Migrants in transit across Central America and the potential spread of chloroquine resistant malaria–a call for action

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Summary

Human migration has shaped the distribution and patterns of infectious diseases transmission throughout history. Migration is one of the contributing factors that has played an important role in the dissemination of drug-resistant *Plasmodium falciparum*. Central America and Mexico are important transit points of an increasing migrant flow originating from countries where chloroquine-resistant *P. falciparum* and *vivax* are prevalent. Surveillance systems, as well as detection and diagnostic capacities in the Central American region, are limited. The additional challenges imposed by the increasingly mobile population in the region are creating the perfect scenario for the emergence or re-emergence of infectious diseases, such as the introduction of chloroquine-resistant malaria. The development and implementation of transborder, collaborative, and ethical migrant health initiatives in the region are urgently needed. The health of migrant people in transit during their migratory route is of our collective interest and responsibility; their exclusion from health programs based on their legal status contradicts international human rights treaties and is inconsistent with ethical global public health practice.

Keywords: Central America; Drug resistance; Malaria; Transients and migrants; Panama

Introduction

Human migration has shaped the distribution and patterns of infectious diseases transmission throughout history. The global distribution of malaria is rooted in social phenomena such as population migration patterns, economic trade, war, and climate change. Similar to the yellow fever flavivirus, the *Plasmodium falciparum* parasite was introduced to the Americas between the mid-1500s and mid-1800s by enslaved Africans. The Spanish, Portuguese, and the English brought approximately seven million enslaved people over three centuries from different regions of the African continent to major city ports such as Veracruz, Cartagena, Salvador, Rio de Janeiro, and the Caribbean. The introduction of *Plasmodium vivax* to the Americas is more heterogenous and related to migratory waves from different source populations extending from Australasia to Eurasia.[1]

Fast-forward to today, malaria continues to be endemic and a critical health problem in many Latin American countries. Successful public health interventions have significantly reduced the disease burden, with several Latin American countries eliminating malaria in the last decade.[2] This noteworthy progress is being threatened by challenges imposed by conflict, economic and social turmoil, climate change, drug and insecticide resistance, the COVID-19 pandemic, and migration. For example, in the region of the Americas, eighteen countries are currently at risk of malaria of which ten failed to meet the global technical strategy to reduce malaria incidence by 40% from 2015 to 2020.[2]

Malaria in the Americas– a snapshot

Migration is one of the contributing factors that has played an important role in the dissemination of drug-

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resistant *P. falciparum*. For example, chloroquine-resistant *P. falciparum* was first reported in Thailand in the late 1950s and in South America in the early 1960s. It spread to most of the world in a matter of two decades, sparing Central America northwest of the Panama Canal, the Hispaniola, and some regions of Southwest Asia.[3] The lack of extension of chloroquine-resistant *P. falciparum* to Central America needs to be better understood. *Anopheles albimanus*, the most common malaria vector in Central America, might demonstrate a lower susceptibility to strains of *P. falciparum* that originate from other regions of the world by refractoriness to oocyst infection.[4] Nevertheless, the introduction of malaria to no-endemic or previously endemic countries by migrant people with sporadic secondary transmission has imposed significant setbacks to malaria control achievements.[5]

In Haiti, previous reports of circulating chloroquine-resistant *P. falciparum* and in-vivo therapeutic efficacy studies had challenged the historic recommendation to treat locally acquired malaria with chloroquine.[6,7] In addition, PfCRT mutations linked to chloroquine resistance were found in 10.5% of travellers with *P. falciparum* returning to France and Canada from Haiti after the 2010 earthquake.[8] Although no chloroquine-resistant *P. falciparum* has been detected in the most recent surveillance conducted between 2016 and 2017, these reports illustrate the need for continued monitoring for drug-resistance markers in the region.[9]

