Meeting Report

Accelerating to Zero: Strategies to Eliminate Malaria in the Peruvian Amazon

Antonio M. Quispe,* Alejandro Llanos-Cuentas, Hugo Rodriguez, Martín Clendenes, Cesar Cabezas, Luis M. Leon, Raul Chuquiyauri, Marta Moreno, David C. Kaslow, Max Grogl, Sócrates Herrera, Alan J. Magill,†
Margaret Kosek, Joseph M. Vinetz, Andres G. Lescano, and Eduardo Gotuzzo

Department of Parasitology, U.S. Naval Medical Research Unit No. 6, Lima, Peru; Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru; Dirección Regional de Salud Loreto, Ministerio de Salud, Iquitos, Peru; Estrategia Sanitaria Nacional de Enfermedades Metaxénicas, Lima, Peru; Instituto Nacional de Salud, Lima, Peru; Ministry of Health, Lima, Peru; Division of Infectious Diseases, Department of Medicine, University of California, San Diego, La Jolla, California; Program for Appropriate Technology in Health, Seattle, Washington; Science Directorship, U.S. Naval Medical Research Unit No. 6, Lima, Peru; Caucaseco Scientific Research Center, Cali, Colombia; Malaria Strategy, Bill & Melinda Gates Foundation, Seattle, Washington; Asociación Benéfica Proyectos de Informática, Salud, Medicina, y Agricultura, Iquitos, Loreto, Peru; School of Public Health and Administration, Universidad Peruana Cayetano Heredia, Lima, Peru

Abstract. In February 2014, the Malaria Elimination Working Group, in partnership with the Peruvian Ministry of Health (MoH), hosted its first international conference on malaria elimination in Iquitos, Peru. The 2-day meeting gathered 85 malaria experts, including 18 international panelists, 23 stakeholders from different malaria-endemic regions of Peru, and 11 MoH authorities. The main outcome was consensus that implementing a malaria elimination project in the Amazon region is achievable, but would require: 1) a comprehensive strategic plan, 2) the altering of current programmatic guidelines from control toward elimination by including symptomatic as well as asymptomatic individuals for antimalarial therapy and transmission-blocking interventions, and 3) the prioritization of community-based active case detection with proper rapid diagnostic tests to interrupt transmission. Elimination efforts must involve key stakeholders and experts at every level of government and include integrated research activities to evaluate, implement, and tailor sustainable interventions appropriate to the region.

INTRODUCTION

Malaria continues to represent a major public health threat, exerting a significant disease burden worldwide.1 Although disease burden is highest in sub-Saharan Africa, malaria also causes a significant burden in other regions such as south and southeast Asia, Oceania, and Central and South America.2,3 Malaria elimination efforts are primarily focused on African countries and particularly on Plasmodium falciparum due to the mortality it causes in the poorest countries in the African region.4 This situation has resulted in an increasing gap in the collective knowledge about how to control this disease in regions where the malaria cases are predominantly caused by Plasmodium vivax,5 the most widely distributed Plasmodium species that causes malaria.6 Plasmodium vivax is biologically and epidemiologically different from P. falciparum and it is not, therefore, appropriate to assume that interventions developed for falciparum malaria are directly transferable to P. vivax.6,7 With 2.8 billion people at risk of acquiring P. vivax malaria,8 the question as to how best to interrupt its transmission and achieve elimination in regions where P. vivax is highly predominant has received little focused attention. More recent research has demonstrated its potential to be an indirect cause of death,9 to adversely impact child growth,10 to cause severe and frequent illness,10 and to demonstrate a reduced response to chloroquine.11,12 Given this, malaria researchers have been working to address key knowledge gaps, characterize the pattern of transmission of malaria, and identify high-risk groups that must be targeted to interrupt transmission, as well as to understand the patterns of human migration in vivax-predominant regions.

In the last two decades, research conducted in Peru has significantly contributed to the expansion of knowledge about malaria, particularly in the fields of vivax malaria epidemiology, diagnostics, therapeutics, and vector biology. The contributions include key epidemiological aspects of vivax transmission such as occupation-related travel,13 high P. vivax parasite genetic diversity,14 clustering and microepidemiology of infection,15,16 the human asymptomatic malaria reservoir,17–19 some sociodemographic20 and microgeographical21 characteristics of the sustainability of malaria transmission, and the serious consequences of severe vivax malaria.22 In addition, with the discovery of P. falciparum strains lacking the histidine-rich protein-2 (PFHRP2)23 and the spread of such strains within Peru, researchers were able to assess and identify better alternatives for rapid diagnostic tests (RDTs) specific for the regional strains.24 Peru has contributed to clinical research in therapeutics and antimalarial resistance, including a clinical trial of tafenoquine,25 and new data on how to improve the utilization of conventional antimalarials within Peru, including mefloquine and artesunate.26–28 Primaquine,29,30 and dihydroartemisinin–piperaquine.31 Furthermore, similar research has contributed to the further understanding of the dynamics of antimalarial resistance, particularly in regards to the resistance to chloroquine,32 sulfadoxine–pyrimethamine,33–36 and mefloquine.34 Finally, research from Peru has contributed to the study of vector biology and ecology, particularly on the behavior,37–40 and population structure41–43 of Anopheles darlingi and Anopheles benarrochi, the two main malaria vectors in the Amazon basin. We anticipate that as a result of the recently developed model of An. darlingi infections,44–46 the importance of these contributions will only continue to increase. All of these scientific contributions were possible mainly because of a highly productive and internationally collaborative malaria research network that has been established in the Peruvian Amazon and north coast.

