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Review

Impact of Malaria in Pregnancy as Latin America Approaches Elimination

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In Latin America, four million pregnancies are at risk of malaria annually, but malaria in pregnancy is largely overlooked. As countries progress toward malaria elimination, targeting reservoirs of transmission is a priority. Pregnant women are an important risk group because they harbor asymptomatic infections and dormant liver stages of *Plasmodium vivax* that cause relapses. Of significant concern is the discovery that most infections in pregnant women fail to be detected by routine diagnostics. We review here recent findings on malaria in pregnancy within Latin America. We focus on the Amazon basin and Northwest Colombia, areas that harbor the greatest burden of malaria, and propose that more sensitive diagnostics and active surveillance at antenatal clinics will be necessary to eliminate malaria from these final frontiers.

Trends

Placental damage may be one of the hallmarks of malaria in pregnancy (MiP), whereas the clinical spectrum of birth outcomes is broad.

As the incidence of patent MiP declines, an increasing proportion of infections are sub-microscopic and asymptomatic; these are considered to be reservoirs of infection.

More sensitive molecular diagnostics are needed at the point-of-care to detect sub-microscopic infections in pregnancy. RDTs lack the sensitivity and specificity to detect low-level infections and are not widely used in Latin America.

There are disparities in access to antenatal services, particularly in indigenous communities in the Amazon basin.

Renewed Focus on Malaria in Pregnancy in Latin America

Pregnant women are at increased risk of adverse clinical outcomes of malaria infection, with potential negative effects on both the mother and the fetus. Until recently the impact of malaria in pregnancy (MiP) in Latin America has been understudied and gained little recognition as a major public health problem. This is largely due to the low prevalence of malaria in the region and the predominance of the apparently benign *Plasmodium vivax* species. Although the clinical burden of MiP is not as high as in sub-Saharan Africa, there is increasing awareness that pregnant women are an important **reservoir of infection** (see Glossary) that may undermine progress toward **malaria elimination**. Detection of asymptomatic infections in pregnant women to block transmission is now a priority. As a result, research efforts have intensified with a focus on malaria control in high-burden areas, such as the Amazon basin, and to reduce transmission in areas with lower endemicity. We review here recent findings on the epidemiology, clinical manifestations, and diagnosis of MiP within Latin America, and offer perspectives on the opportunities for enhanced malaria control in pregnancy as countries progress toward elimination.

Epidemiology of Malaria

Latin America is a geographically and culturally diverse region, spanning countries within Central and South America, a landmass of over 21 million km^2, and a population over 600 million. Malaria is endemic in 21 countries in the region, with an estimated 120 million people living in areas at risk of hypoendemic and unstable transmission [1,2]. The greatest burden of disease (90%) is concentrated in the Amazon basin, a region that borders five countries: Brazil, Colombia, Venezuela, Peru, and Guyana (Table 1 [3]). Overall, the incidence of malaria in this region was drastically reduced over the past decade (76% relative to the year 2000) to approximately 700 000 cases and 800 deaths in 2013. Most of the cases were reported in Brazil (42%), Venezuela (18%), and Colombia (12%) [2], but both Brazil and Colombia are nearing a 75%

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Table 1. Percentage of Population Affected by Malaria, and Geographical Location, in Select Countries of the Amazon Region and Central America[a]

Region	Country	Population in Areas of High Transmission (>1 Case/1000)	Plasmodium Species	Vectors	Main Endemic Regions
Amazon basin	Brazil	2.3%	*P. falciparum, P. vivax*	*An. darlingi, albitarsis, aquasalis*	States in the Amazon forest
	Colombia	14.8%	*P. falciparum, P. vivax*	*An. darlingi, albimanus, nunestovari, neivai, punctimacula, pseudopunctipennis*	States of Antioquia, Choco, Cordoba, and Narino, along the Pacific coast
	Ecuador	1%	*P. falciparum, P. vivax*	*An. darlingi, albimanus*	Provinces of Guayasm, Esmeralda, and Cañasin, the west of the country, and Amazon forest
	Guyana	35.0%	*P. falciparum, P. vivax*	*An. darlingi, aquasalis*	Western and interior areas, especially with gold-mining activities
	Peru	4.5%	*P. falciparum, P. vivax*	*An. darling, pseudopunctipennis, albimanus*	State of Loreto, in the Amazon forest region
	Suriname	15.7%	*P. falciparum, P. vivax*	*An. darlingi*	Interior areas in the Amazon forest (indigenous populations and gold mining areas)
Central America	Belize	0.0%	*P. falciparum, P. vivax*	*An. albimanus, darlingi*	South-eastern districts of Stann Creek and Toledo
	Guatemala	16.1%	*P. falciparum, P. vivax*	*An. darlingi*	South-western state of Escuintla
	Honduras	14.0%	*P. falciparum, P. vivax*	*An. albimanus*	Eastern and north-eastern areas (the border with Nicaragua is a problem area for malaria control)
	Nicaragua	1.3%	*P. falciparum, P. vivax*	*An. albimanus, pseudopunctipennis*	North-eastern areas (along the border with Honduras)
	Panama	4.4%	*P. falciparum, P. vivax*	*An. albimanus, pseudopunctipennis, punctimacula, aquasalis, darlingi*	State of Darien along the border with Colombia (areas with high proportion of indigenous populations)

[a]Adapted from Performance Evaluation [3].

Glossary

Hypnozoites: forms of *P. vivax* liver-stage parasites that remain dormant for weeks to years.
Intermittent preventive treatment in pregnancy (IPTp): antimalarials are given to pregnant women at defined intervals during pregnancy to eliminate parasites and prevent reinfection.
Malaria elimination: the reduction to zero of the incidence of malaria infection in a defined geographical area.
Multigravid: women in their second or greater pregnancy.
Parity-dependent immunity: immunity acquired over successive pregnancies and repeated malaria exposure.
Placental malaria: infection of the placental tissue with parasitized red blood cells.
Primigravid: women in their first pregnancy.
Rapid diagnostic tests: immunochromatographic diagnostic tests that detect parasite antigens.
Relapse: activation and maturation of *P. vivax* hypnozoites to cause a blood-stage infection.
Reservoir of infection: parasites that are difficult to diagnose or treat. For example, asymptomatic infections are difficult to diagnose. *P. vivax* hypnozoites are difficult to treat.
Sequestration: accumulation of parasitized red blood cells in host tissues.
Sub-microscopic: infections that are below the limit of detection by microscopy.
Syncytiotrophoblast: epithelial covering of the highly vascular embryonic placental villi.

decrease in case numbers compared to the incidence reported in 2000 [2]. These successes may be attributed to prompt diagnosis, treatment of confirmed cases, distribution of insecticide-treated bed nets, and indoor residual spraying. It is also likely that the adoption by most countries of the WHO artemisinin combination therapy (ACT) policy for treatment of *Plasmodium*