In Central America, Honduras and Nicaragua have witnessed a substantial increase in *P. falciparum* cases in the last two years. In 2015, Nicaragua reported approximately 2,900 malaria cases in comparison to 29,500 in 2021.[2] Despite several reports of imported chloroquine-resistant *P. falciparum* infections in the area and the detection of PfCRT mutations in 0.8–1.3% of samples examined, such an increment is not related to the introduction of drug-resistant malaria but to health threats related to social, political, economic and gender inequalities.[10–12]

P. vivax is the most important malaria species in Latin America accounting for almost three-quarters of all malaria cases in 2021.[2] In endemic areas, *P. vivax* is most often asymptomatic, representing a major barrier to eradication.[13] In addition, chloroquine resistance has been reported in all high-burden *P. vivax* regions such as in South America, highlighting the need for drug resistance surveillance to guide *P. vivax* control and treatment policies.[13]

Migration through Central America and the risk of introduction of drug-resistant malaria

Migration in the Central American region is intricate. The last decade has witnessed an unparalleled degree of migration to and from the U.S. and a mixed flow of migrants in transit. The roots of this unprecedented level of human mobility through this migratory route are diverse and complex. Harsh European policies have, for example, limited the entry of African migrants across the Mediterranean. In Venezuela, governmental mismanagement has shattered one of the most prestigious healthcare infrastructures in Latin America.[14] The collapse of the healthcare system has led to the re-emergence of once controlled communicable diseases such as measles, diphtheria, and malaria with resultant spillover to neighbouring countries.[14] Central America and Mexico are thus important transit points of an increasing migrant flow originating from countries where chloroquine-resistant *P. falciparum* and *P. vivax* are prevalent.

South America is one the most important migration epicentres to the Mexico-U.S. border. Migrant people from Cuba, Haiti Africa, Asia, Eastern Europe, and other regions of the world converge with citizens from other South American countries in their dangerous yet decisive journey through the Darien Gap and Central America to reach the Mexico-U.S. border. The Panamanian government has identified a record-breaking 228,000 migrant people entering the county irregularly via the Darien Gap as of November of 2022.[15] Of these, approximately 88% originate from *P. falciparum* chloroquine-resistant areas, with Venezuelans representing 65% of all migrant people.[15]

Migrant people can act as asymptomatic malaria reservoirs. In areas of high-level malaria transmission, such as in Africa, partial immunity to malaria infection is associated with asymptomatic parasitemia below the limits of detection by microscopy.[16] Landmark studies have shown evidence of *P. falciparum* infection in up to 60% of African refugees relocated to North America with asymptomatic parasitemia detected up to 3 months after arrival.[17,18] The phenomenon of asymptomatic malaria is not restricted to holoendemic or hyperendemic malaria regions. For example, studies performed in Brazil, Colombia, and Venezuela and in other low-transmission settings such as the Temotu Province in the Solomon Islands, have identified a high proportion of submicroscopic and asymptomatic *P. vivax* and *P. falciparum* infections.[19,20]

Mobile populations should not be viewed as "reservoirs of infection," as an impediment to malaria elimination, or as an excuse for the enactment and implementation of restrictive policies. On the contrary, malaria elimination programs should avoid negative connotations and stigmatization by incorporating effective community engagement activities at distinct points of this mobility system.

In this context, continued surveillance on the emergence or resurgence of the disease in malaria-free Central American areas and for the detection of antimalarial drug resistance markers is imperative. Furthermore, vector-independent forms of transmission, such as through blood transfusions or

accidental inoculation of the skin with blood containing the parasite, coupled with the recent report of imported malaria leading to different chains of nosocomial malaria transmission in a resourceful healthcare setting, emphasize the need of Central American countries for continued adherence and compliance with universal precaution measures.[21]