*Address correspondence to Antonio M. Quispe, Department of International Health, Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, Baltimore, MD 21205. E-mail: aquispe@jhu.edu
†Deceased
SWITCHING FROM CONTROL TOWARD ELIMINATION IN PERU: A WORK IN PROGRESS

In the past, Peru achieved a level of control that twice suggested that malaria elimination might be feasible (Figure 1). First, after peaking with over 90,000 cases in 1944, the malaria burden fell to below 1,500 cases (98% reduction) in 1965, with ~1–2 cases per 10,000 inhabitants reported for approximately two decades.47 Such success was assumed to be related to the combination of dichlorodiphenyltrichloroethane (DDT) use for vector control, epidemiology and laboratory capacity building, and the shift of focus from case management to transmission control within the National Malaria Service, an effort that was initially sponsored by the Rockefeller Foundation and later by the Inter-American Public Health Service and the United Nations Children’s Emergency Fund.48 DDT use was halted initially in Loreto in 1988 and then stopped across the country, a policy change that may explain why over the next decade,49 malaria increased 4-fold in Peru and 50-fold in Loreto.47 After peaking in 1998 with 250,000 cases, the malaria case number dropped to 25,300 cases in 2011, a 90% reduction. The Peruvian authorities quickly responded to this malaria reemergence by updating the national malaria guidelines, introducing mefloquine–artesunate (artemisinin-based combination therapies [ACTs]) as the first line of treatment of P. falciparum malaria.50,51 From 2006 to 2011, Peru implemented the Project of Malaria Control within the Borders of the Andean Region sponsored by the Global Fund. This program implemented a variety of interventions including distributing over 250,000 long-lasting insecticide-impregnated nets (LLIN), using RDTs in remote communities, building capacity for microscopy-based diagnosis, and training community health workers in Loreto only.52 We have not considered whether LLINs function effectively in the Amazon, both because of patterns of mosquito feeding and cultural factors. Moreover, previous observations indicate that the use of transparent LLINs was low, mainly because they failed to provide privacy, shelter, and a sense of security for young children as offered by traditional mosquito nets.53,54 Assessment of peak biting times vis-a-vis sleeping/LLIN usage times remain to be assessed.

The number of falciparum and vivax malaria cases increased alarmingly from 2,238 to 10,243 and from 9,208 to 52,323 cases, respectively, from 2010 to 2014.55 The 2012 flooding and the recent political instability that affected the region are likely contributors to a resurgence of cases. The Amazonian Department of Loreto continues to report the vast majority of malaria cases in Peru at 94%.55 In Loreto, malaria is largely seasonal, disproportionately affects adult men (loggers, fishermen, farmers, and other laborers that live in higher transmission regions or travel often13,20), and is dispersed across riverine communities (Figure 2).56 The epidemiology of malaria in other endemic Amazonian regions such as San Martin and Ucayali vary slightly compared with Loreto. However, in other regions such as on the north coast (Tumbes, Piura, Lambayeque, and La Libertad), the epidemiology is considerably different, occurring with epidemic and sporadic patterns probably related to stochastic factors such as reintroductions.57 On the north coast, the predominant malaria vector is Anopheles albimanus58 and P. falciparum malaria has rarely been reported in this region since 2010. Malaria is highly concentrated within periurban communities59 and across the region, the annual number of malaria cases per 1,000 inhabitants has dropped below 0.01 since 2013.55 Certainly, the malaria vectors do not stop at any border, neither national nor international, so given that the reintroduction of malaria is likely to occur across the borders, there is a strong need for active program alliances that address both national and transnational issues. Programs such as the Amazon Malaria Initiative and the Peru-Brazil International Centers of Excellence for Malaria Research are contributing to build the necessary knowledge to eliminate malaria in the Peruvian Amazon but more needs to be done.

REVIEWING THE AGENDA OF MALARIA ELIMINATION IN PERU: CONFERENCE ORGANIZATION AND AIMS

Early in 2014, a conference was held in the city of Iquitos, the capital of Loreto, on February 16–17 to review the agenda of malaria elimination in Peru. The main objective was to engage the research community and decision makers in a collaborative effort to define the critical knowledge gaps and policy requirements to achieve and sustain malaria elimination in Peru. In attendance were representatives from regional organizations, national organizations, the Ministry of Health, and international participants. In this conference, 25 different organizations were represented (Table 1). Local experts and stakeholders were well represented in the conference. Of the 85 conference participants, 53 were Peruvian, including 34 researchers and authorities from the Loreto region, and 32 were international, most with long track records working on national public health priorities in Peru. Four of the six
board members were Peruvian and 19 of the 30 consulting committee members were Peruvian.

