Published in final edited form as:
Acta Trop. 2012 March ; 121(3): 315–323. doi:10.1016/j.actatropica.2011.06.018.

Prospects for malaria elimination in non-Amazonian regions of Latin America

Sócrates Herrera[a,b], **Martha Lucia Quiñones**[c], **Juan Pablo Quintero**[a], **Vladimir Corredor**[c], **Douglas O. Fuller**[d], **Julio Cesar Mateus**[e], **Jose E. Calzada**[f], **Juan B. Gutierrez**[g], **Alejandro Llanos**[h], **Edison Soto**[i], **Clara Menendez**[j], **Yimin Wu**[k], **Pedro Alonso**[j], **Gabriel Carrasquilla**[l], **Mary Galinski**[m], **John C. Beier**[e], and **Myriam Arevalo-Herrera**[a,b]

[a]Centro de Investigación Científica Caucaseco, Colombia

[b]School of Health, Valle State University, Colombia

[c]National University, Colombia

[d]University of Miami, USA

[e]Fundación para la Educación Superior, Colombia

[f]Gorgas Memorial Institute of Health, Panama

[g]Ohio State University, USA

[h]Cayetano Heredia University, Peru

[i]The Global Fund to Fight AIDS, Tuberculosis and Malaria, Geneve

[j]Barcelona Centre for Internacional Health Research (Hospital Clinic, Universitat de Barcelona), Spain

[K]Laboratory of Malaria Immunology and Vaccinology, NIAD/NIH, USA

[l]Santa Fe de Bogotá Foundation, Colombia

[m]Emory University Atlanta, USA

Abstract

Latin America contributes 1 to 1.2 million clinical malaria cases to the global malaria burden of about 300 million per year. In 21 malaria endemic countries, the population at risk in this region represents less than 10% of the total population exposed worldwide. Factors such as rapid deforestation, inadequate agricultural practices, climate change, political instability, and both increasing parasite drug resistance and vector resistance to insecticides contribute to malaria transmission. Recently, several malaria endemic countries have experienced a significant reduction in numbers of malaria cases. This is most likely due to actions taken by National Malaria Control Programs (NMCP) with the support from international funding agencies. We describe here the research strategies and activities to be undertaken by the Centro Latino Americano de Investigación en Malaria (CLAIM), a new research center established for the non-

Corresponding author: Sócrates Herrera, Centro de Investigación Científica Caucaseco, Cali, 760042, Colombia. Phone: +57-2 521 6228. Fax: +57-2 557 0449. sherrera@inmuno.org.

Amazonian region of Latin America by the National Institute of Allergy and Infectious Diseases (NIAID). Throughout a network of countries in the region, initially including Colombia, Guatemala, Panama, and Peru, CLAIM will address major gaps in our understanding of changing malaria epidemiology, vector biology and control, and clinical malaria mainly due to *Plasmodium vivax*. In close partnership with NMCPs, CLAIM seeks to conduct research on how and why malaria is decreasing in many countries of the region as a basis for developing and implementing new strategies that will accelerate malaria elimination.

Keywords

malaria; *Plasmodium falciparum*; *Plasmodium vivax*; *Anopheles* mosquitoes; vector control; epidemiology; malaria elimination; malaria pathogenesis; non-Amazon regions; Latin America

1. Malaria control in non-Amazonian regions of Latin America

Approximately 170 million people, corresponding to almost 60% of the total population of Latin America (LA) and the Caribbean, live in malaria endemic areas where 1 to 1.2 million clinical malaria cases occur every year(Guerra et al., 2010; WHO, 2009). Sixty percent of these cases are reported from Brazil whereas the remaining 40% of the cases occur in another 20 countries mainly located in the Andean region (PAHO and WHO, 2008; WHO, 2008). *Plasmodium vivax* is the predominant species (~74%) followed by *P. falciparum* (~26%) and *P. malariae* (< 0.1%) (Guerra et al., 2010; WHO, 2009).

During the Global Malaria Eradication Program (GMEP) from 1955 to 1969, several countries in LA made significant progress toward malaria elimination (Gabaldon, 1983; Gabaldon et al., 1961). Importantly, even highly endemic countries such as Venezuela, Colombia, Peru, and Panama significantly reduced malaria transmission. However, parasite resistance to several anti-malarial drugs (Corredor et al., 2010; Feachem et al., 2009; WHO, 2005), mosquito resistance to DDT and other insecticides, economical constraints, and unclear malaria control policies significantly limited the progress of this early program (Roberts and Andre, 1994; WHO, 1998).