Key and evidence-supported interventions against malaria adapted to this vulnerable population must be strengthened in the region. As an example, the performance of the easily available diagnostic modalities, such as microscopy and rapid diagnostic tests (RDTs) in these semi-immune and asymptomatic populations, is suboptimal.[18] In contrast to immigrants with malaria who had travelled to visit friends and relatives (VFRs), who are usually symptomatic and easily diagnosed with microscopy, recently arrived migrant individuals from malaria endemic areas are often asymptomatic and can have low-level parasitemia below the microscopic diagnostic threshold.[18] In addition, the diagnosis of hyperactive malarial splenomegaly or tropical splenomegaly, a common presentation among migrant people originating from highly endemic malaria areas, is complex and determined by the spleen size, elevated anti-malarial antibodies and IgM levels, and not necessarily microscopy.[22] A high index of suspicion is therefore necessary, and PCR for *Plasmodium* spp. should be considered in case of negative thick smears in migrant people originating from highly endemic malaria areas.[18] Accordingly, the U.S. Centers for Disease Control and Prevention (CDC) recommends presumptive anti-malarial treatment for all U.S.-bound refugees from Sub-Saharan Africa within five days of departing to the U.S. Furthermore, if presumptive treatment is not administered before departure, screening with PCR over microscopy is another recommended approach.[23]

Likewise, the World Health Organization has delineated malaria elimination strategies and prevention of re-establishment based on geography and people at risk.[24] Akin to CDC's recommendation in the U.S., targeted testing and treatment (TTaT) could be implemented in ports of entry into areas that are in the elimination or post-elimination phase or with very low to low levels of transmission as is the case in most Central American countries. Another recommended approach is to identify groups at increased risk of infection and provide a full treatment course (i.e., targeted drug administration).[24]

Future directions

Surveillance systems as well as detection and diagnostic capacities in the Central American region are limited. The additional challenges imposed by this increasing mobile population in the region create the perfect scenario for the emergence or re-emergence of infectious diseases, such as the introduction of chloroquine-resistant *P. falciparum* or *P. vivax* or the re-establishment of entities previously eliminated in the region, such as onchocerciasis. There is an imperative and long overdue need for Central American countries, Mexico, and the U.S. to develop transborder collaborative migrant health initiatives. Building an efficient and functional regional health security system requires trustworthy investment from local governments, foreign agencies, and partnerships among public and private entities such as between the diagnostic and laboratory industry and academic centers. Surveillance systems should be strategically established in the corridors commonly used by migrant people in route to the Mexico-U.S. border. Healthcare professionals, governments, and other public and private civil society organizations should define attainable and evidence-based programs under the umbrella of universal health coverage to develop screening and vaccination programs for this vulnerable population.

Malaria screening of migrant people *en route* should consider the feasibility of local testing modalities and logistical limitations, the reliability and validity of the available assays, and the prevalence of malaria and *pfhrp2* deletions in the migrant's region of origin. The introduction of reliable, rapid, and easy to-conduct tests with performance characteristics similar to PCR-based assays, such as the loop-mediated isothermal amplification (LAMP) assay, could aid with the accurate diagnosis of low-density malaria infections in the area.[25] In addition, surveillance systems to detect antimalarial drug resistance in the region need to be established or strengthened through collaborations with existing networks such as the Amazon Network for the Surveillance of Antimalarial Drug Resistance.[26] Finally, the efficient Asian urban malaria vector, *An. stephensi*, has expanded geographically from India, Pakistan, and Iran to Southeast Asia, the Arabian Peninsula, the Horn of Africa, and Nigeria through the movement of people across the region.[27] Such expansion represents a significant threat to malaria control efforts in Africa leading the World Health Organization to release a vector alert in December of 2019.[28] The increasing number of migrant people travelling to Central and South America originating from these *An. stephensi* endemic regions stress the importance of enhancing targeted vector surveillance programs in the area.

In addition, the reduction of malaria incidence in the region in recent years could compromise early detection of new malaria cases due to decreasing awareness of healthcare providers and expertise of the laboratory personnel. Delays in the diagnosis of malaria translate to higher morbidity and mortality. For example, in Brazil, the case-fatality of malaria diagnosed outside the Amazons is several-fold higher and primarily related to delays in considering malaria in the differential diagnosis.[29] The curricula of the health sciences in the

superior education centers of the Central American region need to incorporate competency goals in providing care to multicultural and mobile patient populations.