To meet this objective, the conference integrated two formats for soliciting expert input and achieving consensus. On the first day, individual experts gave presentations that reviewed: past malaria control and elimination efforts; current opportunities and challenges for malaria elimination in the Americas; the potential role of transmission-blocking vaccines, seroepidemiology,

![Annual Parasite Index per reporting communities, Loreto 2013](image)

**Figure 2.** Geographical distribution of reported malaria cases in Loreto, 2013. Distribution of malaria across communities in the Loreto Department. Each bubble represents a reporting community in the national surveillance system. The size of the bubble represents the size of the population of each community, whereas the color represents the Annual Parasite Index (total of subjects that tested smear positive to malaria per 1,000 inhabitants) in the year 2013. The blue lines represent the tributaries of the Amazon river and the dashed line indicates the district boundaries. In 2013, 24% (12/51) of the districts represented over 80% of the total number of malaria cases reported in the Loreto region, whereas 4% of the communities contributed to over 30% of the total number of malaria cases in the same year.

| Table 1 |
|---------|
| **Partners and collaborating organizations** |
| **Acronym** | **Organization name** |
| BMGF | Bill & Melinda Gates Foundation |
| CGHD-CWRU | Case Western Reserve University |
| CSRC | Caucasian Scientific Research Center |
| DGE | Dirección General de Epidemiología (General Epidemiology Directorate) |
| DIRESA Junín | Dirección Regional de Salud de Junín (Junin Regional Health Directorate) |
| DIRESA Loreto | Dirección Regional de Salud de Loreto (Loreto Regional Health Directorate) |
| DIRESA Madre de Dios | Dirección Regional de Salud de Madre de Dios (Madre de Dios Regional Health Directorate) |
| DIRESA Piura | Dirección Regional de Salud de Piura (Piura Regional Health Directorate) |
| DIRESA San Martín | Dirección Regional de Salud de San Martín (San Martín’s Regional Health Directorate) |
| DIRESA Tumbes | Dirección Regional de Salud de Tumbes (Tumbes’ Regional Health Directorate) |
| ESNEM | Estrategia Sanitaria Nacional de Prevención y Control de Enfermedades Metaxenicas (National Sanitary Strategy for the Prevention and Control of Vector Borne Diseases) |
| GRL | Gobierno Regional de Loreto (Loreto Regional Government) |
| ICEMR | Peru–Brazil International Center of Excellence in Malaria Research |
| INS | Instituto Nacional de Salud (National Health Institute) |
| JHBSPH | Johns Hopkins Bloomberg School of Public Health |
| MINS | Ministerio de Salud (Ministry of Health) |
| NAMRU-6 | U.S. Naval Medical Research Unit No. 6 |
| PAHO | Pan American Health Organization |
| PATH | Program for Appropriate Technology in Health |
| PRISMA | Proyectos de Informática, Salud, Medicina, y Agricultura |
| UCSD | University of California, San Diego |
| UNAP | Universidad Nacional de la Amazonía Peruana, Loreto (National University of the Peruvian Amazon) |
| UPCH | Universidad Peruana Cayetano Heredia (Cayetano Heredia Peruvian University) |
and diagnostic technologies in malaria elimination; and the role of social and behavioral considerations in malaria diagnostics and interventions. The discussions included the micro-epidemiology of malaria, various strategies and challenges of malaria elimination in this region, and the benefits and practicalities of a demonstrative elimination project. On the second day, we convened the first meeting of the newly formed Malaria Elimination Working Group, a multiorganizational, multidisciplinary group of malaria researchers convened to support the agenda of malaria elimination in the Amazon region, with a particular focus in the Peruvian Amazon. The group’s goal is to promote innovative solutions to the scientific, technical, operational, financial, and programmatic challenges that decision makers will need to address when pursuing a malaria elimination initiative. The second day’s agenda comprised four different round table discussions led by experts to achieve consensus on several different aspects that were considered highly relevant to malaria elimination. These included: 1) feasibility and project sites, 2) project aims and outcomes, 3) diagnostics, interventions, and methods, and 4) the gaps and priorities in the future research agenda. During the closing discussion of the conference, the moderators of each group presented the outcomes of their discussions.