Since 1969 when the GMEP ended, most countries of the region experienced overall increases in malaria incidence. However, since 2000, substantial decreases in malaria incidence have been observed due to regional policies and efforts to improve malaria surveillance, early case detection, prompt diagnosis and treatment, integrated vector management, and health systems strengthening (WHO, 2009). The initiation of other programs like the “Malaria Control Program in Andean-country Border Regions” (PAMAFRO) sponsored by the Andean Health Organization (ORAS), The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), and The Amazon Network for the Surveillance of Antimalarial Drug Resistance (RAVREDA) sponsored by the Pan American Health Organization/World Health Organization (PAHO/WHO) have significantly influenced the Annual Parasite Index (API) in this region. Moreover, some of the countries from the Mesoamerican region like El Salvador, Costa Rica, Mexico and Nicaragua have decreased malaria incidence by over 90% through intensive control activities (SM2015, 2010). To date, three countries, Argentina, El Salvador and Mexico, have scaled-up their malaria control strategies and are working toward malaria elimination (WHO, 2006). Significantly, these success stories in malaria control strongly encourage the initiation of strategically focused efforts towards malaria elimination throughout the LA region.

2. Key gaps for effective malaria control/elimination in LA

Although malaria elimination in LA countries appears more feasible than in most other regions of the world (Feachem et al., 2009), moving from control to elimination in low-endemic malaria areas of the region still represents a great challenge. Despite increased funding for malaria control in the region, coverage with preventive measures and access to effective treatments still remain below expected levels in some countries. Major gaps include the availability of suitable diagnostic tests with high sensitivity and specificity for mass use, an adequate understanding of the taxonomy, ecology, and behavior of vector species relative to available tools for vector control, increasing limitations in the availability of effective antimalarials, mapping of the extent and spread of drug resistant parasites, and a limited understanding of *P. vivax* biology and epidemiology (WHO, 2008).

2.1 Vectors of malaria parasite transmission

Nine out of 90 anophelines species described in the region have been incriminated as vectors of primary and secondary importance with regard to malaria parasite transmission (Rubio-Palis and Zimmerman, 1997; Sinka et al., 2010) but there is insufficient information on vector species distribution as well as uncertainties regarding the impact of anthropogenic environmental changes on the dynamics of transmission. The great diversity of *Anopheles* species in LA together with the limited understanding of their taxonomy urgently requires integrated approaches to determine which *Anopheles* species and species complexes are serving as malaria vectors in the region. Moreover, besides limitations in effective tools for vector control, NMCPs are likely to be using under-developed Integrated Vector Management (IVM) strategies (WHO, 2011b). There is only a limited understanding of vector biology, particularly mosquito ecology and behavior, geographic distributions and seasonality of vectors and the dynamics of local malaria parasite transmission, all of which limit the ability of health authorities to select and utilize adequate vector control measures. Appropriate IVM strategies for vector control in the diverse environments of LA must consider local malaria epidemiology and how malaria vector species respond to available tools for vector control.

2.2 Malaria Diagnosis and Parasite Genetic Diversity

With malaria, clinical diagnosis is not specific and leads to a high proportion of misdiagnoses, inappropriate use of medicines and exposure to potential drug toxicity, and wastage of economical resources. Although microscopic diagnosis using Giemsa stained thick smears has been the reference method for field malaria diagnosis for ~100 years, it has numerous limitations. These include the lack of personnel with appropriate or adequate training in slide preparation techniques, an overwhelming workload, poor microscope maintenance and the substandard quality of essential laboratory supplies(Wongsrichanalai et al., 2007). Rapid Diagnostic Tests (RDT) have become popular because they are simple to perform, easy to interpret, have high specificity and sensitivity, and do not require electricity or much capital investment. However, although RDTs are sufficiently effective to detect malaria parasites in symptomatic patients seeking medical attention, standardized protocols for Quality Assurance (QA), especially to confirm potentially large numbers of negative results are not yet available. Their usefulness for active case detection programs still needs validation. As an alternative, DNA-PCR techniques are highly sensitive and specific but require further development to be adapted for broad-based field work (Moonen et al., 2010). One of the most serious limitations for malaria control is the difficulty in detecting and treating low-density infections particularly in asymptomatic patients (Coleman et al., 2002a; Coleman et al., 2002b). As well, there is a need to define how to approach diagnosis and treatment in those countries moving toward malaria elimination, .e.g. El Salvador or Costa Rica where the incidence has decreased by more than 90% (SM2015, 2010).

