Parasite Removal for Malaria Elimination in Costa Rica

Rodrigo Marín Rodríguez[1] and Luis Fernando Chaves[2,*]

In Costa Rica, malaria parasite removal via treatment shift and focalized mass drug administration (MDA) largely decreased malaria transmission between 2006 and 2009, and led to malaria elimination from 2013 to 2015. These results can help to shape a regional strategy for malaria elimination in Mesoamerica and México.

Reducing Malaria Transmission

A condition for eliminating malaria is reduction in transmission [1]. The work of Ronald Ross set the stage for the use of vector control as a major tool for reducing malaria transmission [2]. Malaria elimination was achieved for the first time in Mesoamerica when the Panamá Canal, a major interoceanic passage, was built [3]. During the Canal`s construction, William Crawford Gorgas employed different vector-control strategies to reduce and eliminate the transmission of several vector-borne diseases, as these, often lethal, diseases stopped previous attempts to build this major interoceanic passage [3]. Coincidentally, while the theory [2] and scientific evidence [3] that still serve as the basis for mosquito control in mosquito-borne diseases developed, Robert Koch proposed that malaria transmission could be reduced if parasites were removed from human populations through antimalarial drug use [4]. Mass drug administration (MDA), the concerted population-wide use of drugs, is not as widely implemented as vector control to reduce malaria transmission, but available evidence supports its potential for eliminating malaria [5]. Indeed, MDA and proper treatments have shown their ability to reduce malaria transmission [5,6]. Here, we want to highlight the impact that a focalized MDA and treatment shift, both based on supervised 7-day treatments (Box 1), had on accelerating the malaria elimination process in Costa Rica, where systematic indoor residual spraying stopped in 1990 [7].

The Context of Malaria Transmission in Costa Rica: Malaria Transmission in Mesoamerica and México

Mesoamerica, including México, is a geographical region where malaria transmission has been decreasing since 2000 (Figure 1A). This decrease might reflect improved surveillance, diagnostics, and case treatment in line with several multilateral strategic plans for malaria elimination in the region [7–9]. Prior to 2015, most of the malaria cases in the region were reported in Guatemala and Honduras. Since 2015, however, increased transmission made Nicaragua the regional epicenter of malaria cases (Figure 1A). In this region, most malaria cases are due to Plasmodium vivax, which accounts for over 90% of the regional cases (Figure 1B). Malaria infections are susceptible to chloroquine-based treatments in most of Mesoamerica and México [8,10], except in Panamá, where recurrent transmission of chloroquine-resistant Plasmodium falciparum strains [9] forced a shift to artemisinin combined therapy (ACT) as the first line of treatment for P. falciparum malaria cases (Box 1). As a geographic region with strong historical and cultural ties, all nations in Mesoamerica and México are committed to eliminate malaria by 2020 [8]. Efforts have been concentrated on switching the focus from malaria control to malaria elimination, and fostering an environment where common strategies, and new actions, are implemented in harmony throughout the region [8]. El Salvador and Costa Rica are the only nations in Mesoamerica that had been able to transiently eliminate the disease for periods of time longer than 1 full year, although not over the 3 years needed to attain a WHO certification of malaria elimination [1]. In that sense, the experience of Costa Rica, the country that saw the sharpest decrease in malaria transmission after 2000, may be of interest for other nations in the region and elsewhere.