FEASIBILITY OF A MALARIA ELIMINATION PROJECT IN THE PERUVIAN AMAZON

The group concluded that implementing a malaria elimination project in the Peruvian Amazon is feasible, although its success will require a clear financial and political commitment from the Peruvian government. For this purpose, it will be crucial to establish a comprehensive regional strategic plan to guide this project. Peruvian public health activities should continue to focus on basic prevention and control and to introduce new tools and new strategies as they are developed. The implemented measures must be integrated, culturally appropriate, and sustainable in terms of both financing and political support. The incorporation of other regional and local authorities (such as provincial governors and local leaders at the city and village levels) will also be important. A critical aspect of the strategy will be the identification of asymptomatic parasitemic individuals, who are important reservoirs for continuing transmission, and monitoring how subsequent interventions affect this population’s potential for maintaining local malaria transmission. Targeted parasite elimination strategies that are appropriate to the region must be used to overcome the limitations of passive case detection and the difficulties in providing proper coverage to the isolated high-risk populations (either remote communities or migratory subpopulations such as loggers and gold miners). Several criteria should be considered in the selection of study sites: they should have a large population with low annual parasite index (API < 1) and cultural and political accessibility. The setting must allow for the incorporation of new validated tools to augment standard control measures. In addition, the study sites must be close to each other, potentially within the same river basin, and the regions surrounding the study area must have control measures in place to prevent reintroduction. Finally, considering the ethical implications, it must be determined whether these interventions are in the public health interest of the study sites, and if successful, these interventions should be scaled up to include neighboring communities.

AIMS AND OUTCOMES OF A MALARIA ELIMINATION PROJECT

The group discussed various outcomes that might be useful in assessing the impact of a malaria elimination strategy in the Peruvian Amazon. Many indicators were evaluated but only a few were recommended by the group to be considered relevant to measure the impact of a malaria elimination project. These included the following: burden of disease, API, positivity index, incidence rate, seroprevalence, population structure of the vector species, human biting rate, sporozoite index, and vector density. Furthermore, the group stressed the relevance of adapting or developing some process indicators. These indicators should at least allow a proper measurement of the project coverage, community responsiveness, capacity building, as well as the actions to convert the project inputs into specific human behavior changes. Consensus could not be reached regarding a reasonable time frame within which malaria elimination could be achieved in the study sites, primarily because of uncertainties of funding and variations on approaches. However, the group agreed on several themes that will be essential when considering malaria elimination as the ultimate goal. These include an integrated strategy with properly financed, independent, and dedicated resources and the subsequent integration of the proposed diagnostic and intervention measures into the health system. Also, it will be essential to improve logistic communication and programmatic monitoring activities among involved interdisciplinary and intersectoral groups. In the scope of a malaria elimination project, there was a strong agreement that it would be critical to involve public health and political authorities at the highest political level to achieve programmatic stability.

KEY ASPECTS OF DIAGNOSTICS, INTERVENTIONS, AND THEIR IMPLEMENTATION IN THE PERUVIAN AMAZON

Participants in this roundtable carried out a lively discussion on the need for improving current regional diagnostic platforms with more sensitive but portable diagnostics, particularly for targeting rural communities and hard-to-reach high-risk populations such as loggers, farmers, and fishermen. In this discussion, the group emphasized that it will be critical to introduce sufficiently sensitive RDTs that are appropriate for the Peruvian context as well as to address the administrative and logistical barriers that might prevent a regular and continuous supply. This is particularly true for both P. falciparum and P. vivax, given the high prevalence of PfHRP2,23 its multiple genetic origins,24 and the considerable variability in the diagnostic accuracy of some of the pan-lactate dehydrogenase–detecting RDTs in the Peruvian Amazon.60 In addition, its implementation should follow locally adapted guidelines. The group recommended that interventions should be implemented as an integrated package, accounting for the local sociocultural barriers to classical interventions such as bed nets and indoor residual spraying and placing interventions into a local context to maximize impact. It will be essential to monitor and evaluate programs and interventions from a research perspective.
Malaria elimination in the Peruvian Amazon is a feasible and important goal, but will require:

1. A comprehensive regional strategic plan and integrative control measures that are culturally and contextually appropriate as well as politically and financially sustainable.
2. Study sites for new control measures should have large populations, low transmission, and be accessible but resistant to contamination of effect.
3. Evaluation of four types of indicators: morbidity/mortality, surveillance/monitoring, entomological, and process indicators.
4. That rapid diagnostic tests (RDTs) be introduced for active case detection, ideally with local production at some point, and that microscopy should be maintained while its quality is improved.
5. Interventions that prioritize active detection with RDTs and treatment with artemisinin-based combination therapy with primaquine over bed nets and spraying, which have limited effectiveness in this setting, while establishing a continual supply chain for tests and antimalarial drugs.
6. Research to address knowledge gaps in vector behavior, insecticide resistance, the social determinants of malaria, and cultural perspectives toward particular interventions, while working to develop and implement novel assays for detection and therapeutics.
7. Integration of the program into the existing health system, a communication platform between stakeholder groups, and intersectoral collaboration between stakeholders and officials at all levels of government.