Another critical issue regarding malaria parasites is the pattern of genetic diversity in parasite populations with low recombination rates and relatively high population differentiation as it occurs in LA. This issue is particularly relevant in the context of parasite drug resistance and the importance of polymorphisms for vaccine development.

Low levels of transmission characterize malaria in LA, and as a consequence, multiplicities of infection are also low, as consequence a low rates of decay of genetic linkage as relatively high indexes of differentiation between parasite populations. (Anderson et al., 2000)

These factors constitute a useful epidemiological tool to follow patterns of migration and the dissemination of genotypes of epidemiological relevance (e.g. drug resistance genotypes) in countries where the complex geography creates natural barriers (and a variety of optimal niches for a number of different vector species) that impede the spread of mosquito vectors and contribute to the isolation and genetic differentiation of *Plasmodium* populations. (Machado et al., 2004)

An understanding of the population genetics and the nature of *Plasmodium* genetic diversity in LA conditions is key to explain how selective forces, such as immune responses, vaccine trials, and drug administration policies, act upon parasite populations.

2.3 Limitations of the antimalarial drug arsenal

In order to face Malaria Multidrug Resistance (MDR), in 1998 WHO recommended the use of artemisinin based combination therapies (ACTs) (Bosman and Mendis, 2007; WHO, 1998), and since then, countries have been using these antimalarials with the rather common belief that artemisins are not vulnerable to resistance. In 2009, *P. falciparum* strains resistant to artemisinin were first described in the Thailand/Cambodia border (WHO, 2011a). There have been suggestions that there appears to be emergence of artemisinin tolerance or resistance in African countries and Thailand, apparently due to operational constraints, political instability or a lack of dedicated funds for their correct use (Dondorp et al., 2010). Therefore, WHO recently recommended increasing the length of the follow-up for some ACTs to 42 days as well as the use of PCR techniques to distinguish between recrudescence and reinfection. This recommendation has increased the cost of therapeutic efficacy studies (WHO, 2008, 2009). Currently there is growing concern about the catastrophic result that would produce the dissemination of parasite strains resistant to artemisinin.

Besides these constraints, there is an urgent need to develop new antimalarials with activity against parasite liver forms. Primaquine is the only treatment available today to eliminate *P. vivax* liver parasite stages, and it requires extended therapeutic regimens of 7 to 14 days to effectively eliminate liver parasite forms. While insufficient treatment may result in drug resistance, extended treatment may lead to lack of compliance which would also result in high risk of primaquine resistance. In addition, this antimalarial has serious toxicity problems in populations with glucose-6-phosphate dehydrogenase (G6PD) deficiency (Wells and Poll, 2010) and a systematic screening of this deficiency is not always performed. In addition, there is a general lack of information about G6PD prevalence in the LA region.

2.4 Health system gaps

Following policies established by the World Bank (World Bank, 1993) many countries of the LA region began processes of health reform, including decentralization. In some countries, decentralization was also applied in NMCPs and the transition process coincided with a decrease in malaria incidence reports, which may be attributed to deficiency in data collection and, therefore, to malaria underreporting. It has also been shown, that as an effect of decentralization, those municipalities with fewer trained and experienced health care

workers in malaria control programs had a greater number of malaria cases. Moreover, in small municipalities where malaria control programs are carried out by local hospitals, it was observed that when there was delay in salary payments the number of malaria cases decreased significantly, most likely because all cases were not being registered. Thus, the goal of health sector reform to increase access to health services for poor people has been operationally complicated (Carrasquilla, 2006; PAHO, 2006).

