since 2016, malaria cases have increased in Brazil (World Health Organization, 2018).

Parallel with the malERA and the World Health Organization advocacy for malaria elimination (Rabinovich *et al.*, 2017), the National Institutes of Health International Centers of Excellence for Malaria Research (ICEMR) constitute research centers in malaria-endemic regions (Rao, 2012). ICEMR’s main goal is to help build local capacity for malaria control and elimination. Its applied research has led to new tools, i.e., a malaria molecular epidemiology toolbox for genotyping parasites (Pacheco *et al.*, 2015). In Brazil, this toolbox was applied to endemic malaria hotspots in Western Amazonia and the authors found high genetic diversity of *P. vivax* (Barbosa *et al.*, 2014; Fontoura *et al.*, 2016). This suggests multiple

sources of infection that maintain ongoing malaria transmission. This further complicates current malaria elimination efforts.

There are challenges to fully achieve the goals of the malaria elimination policy in Brazil. One assumption is that clinical symptoms can be prevented by efficacious antimalarial treatments. However, current treatments lead to asymptomatic hosts who can infect mosquito vectors, i.e., *An. darlingi* (Sallum *et al.*, 2019); this may further cause clinical infections in other susceptible humans in another region. A well-known prospective cohort study in a rural settlement showed that *P. falciparum* disappearance and *P. vivax* decline are transient (Vitor-Silva *et al.*, 2016). The interruption of the active case detection strategy was followed by a resurgence of both parasites in the same locality 3-years later (Vitor-Silva *et al.*, 2016). Another prospective cohort study ended transmission of *P. falciparum*, but did not eliminate *P. vivax* prevalence (Barbosa *et al.*, 2014). After the interruption of this study, malaria rebounded in the locality. In addition, *P. vivax*-malaria poses multiple challenges: (1) asymptomatic malaria, (2) submicroscopic malaria, (3) relapsing malaria, (4) malaria in pregnancy, (5) G6PD issue, (7) transfusion-transmitted malaria, and so on (Lacerda *et al.*, 2012; Monteiro *et al.*, 2014b; Alho *et al.*, 2017; Costa *et al.*, 2017; Recht *et al.*, 2017).

Decreasing malaria burden in the epidemiological analysis 1979-2018 may lead to the logical fallacy that malaria elimination is within reach. The epidemiological scenario is truly dynamic and trends can change directions suddenly. The current World Malaria Report reported an increase in malaria in Brazil and Venezuela (World Health Organization, 2018). Interestingly, the promising eradication of malaria in Venezuela was certified by the Pan American Health Organization in 1961 (Kerr, 1963). About 60 sixty years later Venezuela is the hub of a humanitarian crisis with possible spillover of vector-borne diseases including malaria to neighbor countries, including Brazil (Grillet *et al.*, 2019).

Socio-environmental factors maintain malaria residual transmission in Brazil. The

gold mining scenario studied in the 1990s (Vosti, 1990) is still active in Amazonia (Silva-Nunes *et al.*, 2012). Furthermore, urban malaria (Recht *et al.*, 2017), indigenous malaria (Leandro-Reguillo *et al.*, 2015) and country border malaria (Chuquiyaury *et al.*, 2012) are examples of other scenarios that maintain active malaria transmission in Brazil.

An important byproduct of such socio-environmental factors includes human mobility, which leads to the exportation of malaria from Amazonia to southern Brazilian counties (Taulil, 2011). Parasites imported from Amazonia in this fashion fuel bromeliad-malaria on the Atlantic coast (Lorenz *et al.*, 2015). Bromeliad-malaria is the transmission of *Plasmodium* spp. by a bromeliad mosquito species (*Anopheles cruzii*) to humans or monkeys in the Atlantic forest. Generally *P. vivax* or *P. malariae* are transmitted to humans, and *P. brasilianum* or *P. simium* are transmitted to monkeys. However, *Plasmodium simium* caused an outbreak of malaria cases in inhabitants in Rio de Janeiro in 2015-16 (Brasil *et al.*, 2017). The simian malaria issue is not novel; back in the 1960s, Deane described this phenomenon that challenged the eradication paradigm (Deane, 1969; Palacios Fraire, 1975).

Proposals for new technological breakthroughs are needed. Perhaps, it is the time to go beyond the available malaria commodities and to reconcile with the practical malariology adopted in the first half of the twentieth century (Baird, 2017). Practical malariologists conceived precise modifications to natural or man-made environments aimed at making those less hospitable to specific anopheline mosquito vector species (Baird, 2017). Practical malariology achieved very significant reductions in burdens of morbidity and mortality (Killeen *et al.*, 2002; Killeen, 2003). Adult vector control is not effective with the current tools. The insecticide-impregnated bednets can have long-term drawbacks, such as the changing behavior of mosquito vectors' biting peaks (Ferreira *et al.*, 2017). A promising tool for adult vector control is the endectocide drug ivermectin (Chaccour *et al.*, 2015). The experimental effect of this

drug was recently tested with good prospects for use against *P. vivax* transmission in Amazonia, by suppressing the numbers of adult mosquito vectors (Pinilla *et al.*, 2018). However, basic knowledge about mosquito vector species in transmission areas is still lacking (Bourke *et al.*, 2018). A recent study showed that *An. darlingi* (now this species is identified as *Nyssorhynchus darlingi*) has high vectorial capacity (up to 1.5 infected bites per person/day), which is responsible for the high *P. vivax* propagation in Amazonian rural communities (Sallum *et al.*, 2019). These authors compared such epidemiological metrics to those observed for *P. falciparum* in sub-Saharan Africa

regions. The malaria community is now becoming aware of the lack of comprehensive understanding of this important element (mosquito vectors) of the malaria elimination endeavor (Baia-da-Silva *et al.*, 2019).