Parasite Removal in the Huétar Caribe Region of Costa Rica

In 2005 malaria cases reached a peak in Costa Rica, with 3541 (Figure 1C). At this time, Costa Rica reported more cases of malaria than Nicaragua, Belize, or El Salvador, and had a case number similar to the 3667 reported in Panamá (Figure 1A). Over 90% of the Costa Rican cases occurred in the Limón province, mainly in the Matina, Limón, and Talamanca counties (Figure 1C). This spatial pattern started in the 1990s and reflected the infrastructure collapse associated with the 1991 Limón earthquake and several natural catastrophes that hit Limón province, which included Hurricane Cesar in 1996 and Hurricane Mitch in 1998, and probably interannual climatic cycles driven by El Niño Southern Oscillation [7]. Moreover, since 1997, a 14-day treatment was shifted to a 5-day radical cure (Box 1) [7]. Also, all clinically diagnosed cases needed to be confirmed by thick blood examination at local health posts before the prescription of treatment, a policy that led to delays in treatment delivery in remote areas [7]. The treatment shift from the 14-day to the 5-day radical cure was not without consequence, given that it reduced the overall primaquine dose, increasing the number and frequency of P. vivax malaria relapses [7]. Relapses were associated with repeated transmission in the same households, a very common situation in Talamanca county [7]. Similar adverse outcomes for the 5-day radical cure have been reported elsewhere in Latin America [11] and other world regions with predominant P. vivax transmission [6]. Given this situation in 2006, an MDA was performed in Talamanca (Figure 1C) using the 7-day 'Talamanca' treatment (Box 1), which ensured a pharmacokinetically

Box 1. Common Malaria Treatments in Mesoamerica and México

In Mesoamerica and México, chloroquine and primaquine are used as first-line drugs for Plasmodium vivax malaria, given that infections are sensitive to both drugs (Table I) [10]. Chloroquine is the first-line drug for Plasmodium falciparum malaria cases in the region, with the exception of Panamá [9], where all infections are treated with standard artemisinin combined therapy (ACT) dosages [10]. ACTs are used only for chloroquine-resistant P. falciparum malaria cases in the rest of Mesoamerica and México [10].

Table I. Common Chloroquine and Primaquine Dosages for Plasmodium vivax Infections [10]

Treatment	Goal	Frequency	Chloroquine[a] (mg/kg of patient weight)	Primaquine[a] (mg/kg of patient weight)
Suppressive	Parasitemia reduction in single patients	Unique	10	0.25
Monthly	Parasitemia reduction in populations from endemic areas	Unique	10	0.75
5-day Radical cure	PRSP[b]	5 days, daily	25 total (administered in 3 days using 10, 10, and 5)	0.25
14-day	PRSP and MDA	14 days, daily		0.25
7-day [7]	PRSP, HPC, and MDA	7 days, daily		0.5
7-day 'Talamanca' [7]	MDA in HPC	7 days, daily	1500 total for adults[c], 600 (four 150 mg tablets) in the first day, and 450 (three 150 mg tablets) in the second and third days	210 total for adults[c] in a 30 mg daily dose (two 15 mg tablets)
8-week	Protection of high-risk rural populations	8 weeks, weekly	10	0.75
Unique dose	PRSP, HPC, and MDA	Monthly for 3 months every 6 months for 3 years	10	0.75

[a]Per dose, unless noted otherwise.
[b]PRSP, parasite removal in single patients; MDA, mass drug administration; HPC, households with persistent cases.
[c]No weight adjustment, but half dose for children under 12 years of age.

sufficient dose of primaquine to eliminate P. vivax relapses [6]. When planning the Talamanca MDA, the Ministry of Health considered results from studies showing that mutations in the gene encoding G6PD (the enzyme glucose-6-phosphate dehydrogenase, which is essential for hemoglobin metabolism), associated with primaquine-induced severe hemolytic anemia, an often lethal condition, were not reported in Caribbean populations from Costa Rica [12]. The Talamanca MDA was supervised by local technicians from the National Program for Integrated Vector Management (NPIVM) of Costa Rica's Ministry of Health, and not by volunteers, who had, before, administered treatment to febrile malaria cases. During and after the 2006 MDA, volunteers have only assisted trained staff from the Ministry of Health to reach malaria-affected individuals and communities in Talamanca and remote areas of Costa Rica. For the MDA dosage was based on age, having a fixed number of pills for two age groups (Box 1). The 7-day 'Talamanca' dosage was designed to simplify administration by NPIVM staff, who supervised each MDA patient with a protocol that included consultation with a physician in case of adverse reactions, related to hemolytic anemia symptoms, or when fever did not stop after the full treatment was administered. During this MDA no major adverse reactions were observed. The 2006 Talamanca MDA was implemented in the Costa Rican Caribbean during the dry season, which occurs in August and September. The MDA covered nearly 25% of the Talamanca county population, targeting over 90% of the households with recurrent malaria cases. Following the MDA there was a sharp decrease in annual malaria cases in Talamanca, which went from nearly 100 annual cases in 2006 to 20 in 2007 (Figure 1C). The change to the 7-day treatment that started in 2006 was gradually extended to all counties in Limón province, covering all of Matina, Limón, and Talamanca by 2008. This resulted in over a 90% decrease in malaria cases in these three counties – from 2913 cases in 2006 to 262 in 2009 (Figure 1C). This change was associated with a breakpoint (Figure 1D), that is, a time when the dynamics of a phenomenon developing in time change abruptly or shift into