In the U.S., expansion of the pool of migrant people that fall under the CDC's evidence-based guidance should be reconsidered to include malaria screening with molecular methods or provision of presumptive malaria treatment for migrant individuals originating from regions of high-intensity malaria transmission that cross the border irregularly and not limited to those under a humanitarian-based immigration status.

The health of migrant people in transit during their migratory route is of our collective interest and responsibility. Their exclusion from health programs based on their legal status contradicts international human rights treaties and is inconsistent with ethical global public health practice.[30] A transregional coordinated initiative to safeguard the health of the migrant and local population through integrated disease surveillance, timely response to outbreaks, and provision of culturally and linguistically appropriate services to safeguard human rights and freedom should be a regional public health and research priority.

Contributors

NIAH was responsible for conceptualizing the viewpoint and writing the first draft; CFP, AHM, BMR, JAS, LN, JA performed critical revisions of the viewpoint and contributed to the writing. All authors reviewed and agreed on the final version of the viewpoint.

Declaration of interests

LN is a GSK employee. All the information in this paper is of her own responsibility and doesn't reflect the position of GSK. All other authors declare no competing interests.

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References

1 Rodrigues PT, Valdivia HO, de Oliveira TC, et al. Human migration and the spread of malaria parasites to the New World. *Sci Rep*. 2018;8(1):1993.
2 World Health Organization. *World malaria report*. Geneva: World Health Organization; 2022.
3 Packard RM. The origins of antimalarial-drug resistance. *N Engl J Med*. 2014;371(5):397–399.
4 Baton LA, Ranford-Cartwright LC. Ookinete destruction within the mosquito midgut lumen explains Anopheles albimanus refractoriness to Plasmodium falciparum (3D7A) oocyst infection. *Int J Parasitol*. 2012;42(3):249–258.
5 Tatem AJ, Smith DL. International population movements and regional Plasmodium falciparum malaria elimination strategies. *Proc Natl Acad Sci U S A*. 2010;107(27):12222–12227.
6 Raccurt CP, Brasseur P, Ciceron M, Parke DM, Zervos MJ, Boncy J. In vivo study of Plasmodium falciparum chloroquine susceptibility in three departments of Haiti. *Malar J*. 2017;16(1):313.
7 Okech BA, Existe A, Romain JR, et al. Therapeutic efficacy of chloroquine for the treatment of uncomplicated Plasmodium falciparum in Haiti after many decades of its use. *Am J Trop Med Hyg*. 2015;92(3):541–545.
8 Gharbi M, Pillai DR, Lau R, et al. Chloroquine-resistant malaria in travelers returning from Haiti after 2010 earthquake. *Emerg Infect Dis*. 2012;18(8):1346–1349.
9 Rogier E, Herman C, Huber CS, et al. Nationwide monitoring for Plasmodium falciparum drug-resistance alleles to chloroquine, sulfadoxine, and pyrimethamine, Haiti, 2016-2017. *Emerg Infect Dis*. 2020;26(5):902–909.
10 Patel JC, Taylor SM, Juliao PC, et al. Genetic evidence of importation of drug-resistant Plasmodium falciparum to Guatemala from the democratic republic of the Congo. *Emerg Infect Dis*. 2014;20(6):932–940.
11 Fontecha G, Pinto A, Archaga O, et al. Assessment of Plasmodium falciparum anti-malarial drug resistance markers in pfcrt and pfmdr1 genes in isolates from Honduras and Nicaragua, 2018-2021. *Malar J*. 2021;20(1):465.
12 World Health Organization. *Front matter*. World Health Organization; 2020.