2.5 Education and socio-economical development

Despite educational programs, health promotion and disease prevention activities are not always successful because educational materials designed at central levels by officers of health ministries do not consistently take into account the perspective and beliefs of the affected target populations. In the case of malaria, which generally occurs in poor communities with low levels of education, popular knowledge and beliefs about the disease greatly influence the outcomes of any efforts on disease promotion, prevention, detection and treatment. Public health activities for malaria control need to include active community participation (Nieto et al., 1999), and educational materials designed according to cultural and ethnographic characteristics of the target population must be made available to increase knowledge and improve practices for malaria control (Carvajal et al., 2010). For example, the risk of malaria in an endemic area of the Colombian Pacific coast has been associated with the knowledge of the population about control measures; those with a knowledge of the disease and preventative practices (e.g., mosquito breeding site elimination) have significant lower risk (RR 0.49, 95%CI 0.26, 0.95) of malaria (Mendez et al., 2000). Educational interventions to increase knowledge and practices (e.g., treated bed nets, no self medication) decreased the risk of malaria (RR 0.58, 95% CI 0.39, 0.87) (Alvarado et al., 2006) and such programs generally are more cost effective than more traditional control programs lacking an educational component (Giron et al., 2006; Kroeger et al., 1996). Likewise, vector control programs are more effective with community involvement, and generally, better results are obtained from government-supported community-based programs (Ruebush and Godoy, 1992). Moreover, research suggests that the participation of women in malaria control programs is critical, indicating a need to better understand how women influence their local environment, family habits, hygiene, and prophylactic activities (Rodríguez et al., 2003).

The education and preparation of health care staff along with scientists in specialized topics are compromised when governments are forced to lay-off doctors and nurses to meet new civil services ceilings and reduce their costs on health in favor of productive sectors of the economy (Rodríguez et al., 2003; Stratton et al., 2008). Another reality is that malaria risk is determined by the prevailing economic and political systems. For example, during the 1980s the number of malaria cases increased in numerous endemic countries due to cuts in public spending on health and education due to need to free national resources for servicing national debts. Moreover, although donor investment for fighting malaria has increased in recent years, the funds available are clearly not sufficient to meet the financial needs of high-priority malaria control programs and for malaria elimination in high-burden countries. Moreover, there is no guarantee that current donors will be a long term sustainable source of financing for malaria elimination. Therefore, countries must explore innovative alternatives to self-finance malaria elimination programs (Feachem et al., 2010), including greater community participation.

2.6 Bio-medical research hope for the future

A major structural gap for malaria control and elimination programs is the lack of evidence-based field research and rigorous evaluation of the impact or the reasons for failure of the different control measures. Although there is growing enthusiasm about the possibility of malaria elimination in LA and other regions, NMCPs could certainly be doing better with

the currently available tools to control malaria. There is a growing consensus that elimination may not be possible with the current control tools and state of knowledge. In order to address the gaps in knowledge, during the last two years a comprehensive and multidisciplinary global research and development (R&D) agenda for malaria elimination and eventual global malaria eradication (malERA) has been defined with the participation of a group of prominent scientists, public health decision makers, control program managers and funders (Alonso et al., 2011). The most significant gaps for the LA region are centered on three key points. First, it is recognized that malaria caused by *P. falciparum* and *P. vivax* is a disease with different spectra in different target groups and epidemiological settings, and both species can be transmitted in LA by all described anopheline vector species, which have diverse breeding and feeding habits. However, there is a lack of fundamental baseline data on the bionomics and vector potential of primary and secondary vector species responsible for malaria parasite transmission in the region. Second, current malaria control and elimination programs face significant challenges in understanding the heterogeneity of transmission dynamics, including differences in parasites, vectors, and human social and environmental factors. Third, countries in this region face different combinations of problems such as insufficient financial, social and human resources, poorly performing health systems and lack of political will.

Moreover, despite the progress in malaria control in the LA region over the last several years, there is insufficient documentation of how changing demographic patterns of human populations are related to changes in vector population behavior, their parasite transmission potential, and their adaptations to avoid the lethal effects of vector control measures. Better malaria control and elimination can only be achieved by better understanding the complex relationships between malaria and anthropogenic changes such as intense deforestation, illegal agriculture, political instability, and possibly climate change (Feachem et al., 2009; Vittor et al., 2009; WHO, 2006).