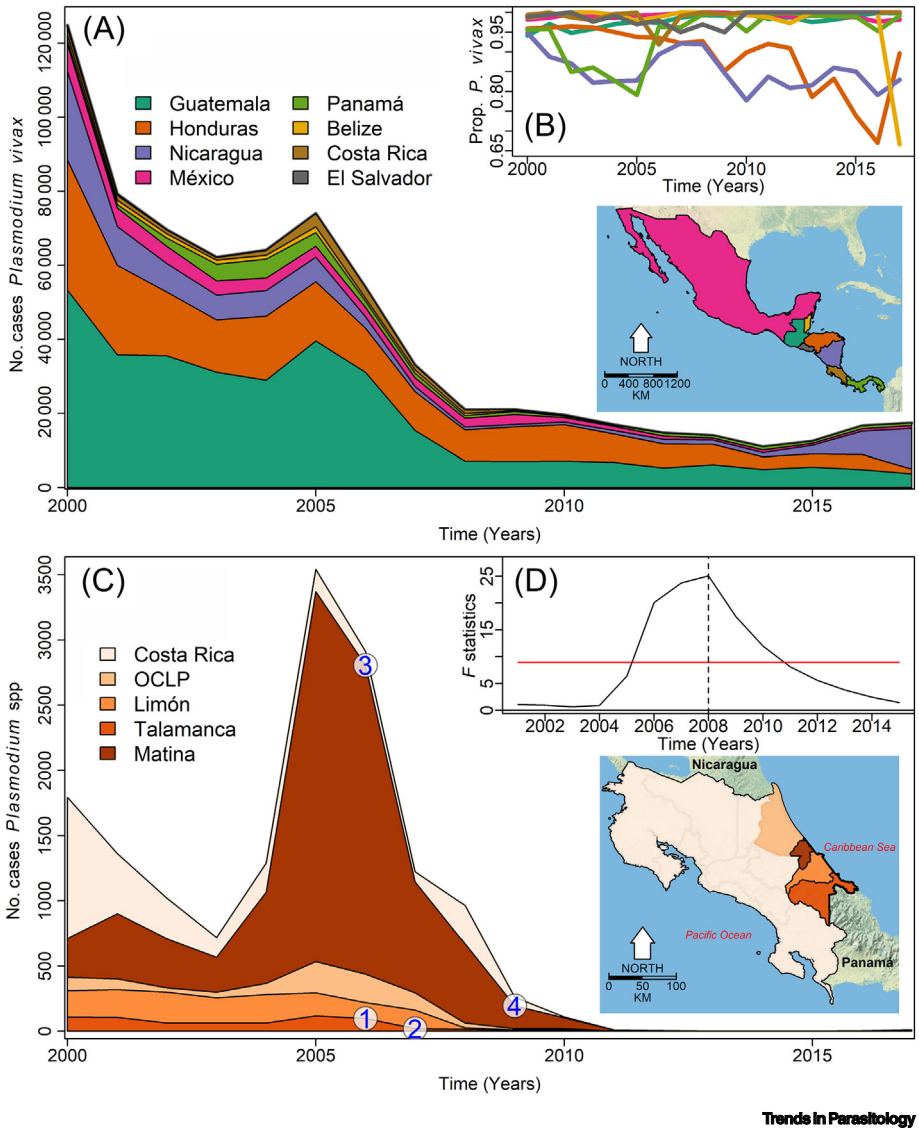

Figure 1. Malaria Trends in Mesoamerica, México, and inside Costa Rica. (A) Annual Plasmodium vivax case numbers in Mesoamerica and México. Colors identify each country, and band size is proportional to the number of cases in each country. Data from Pan American Health Organization (PAHO)[i]. (B) Proportion of P. vivax cases, by country, in Mesoamerica and México. Data from PAHO[i]. (C) Annual P. vivax case numbers in Costa Rica. Data are from the epidemiological bulletins by Ministerio de Salud[ii]. Colors identify counties in Limón province, where malaria has had the largest case burden: Matina, Talamanca, and Limón, as well as other counties in Limón province (OCLP), and the rest of the country (Costa Rica in the inset color legend). In the figure, the blue numbers indicate policy shifts and their outcomes; specifically, □ indicates the number of cases when the Talamanca antimalaria mass drug administration was implemented (2006); □ indicates the decrease in malaria cases after 1 year in Talamanca (2007); □ indicates the start of the 7-day treatment shift in Limón province (2006); and □ indicates the number of malaria cases when the 7-day treatment was fully implemented in Limón province (2009). (D) Breakpoint analysis of malaria cases in Costa Rica. The analysis is based on annual F statistics which are compared against a threshold value (red horizontal line), and the maximum value, observed in 2008 (broken vertical line), was chosen as a regime shift breakpoint [15].

a new regime, that is, a state with a regular pattern of events over time [13]. Thus, malaria transmission moved from an endemic regime to a pre-elimination regime, where the mean (± SD) annual number of malaria cases decreased from 2192 ± 1579 in 2000–2009 to 18 ± 38 in 2010–2017. Remarkably, from 2013 to 2015, during 33 months, there were no local malaria cases in Costa Rica [1]. From 2016 onwards, the 7-day treatment was included in Costa Rica's national malaria norm [7]. This norm mandated the use of the 7-day treatment, already used by the Ministry of Health during malaria outbreaks, to all health centers administered by the Costa Rican Social Security Trust (Caja Costarricense de Seguro Social), the public

trust in charge of administering universal health care in the country [7].

Lessons for Malaria Elimination in Mesoamerica and México