GAPS AND PRIORITIES IN THE FUTURE RESEARCH AGENDA

Several recommendations were made regarding key elements of the future research agenda (Table 2). These include that research and evaluation of a malaria elimination project should have clear and achievable milestones, progress from simple to more complex interventions, and involve all the different stakeholders (national and local government, academia, and nongovernmental organizations). Its implementation should be carefully planned to overcome operational challenges by identifying and integrating key providers within the project. Mobile and internet coverage is currently restricted mainly to periurban Iquitos, which represents a major barrier for the development of public health interventions. The implementation and operational research should incorporate social science and account for the social determinants of malaria to find culturally acceptable ways to intervene. Integrated approaches should be considered as means to strengthen the impact of any malaria elimination project, particularly in the most remote communities, as well as to sustain the political will and support. Importantly, the focus of elimination efforts must be on the most important reservoirs of maintaining malaria endemicity and transmission rather than solely on symptomatic individuals. Such an approach will require better tools to efficiently identify carriers (serology and molecular assays complementary to RDTs and microscopy). Research on vector behavior, including monitoring and surveillance for insecticide resistance, as well as research on the local customs and preferences for bed net usage are crucial for understanding and deploying effective and widely used vector control interventions. With regards to therapeutics, there is a need for improved policies to establish a streamlined process to incorporate new drugs into the Peruvian national formulary.

CONCLUSIONS AND FUTURE DIRECTIONS

Several key conclusions and points of consensus arose from this meeting. The most important one is that malaria elimination in the Peruvian Amazon can be achievable and should be a national and international priority. A comprehensive regional strategic plan needs to be developed that addresses key technical, operational, and economical considerations such as the ones recommended by the World Health Organization. It was strongly recommended to first pilot such a strategy in suitable sites in the region to establish efficacy and acceptability. When such a strategy is implemented, it will be important to monitor and evaluate progress through a variety of metrics and to set intermediate goals on the path to regional elimination. Targeted parasite elimination strategies that are appropriate to the region must be used, stressing active case detection using sufficiently sensitive and effective RDTs and species-specific treatment of the asymptomatic reservoir. This is particularly important in the case of P. falciparum malaria, which must be treated with ACT and primaquine to interrupt transmission. The strategy must facilitate the communication between key stakeholders from the region and political support at all levels of government, and the program should be incorporated into established health-care systems to improve acceptability and sustainability. The progression of such a strategy should be flexible to allow new knowledge of the social determinants of malaria, cultural acceptability of key interventions, and novel tests and treatments to be incorporated throughout the effort. An agreement on the relevance of pursuing malaria elimination as a goal was reached during the conference, and the necessary components and characteristics of this effort were described. Moving forward, further details should be elaborated as commitments from a critical mass of stakeholders are obtained.

Received May 18, 2015. Accepted for publication February 7, 2016.

Acknowledgments: We thank Steve Kern from the Bill & Melinda Gates Foundation (BMGF) for his support and guidance during the planning of this conference; Diego Borjas and Bertha Suarez from Universidad Peruana Cayetano Heredia (UPCH) for their diligent support of conference activities; and Jessica Rothstein, Josiah L. Kephart, and Ryan Max from Johns Hopkins Bloomberg School of Public Health (JHBSPH) for reviewing and editing the initial drafts of the manuscript. We also thank the members of the Malaria
Elimination Working Group Board (Eduardo Gotuzzo, Andres G. Lescano, Margaret Kosek, Joseph M. Vinetz, Alejandro Llanos-Cuentas, and Antonio M. Quispe) and the consulting committee, which originally consisted of the following members: Hugo Rodriguez, Cristian Carey, Martin Casapía, Graciela Meza, Carmen Montalván, César Padilla, and Mosén Silvina from Dirección Regional de Salud de Piura (DIRESA) Loreto; Fernando Orihuela from DIRESA Junín, Jorge Ascencio from DIRESA Madre de Dios; Edwar J. Pozo from DIRESA Piura; Carlos LLuén from DIRESA San Martín; Fernando Quintanilla from DIRESA Tumbes; Cesar Cabezas, Pedro Valencia, and Javier Aramburu from the Instituto Nacional de Salud; Martin Clendenens and Jorge Escobedo from the Estrategia Sanitaria Nacional de Prevención y Control de Enfermedades Metaxasis, Ministry of Health, Peru; Luis M. Leon, Jose de la Saca, Carmen, Elena Ogusuku, Bernardo Ostos, and Alexander Tavey from Ministerio de Salud; Martin Yaguí from Dirección General de Epidemiología, Peru; Guillermo Gonzalez and Fernando Llanos from Pan American Health Organization; Raul Chuquiyauri, Dionicia Gamboa, and Angel Rosas from UPCH; Max Grogl, Adam Armstrong, G. Christian Badalvi, Vince R. Gerbasi, Salomon Durand, Amy Morrison, Kyle Peterson, and Gisela Vasquez from U.S. Naval Medical Research Unit No. 6; Sócrates Herrera, Caucaseco Scien-

Authors’ addresses: Antonio M. Quispe, Department of Parasitology, U.S. Naval Medical Research Unit No. 6, Lima, Peru, and Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, and Asociación Benéfica Proyectos de Investigación, Salud, Agricultura, y Medio Ambiente, Piura, Peru; E-mail: mkosek@jhmi.edu. Andres G. Lescano, Department of Para-
sitology, U.S. Naval Medical Research Unit No. 6, Lima, Peru, and School of Public Health and Administration, Universidad Peruana Cayetano Heredia, Lima, Peru, E-mails: willy.lescano@med.navy.mil or wlescano@hotmail.com.