13 Ladeia-Andrade S, Menezes MJ, de Sousa TN, et al. Monitoring the efficacy of chloroquine-primaquine therapy for uncomplicated Plasmodium vivax malaria in the main transmission hot spot of Brazil. *Antimicrob Agents Chemother*. 2019;63(5).
14 Tuite AR, Thomas-Bachli A, Acosta H, et al. Infectious disease implications of large-scale migration of Venezuelan nationals. *J Trav Med*. 2018;25(1).
15 MIGRACIÓN - irregulares en Tránsito por Darién por País. Available in: https://www.datosabiertos.gob.pa/dataset/migracion-irregulares-en-transito-por-darien-por-pais-2022; 2022. Accessed December 27, 2022.
16 Lindblade KA, Steinhardt L, Samuels A, Kachur SP, Slutsker L. The silent threat: asymptomatic parasitemia and malaria transmission. *Expert Rev Anti-infect Ther*. 2013;11(6):623–639.
17 Maroushek SR, Aguilar EF, Stauffer W, Abd-Alla MD. Malaria among refugee children at arrival in the United States. *Pediatr Infect Dis J*. 2005;24(5):450–452.
18 Ndao M, Bandyayera E, Kokoskin E, Gyorkos TW, MacLean JD, Ward BJ. Comparison of blood smear, antigen detection, and nested-PCR methods for screening refugees from regions where malaria is endemic after a malaria outbreak in Quebec, Canada. *J Clin Microbiol*. 2004;42(6):2694–2700.
19 Recht J, Siqueira AM, Monteiro WM, Herrera SM, Herrera S, Lacerda MVG. Malaria in Brazil, Colombia, Peru and Venezuela: current challenges in malaria control and elimination. *Malar J*. 2017;16(1):273.
20 Harris I, Sharrock WW, Bain LM, et al. A large proportion of asymptomatic Plasmodium infections with low and sub-microscopic parasite densities in the low transmission setting of Temotu Province, Solomon Islands: challenges for malaria diagnostics in an elimination setting. *Malar J*. 2010;9:254.
21 Coppee R, Sarrasin V, Zaffaroulah R, et al. Nosocomial malaria transmissions resolved by genomic analyses - a retrospective case report study in France (2007-2021). *Clin Infect Dis*. 2023;76(4):631–639.
22 Bisoffi Z, Leoni S, Angheben A, et al. Chronic malaria and hyperreactive malarial splenomegaly: a retrospective study on the largest series observed in a non-endemic country. *Malar J*. 2016;15:230.
23 U.S. Department of health and human services. C.D.C. guidelines for the U.S. domestic medical examination for newly arriving refugees. Available at: http://www.cdc.gov/immigrantrefugeehealth/guidelines/domestic/domestic-guidelines.html. Accessed April 4, 2022.
24 World Health Organization. *WHO guidelines for malaria, 25 November 2022*. Geneva: World Health Organization; 2022. Contract No.: WHO/UCN/GMP/2022.01 Rev.3.
25 Ljolje D, Abdallah R, Lucchi NW. Detection of malaria parasites in samples from returning US travelers using the Alethia(R) Malaria Plus LAMP assay. *BMC Res Notes*. 2021;14(1):128.
26 Nsanzabana C, Djalle D, Guerin PJ, Menard D, Gonzalez IJ. Tools for surveillance of anti-malarial drug resistance: an assessment of the current landscape. *Malar J*. 2018;17(1):75.
27 Sinka ME, Pironon S, Massey NC, et al. A new malaria vector in Africa: predicting the expansion range of Anopheles stephensi and identifying the urban populations at risk. *Proc Natl Acad Sci U S A*. 2020;117(40):24900–24908.
28 World Health Organization. *Vector alert: Anopheles stephensi invasion and spread: Horn of Africa, the Republic of the Sudan and surrounding geographical areas, and Sri Lanka: information note*. Geneva: World Health Organization; 2019. Contract No.: WHO/HTM/GMP/2019.09.
29 de Pina-Costa A, Brasil P, Di Santi SM, et al. Malaria in Brazil: what happens outside the Amazonian endemic region. *Mem Inst Oswaldo Cruz*. 2014;109(5):618–633.
30 Beckett AG, Viaud L, Heisler M, Mukherjee J. Misusing public health as a pretext to end asylum - title 42. *N Engl J Med*. 2022;386(16):e41.