The experience with 7-day treatments was fundamental to accelerate the malaria pre-elimination stage in Costa Rica. In Mesoamerica, a region highly vulnerable to malaria and other vector-borne and parasitic diseases [14], only El Salvador, Belize, and Costa Rica are on track to achieve malaria elimination by 2020 [1]. Costa Rica was able to abruptly reduce the high malaria case burden of 2005, being the first nation to achieve the landmark of no local malaria cases for a full year in Mesoamerica in 2013, and without either passively or actively detected cases for 33 months until 2015. Thus, the Costa Rican experience is highly informative for other nations in Mesoamerica and México, where the regional malaria burden only accounts for less than 1% of the global burden, as most cases are due to chloroquine-sensitive P. vivax parasites [8,14]. Costa Rica's experience illustrates how focalized MDAs, combined with a malaria treatment shift that minimizes the likelihood of P. vivax relapses, could become a major tactic in the strategy for malaria elimination. Data from Costa Rica show that 7-day treatments are a good choice for MDAs, given their relatively short duration, which increases full adherence [7]. The supervised implementation of 7-day treatments by trained technical staff, as done by NPIVM inspectors in Costa Rica, can help to monitor adverse reactions to primaquine in populations with a low frequency, but imprecise estimates, of G6PD mutations associated with primaquine-induced hemolytic anemia. Finally, Costa Rica's tactics can help to accelerate malaria elimination in parts of the world with key epidemiological similarities: a low frequency of primaquine-sensitive G6PD mutations and chloroquine-sensitive malaria parasites.

Resources

[i]www.paho.org/hq/index.php?option=com_content&view=article&id=2632:2010-interactive-malaria-statistics&Itemid=2130&lang=en

[ii]www.ministeriodesalud.go.cr/index.php/biblioteca-de-archivos/centro-de-informacion/material-publicado/boletines-1/boletines-vigilancia-de-la-salud

[1]Dirección de Vigilancia de la Salud, Ministerio de Salud, San José, San José, Costa Rica
[2]Instituto Costarricense de Investigación y Enseñanza en Nutrición y Salud (INCIENSA), Tres Ríos, Cartago, Costa Rica

*Correspondence:
lfchavs@gmail.com (L.F. Chaves).

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