This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

REFERENCES

1. WHO, 2014. World Malaria Report. Geneva, Switzerland: WHO.
2. Gotuzzo PW, Elyazar IR, Bandyopadhyay NK, Guerra CA, Patil AP, Tatem AJ, Howes RE, Myers MF, George DB, Horby P, Wertheim HF, Price RN, Mueller I, Baird JK, Hay SI, 2012. A long neglected world malaria map: Plasmodium vivax endemicity in 2010. PLoS Negl Trop Dis 6: e1814.
3. Gething PW, Patil AP, Smith DL, Guerra CA, Elyazar IR, Johnston GL, Tatem AJ, Hay SI, 2011. A new world malaria map: Plasmodium falciparum, malaria, agriculture, trade. Malar J 10: 378.
4. The mLeERA Consultative Group on Vaccines, 2011. A research agenda for malaria eradication: vaccines. PLoS Med 8: e1000398.
5. Guerra CA, Howes RE, Patil AP, Gething PW, Van Boeckel TP, Temperley WH, Kabaria CW, Tatem AJ, Manh BH, Elyazar IR, Baird JK, Snow RW, Hay SI, 2010. The international limits and population at risk of Plasmodium vivax transmission in 2009. PLoS Negl Trop Dis 4: e774.
6. Baird JK, 2010. Eliminating malaria—all of them. Lancet 376: 1883–1885.
7. Bousema T, Drakeley C, 2011. Epidemiology and infectivity of Plasmodium falciparum and Plasmodium vivax gametocytes in relation to malaria control and elimination. Clin Microbiol Rev 24: 377–410.
8. Douglas NM, Pontoreringo GJ, Lambah DA, Yeo TW, Kenigalangem, E, Poespoprodjo J, Ralph AP, Bangs MJ, Sugarto P, Anstey NM, Price RN, 2014. Mortality attributable to Plasmodium vivax malaria: a clinical audit from Papua, Indonesia. BMC Med 12: 217.
9. Lee G, Yori P, Olortegui MP, Pan W, Cauffield L, Gilman RH, Sanders JW, Delgado HS, Kosek M, 2012. Comparative effects of vivax malaria, fever and diarrhoea on child growth. Int J Epidemiol 41: 531–539.
10. Price RN, Tijtira E, Guerra CA, Yeung S, White NJ, Anstey NM, 2007. Vivax malaria: neglected and not benign. Am J Trop Med Hyg 77: 79–87.
11. Price RN, Douglas NM, Anstey NM, 2009. New developments in Plasmodium vivax malaria: severe disease and the rise of chloroquine resistance. Curr Opin Infect Dis 22: 430–435.
12. Arevalo-Herrera M, Quinones ML, Guerra C, Cepedés N, Giron S, Ahumada M, Pineros JG, Padilla N, Terrientes Z, Rosas A, Padilla JC, Escalante AA, Beier JC, Herrera S, 2012. Malaria in selected non-Amzonian countries of Latin America. Acta Trop 121: 303–314.
13. Parker BS, Paredes Olortegui M, Penatrozo Y, Escobedo K, Florin D, Rengifo Pinedo S, Cardenas Greffa R, Capcha Vega L, Rodriguez Ferrucci H, Pan WK, Banda Chavez C, Vinetz JM, Kosek M, 2013. Hyperendemic malaria transmission in areas of occupation-related travel in the Peruvian Amazon. Malar J 12: 178.
14. Kosek M, Yori PP, Gilman RH, Calderon M, Zimic M, Chiuquiyauri R, Jeri C, Pineda-Cancino V, Matthis MA, Llanos-Cuentas A, Vinetz JM, 2012. High degree of Plasmodium vivax diversity in the Peruvian Amazon demonstrated by tandem repeat polymorphism analysis. Am J Trop Med Hyg 86: 580–586.
15. Branch Ø, Casapia WM, Gamboa DV, Hernandez JN, Alava FF, Roncal N, Alvarez E, Perez EJ, Gotuzzo E, 2005. Clustered local transmission and asymptomatic Plasmodium falciparum
and Plasmodium vivax malaria infections in a recently emerged, hypoenzootic Peruvian Amazon community. Malar J 4: 27.

16. Bautista CT, Chan AS, Ryan JR, Calampa C, Roper MH, Hightower AW, Magill AJ, 2006. Epidemiology and spatial analysis of malaria in the northern Peruvian Amazon. Am J Trop Med Hyg 75: 1216–1222.

17. Vinetz JM, Gilman RH, 2002. Asymptomatic Plasmodium parasitemia and the ecology of malaria transmission. Am J Trop Med Hyg 66: 639–640.