The Centenary Brazilian fight against malaria has been benefitted from national programs of malaria control and technological innovations (Figure 6). Focus, on the other hand, should be on the changing cost-benefit perception of society and environment disturbances caused by new economic enterprises. Malaria elimination in Brazil in the next decade will require a strategy that combines the lessons from

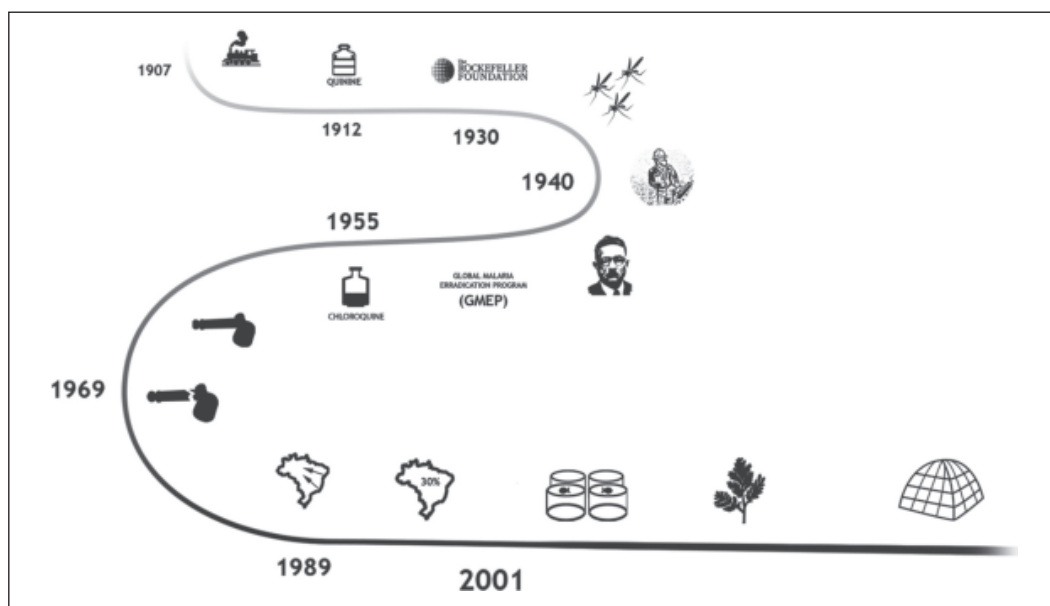


Figure 6. Infographic of the history of malaria emergence and elimination in Brazil.

Brazil. (1907) The Devil's Railroad: the Madeira-Mamoré epidemic. (1912) Introduction of quinine as therapeutic and/or prophylactic measure. (1930) The role of Rockefeller Foundation to the eradication of an African malarial vector in Brazil: a successful study case for malaria eradication. (1940) The American epidemiologist Fred Soper headed the campaign responsible for eliminating *Anopheles arabiensis* in Brazil, and used this example as the main reason for the eminent success of the Global Malaria Eradication Program in 1950's. (1955) Chloroquine, a synthetic lab-made quinine drug, was a technological breakthrough in this period because it could be produced in large scales in an industrial approach. (1969) Initial successful outcomes of the GMEP with malaria elimination in some parts of the world were achieved. However, the 1968 magnum opus Rachel Carson's Silent Spring buried attempts of widespread use of DDT due to its bioaccumulation in top predators in the food chains. This culminated with the end of the GMEP in 1969. (1989) Period of migratory influx and alterations of natural habitats in the Amazon during 1970-1980, concurrently with the new economic model named as the Free Economic Zone, settled in Manaus, which attracted multinational entrepreneurs, triggering migratory flow from other states of Brazil to Amazon. (2001) a new economic cycle began in the Amazon, aiming at empowering the overall economy, involving agroforestry activities, particularly fish farming, causing the development of permanent larval habitats for malarial mosquitoes. Treatment of *P. falciparum* with Artemisinin-based combination therapy (ACT) started free for all ages in public sector. Insecticide Treated bed Nets (ITNs) and Long Lasting Insecticide-treated Nets (LLINs) are distributed free of charge to all age groups.

the past and a capability of adapting to an evolving epidemiological, socio-economic, and technological setting. As Brazil continues its path to eliminate malaria, it will be crucial that attention does not wane as the situation continues to improve.

CONCLUSIONS

Brazil has seen an impressive reduction in malaria hospitalizations and mortality in the past 3 decades, but complete malaria elimination in Brazil in the near future remains unlikely. On the one hand, eliminating malaria deaths in children less than 5 years and *P. falciparum* severe cases by 2030 are achievable goals under the current malaria policy. On the other hand, eliminating *P. vivax* malaria transmission and morbidity seems unattainable with the available technological breakthroughs. Overall, this evidence suggests that malaria elimination might not be generally achieved in Brazil in the next decade.

Complete malaria elimination in the near future in Brazil will require better tools for the challenges posed by *P. vivax* transmission and morbidity. Specifically, new drugs that can cure relapsing patients with *P. vivax* and/or block transmission to competent malaria vectors certainly are needed.

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Competing interests

None declared.

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