2.6 Understanding malaria immunity and development of malaria vaccines

Another significant gap for malaria elimination is the lack of a malaria vaccine that could complement all current measures, particularly during advanced malaria elimination phases when the cost effectiveness of other strategies may decrease (Marsh, 2010). Repeated exposure to *Plasmodium* in malaria endemic areas eventually leads to significant degrees of clinical immunity (Artavanis-Tsakonas et al., 2003). In areas of intense transmission particularly in Africa, *P. falciparum* induces significant mortality in children but adult individuals are able to develop an almost normal daily routine, even when they are harboring clinically silent infections (Schofield and Mueller, 2006). However, the mechanisms of this immunity are not yet deciphered and its parasite targets have not been completely identified, although they would be most valuable for the development of vaccines that protect from disease and/or block parasite transmission to mosquito and therefore its further dissemination. Identifying the targets of these antibodies or mosquito functionally relevant components susceptible to transmission blocking would be equally valuable as a basis for developing malaria vaccines (Arevalo-Herrera et al., 2010). Despite these limitations, progress has been achieved in identifying some valuable parasite components that are targets of immune responses and therefore likely good candidates for vaccine development (Arevalo-Herrera et al., 2010; Good and Doolan, 2010). Unfortunately, efforts have been almost exclusively concentrated in developing vaccines that target *P. falciparum* (Crompton et al., 2010; Moorthy et al., 2009), therefore vaccine candidates such as the RTS-S directed to block the *P. falciparum* pre-erythrocytic development, are currently under advanced phase III clinical testing in Africa (Cohen et al., 2010a). However, such a vaccine is likely to have very limited effects in the LA region. First, because *P. vivax* dominates, *P. falciparum* in LA accounts for <30% of cases in most areas and even <10% in numerous areas. Second,

as countries in the LA region are challenged with the need for elimination, there is a need for vaccines that block transmission; the value of RTS-S appears to be basically preventing clinical complications in African children. Since severe and complicated disease is minimal in LA, vaccinated communities would have little benefit from vaccination. Indeed, use of PfRTS-S in LA might create false expectations in the communities and would spoil further efforts to engage the communities in the deployment of much needed *P. vivax* vaccines.

3. Prospects for malaria elimination

3.1 Recent malaria control initiatives toward elimination

The Roll Back Malaria program was launched in 1998 by the WHO, as a strategy to reduce severe malaria morbidity and mortality particularly in children less than five years old and in adults. The RBM agenda, involves programmatic components that must proceed simultaneously and suitably to prevent failures: 1) Early diagnosis and prompt treatment, 2) Strengthening and expansion of peripheral diagnostic Centers, 3) Enhancing passive case detection at all rural health out lets, 4) Ensuring the availability of adequate and trained staff and sufficient Anti Malarial Drugs, 5) Effective monitoring, supervision and evaluation, and 6) Capacity building by strengthening training and research components (Roll Back Malaria, 2008).

With significant support from multilateral sources like the GFATM and ORAS, during the last six years Colombia, Ecuador, Peru and Venezuela implemented the PAMAFRO project to reduce malaria in the country borders. A total of 23 Border States (719 municipalities and >6000 communities) have worked towards the goal by 2010 of decreasing malaria incidence (Annual Parasitical Index) by 50% and overall mortality by 70%. Although a final assessment of the impact of this project was to achieve an API <10 in all involved countries, reports for 2008 showed that Peru was the only country to achieved the goal, whereas Colombia, Ecuador and Venezuela only reached 40 – 85% of the planned achievement (PAMAFRO, 2009). This project has been geographically complemented by the RAVREDA/AMI program financially supported by several funding agencies for the surveillance of anti-malarial drug resistance in eight countries of the Amazon region. These countries have validated and adopted operational solutions to critical aspects of malaria surveillance and control that have contributed to a significant reduction in the API in these countries. Unfortunately, these programs did not include adequate evaluation strategies and supporting research components. Therefore, documentation of the real impact and constraints are unfortunately lacking. The RAVREDA/AMI program is currently being extended to the Mesoamerican region.

Another important malaria intervention is currently being initiated in the frame of the Mesoamerican Health Initiative 2015 (SM2015, 2010) which is aimed at closing or narrowing down several other critical health problems. This five year initiative is co-sponsored by the Bill and Melinda Gates Foundation (BMGF), the Instituto Carlos Slim de la Salud (ICSS), the Spanish Agency for International Cooperation (AECID), the Inter American Development Bank (IADB) and the Ministries of Health (MOH) of Mesoamerican countries. The region is targeting vector-borne diseases (SM2015, 2010). The malaria operational strategy of SM2015 is planned as a proof-of-concept to evaluate whether malaria transmission could be eliminated in selected areas of the region, so as to provide evidence-based interventions.