18. Roshanravan B, Kari E, Gilman RH, Cabrera L, Lee E, Metcalfe J, Calderon M, Lescano AG, Montenegro SH, Calampa C, Vinetz JM, 2003. Endemic malaria in the Peruvian Amazon region of Iquitos, Peru. J Am Mosq Control Assoc 19: 230–235.

19. da Silva-Nunes M, Moreno M, Conn JE, Gamboa D, Abeles S, 2005. Molecular evidence for malaria importation in an Amazonian community. Am J Trop Med Hyg 72: 409–412.

20. Quispe AM, Pozo E, Durand S, Baldeviano GC, 2005. Microsatellite markers reveal the presence of the Plasmodium falciparum parasite in the Amazon basin of Peru. Malar J 4: 28.

21. Vinetz JM, Gilman RH, 2002. Asymptomatic Plasmodium parasitemia and the ecology of malaria transmission. Am J Trop Med Hyg 66: 639–640.

22. Vinetz JM, Gilman RH, 2002. Asymptomatic Plasmodium parasitemia and the ecology of malaria transmission. Am J Trop Med Hyg 66: 639–640.

23. Gamboa D, Ho MF, Bendezu J, Torres K, Chiodini PL, 2003. Endemic malaria in the Peruvian Amazon region of Iquitos, Peru. J Am Mosq Control Assoc 19: 230–235.

24. Gamboa D, Ho MF, Bendezu J, Torres K, Chiodini PL, 2003. Endemic malaria in the Peruvian Amazon region of Iquitos, Peru. J Am Mosq Control Assoc 19: 230–235.

25. Vinetz JM, Gilman RH, 2002. Asymptomatic Plasmodium parasitemia and the ecology of malaria transmission. Am J Trop Med Hyg 66: 639–640.

26. Vinetz JM, Gilman RH, 2002. Asymptomatic Plasmodium parasitemia and the ecology of malaria transmission. Am J Trop Med Hyg 66: 639–640.

27. Vinetz JM, Gilman RH, 2002. Asymptomatic Plasmodium parasitemia and the ecology of malaria transmission. Am J Trop Med Hyg 66: 639–640.

28. Vinetz JM, Gilman RH, 2002. Asymptomatic Plasmodium parasitemia and the ecology of malaria transmission. Am J Trop Med Hyg 66: 639–640.

29. Vinetz JM, Gilman RH, 2002. Asymptomatic Plasmodium parasitemia and the ecology of malaria transmission. Am J Trop Med Hyg 66: 639–640.

30. Vinetz JM, Gilman RH, 2002. Asymptomatic Plasmodium parasitemia and the ecology of malaria transmission. Am J Trop Med Hyg 66: 639–640.

31. Vinetz JM, Gilman RH, 2002. Asymptomatic Plasmodium parasitemia and the ecology of malaria transmission. Am J Trop Med Hyg 66: 639–640.

32. Vinetz JM, Gilman RH, 2002. Asymptomatic Plasmodium parasitemia and the ecology of malaria transmission. Am J Trop Med Hyg 66: 639–640.

33. Vinetz JM, Gilman RH, 2002. Asymptomatic Plasmodium parasitemia and the ecology of malaria transmission. Am J Trop Med Hyg 66: 639–640.

34. Vinetz JM, Gilman RH, 2002. Asymptomatic Plasmodium parasitemia and the ecology of malaria transmission. Am J Trop Med Hyg 66: 639–640.

35. Vinetz JM, Gilman RH, 2002. Asymptomatic Plasmodium parasitemia and the ecology of malaria transmission. Am J Trop Med Hyg 66: 639–640.

36. Vinetz JM, Gilman RH, 2002. Asymptomatic Plasmodium parasitemia and the ecology of malaria transmission. Am J Trop Med Hyg 66: 639–640.

37. Vinetz JM, Gilman RH, 2002. Asymptomatic Plasmodium parasitemia and the ecology of malaria transmission. Am J Trop Med Hyg 66: 639–640.

38. Vinetz JM, Gilman RH, 2002. Asymptomatic Plasmodium parasitemia and the ecology of malaria transmission. Am J Trop Med Hyg 66: 639–640.

39. Vinetz JM, Gilman RH, 2002. Asymptomatic Plasmodium parasitemia and the ecology of malaria transmission. Am J Trop Med Hyg 66: 639–640.

40. Vinetz JM, Gilman RH, 2002. Asymptomatic Plasmodium parasitemia and the ecology of malaria transmission. Am J Trop Med Hyg 66: 639–640.

41. Vinetz JM, Gilman RH, 2002. Asymptomatic Plasmodium parasitemia and the ecology of malaria transmission. Am J Trop Med Hyg 66: 639–640.

42. Vinetz JM, Gilman RH, 2002. Asymptomatic Plasmodium parasitemia and the ecology of malaria transmission. Am J Trop Med Hyg 66: 639–640.

43. Vinetz JM, Gilman RH, 2002. Asymptomatic Plasmodium parasitemia and the ecology of malaria transmission. Am J Trop Med Hyg 66: 639–640.

44. Vinetz JM, Gilman RH, 2002. Asymptomatic Plasmodium parasitemia and the ecology of malaria transmission. Am J Trop Med Hyg 66: 639–640.

45. Vinetz JM, Gilman RH, 2002. Asymptomatic Plasmodium parasitemia and the ecology of malaria transmission. Am J Trop Med Hyg 66: 639–640.
patient-derived *Plasmodium vivax* in the Peruvian Amazon. *Am J Trop Med Hyg* 75: 610–616.

46. Abeles SR, Chuquiyauri R, Tong C, Vinetz JM, 2013. Human host-derived cytokines associated with *Plasmodium vivax* transmission from acute malaria patients to *Anopheles darlingi* mosquitoes in the Peruvian Amazon. *Am J Trop Med Hyg* 88: 1130–1137.

47. Aramburú Guarda J, Ramal Asayag C, Witzig R, 1999. Malaria reemergence in the Peruvian Amazon region. *Emerg Infect Dis* 5: 209–215.

48. Griffing SM, Gamboa D, Udhayakumar V, 2013. The history of 20th century malaria control in Peru. *Malar J* 12: 303.

49. Roberts DR, Laughlin LL, Hsheih P, Legten LJ, 1997. DDT, global strategies, and a malaria control crisis in South America. *Emerg Infect Dis* 3: 295–302.

50. Williams HA, Vincent-Mark A, Herrera Y, Chang OJ, 2009. A retrospective analysis of the change in anti-malarial treatment policy: Peru. *Malar J* 8: 85.

51. Neyra D, Cabezas CK, Ruebush TK 2nd, 2003. El proceso de adecuación y cambio en la política del tratamiento de la malaria por *Plasmodium falciparum* en el Perú, 1990–2001. *Rev Peru Med Exp Salud Publica* 20: 162–171.

52. PAMAFRO, 2009. Compartiendo Lecciones Aprendidas Del PAMAFRO. Available at: http://www.orasconhu.org/pamafro/compartiendo-lecciones-aprendidas-del-pamafro. Accessed May 1, 2015.

53. Grietens KP, Mucla Ribera J, Soto V, Tenorio A, Hoibak S, Aguirre AR, Toomer E, Rodriguez H, Llanos Cuentas A, D’Alessandro U, Gamboa D, Erhart A, 2013. Traditional nets interfere with the uptake of long-lasting insecticidal nets in the Peruvian Amazon: the relevance of net preference for achieving high coverage and use. *PLoS One* 8: e50294.

54. Harvey SA, Olortegui MP, Leontsini E, Pezo CB, Pezantes LM, Winch PJ, 2008. The whole world will be able to see us: determining the characteristics of a culturally appropriate bed net among mestizo communities of the Peruvian Amazon. *Am J Trop Med Hyg* 79: 834–838.

55. MINSA-DGE, 2015. Situational Room Report: Epidemiological Week 01. Peru: Ministerio de Salud del Perú, Dirección General de Epidemiología.

56. Delgado-Ratto C, Soto-Calle VE, Van den Eede P, Gamboa D, Rosas A, Abath EN, Rodriguez Ferrucci H, Llanos-Cuestas A, Van Geertruyden JP, Erhart A, D’Alessandro U, 2014. Population structure and spatio-temporal transmission dynamics of *Plasmodium vivax* after radical cure treatment in a rural village of the Peruvian Amazon. *Malar J* 13: 8.

57. Baldeviano GC, Akinyi S, Arrospide S, Gonzalez RV, Sanchez JF, Macedo S, Conde S, Tapia L, Salas C, Gamboa D, Herrera Y, Edgel AG, Udhayakumar V, Lescano AG, 2015. Molecular epidemiology of *Plasmodium falciparum* malaria outbreak, Tumbes, Peru, 2010–2012. *Emerg Infect Dis* 21: 797–803.

58. Guthmann JP, Hall AJ, Jaffar S, Palacios A, Lines J, Llanos-Cuestas A, 2001. Environmental risk factors for clinical malaria: a case-control study in the Grau region of Peru. *Trans R Soc Trop Med Hyg* 95: 577–583.

59. Rosas-Aguirre A, Llanos-Cuestas A, Speybroeck N, Cook J, Contreras-Mancilla J, Soto V, Gamboa D, Pozo E, Pereira MO, Soares IS, Theisen M, D’Alessandro U, Erhart A, 2013. Assessing malaria transmission in a low endemicity area of north-western Peru. *Malar J* 12: 339.

60. Malhia J, Gamboa D, Bendeuz J, Sanchez L, Chops L, Gillet P, Jacobs J, 2012. Rapid diagnostic tests for malaria diagnosis in the Peruvian Amazon: impact of pfhrp2 gene deletions and cross-reactions. *PLoS One* 7: e43094.