3.2 Overall CLAIM plan for inter-disciplinary and multi-country approaches

The Center was originally created as a consortium of multiple public and private research centers from, Colombia, Guatemala, Panama and Peru in the first phase of the program with activities in 21 sentinel malaria endemic sites. However, it envisages in a second phase,

extending its activities to other countries of the region such as the Dominican Republic, Ecuador, Haiti and Honduras and most likely other neighbor countries will join the CLAIM project in further phases. (Figure 1)

Unless a comprehensive and integrated approach is used for malaria control/elimination, the risk of failure is great. Therefore, our strategy for CLAIM consists of articulating and helping to address in a coordinated fashion different disciplinary sectors of malaria control as repeatedly recommended by other malaria programs (Roll Back Malaria, 2008; Shretta et al., 2007; TDR/WHO, 2009) based on its close interaction with ongoing control programs that includes: 1) Improved diagnosis, 2) Drug efficacy and drug resistance assessment, 3) Vector control, 4) Modeling, 5) Monitoring, evaluation and surveillance, 6) Vaccines development, 7) Integration strategies, and 8) Health systems and operational research.

3.3 Specific projects aimed at malaria elimination in Latin America

3.3.1 Epidemiology of malaria transmission in low to moderate settings of LA

—The diversity of the ecology and parasite populations in the areas of influence of CLAIM will be related to the epidemiology and malaria clinical findings in order to establish a scientific framework that may support the development of new intervention strategies in LA. CLAIM has established a network of sentinel sites integrating bio-geographic criteria (vector and ecological conditions) and epidemiological information is being established. The sentinel sites will provide baseline information on malaria ecology and epidemiology with the goal of characterizing parasite and vector populations resilient to control interventions. Such a network will support current efforts directed to develop population models to quantify disease dynamics and malaria risk-maps to support the elimination activities developed by the MOH.

CLAIM will specifically study:

1. The epidemiology of seasonal malaria and its relationship with parasite population diversity.
2. The environmental, social, and other types of risk factors associated with malaria transmission in non-Amazonian areas of LA countries.

The proposed aims are directed to determine the real prevalence and incidence of malaria by considering both symptomatic and asymptomatic individuals living in seasonal areas in LA. A total of 21 sentinel malaria endemic sites will be included and studies will be carried out in three phases: 1) A census of the sentinel sites population using a demographic questionnaire and houses coordinates using a GPS system, 2) Malaria diagnosis in the selected sentinels sites including random sampling to identify asymptomatic gametocyte carriers, 3) These studies will also assess the use of anti-malarial drugs, adherence to treatment protocols, self-medication and prophylaxis. Additionally, parasite MDR, the nature of resistance genotypes, and the genetic diversity of parasite populations will be assessed and 4) Clinical and parasitological follow-up of asymptomatic individuals in selected areas.

CLAIM generates an exceptional opportunity to study and define the dynamics of malaria epidemiology taking advantage of the availability and feasibility of new sequencing methods that currently allow studying *P. falciparum* genetic variation at the genome level and knowing in high detail the type and pattern of genetic variation in *Plasmodium* populations in LA. This is important as a way to determine the extent of genetic differentiation between populations, establish patterns of human migration and their contribution to the dissemination of drug resistance genotypes as well as the magnitude of genetic exchanges between populations. This type of approach can shed light on the contribution of specific

types of mutations (deletions, duplications, rearrangements, SNPs) and their effect on fitness on *Plasmodium* populations that are transmitted under the conditions of LA.

Moreover, this information will constitute an important baseline of genetic diversity data against which the effects of vaccine trials can be evaluated in the field, establish drug resistance dissemination patterns and, in addition to environmental and human demographic data, can be particularly useful for the epidemiological modeling of malaria transmission under different circumstances.

CLAIM would also generate a unique opportunity to understand the epidemiological dynamics of acquired immunity and its relationship with *P. vivax* antigenic diversity. We are proposing to apply the power of next-generation sequencing to investigate antigenic sequence variation within this clinical sample set to an unprecedented depth. Through multiplexed sequencing of PCR-amplified antigenic loci, we will characterize the genetic profile of each sample at selected loci most likely engendering acquired immunity. By longitudinal follow up we will assess relative changes in genotypes and multiplicity of subsequent infections in individuals, and define the infection burden required to build up clinical immunity. We will also identify genetic loci that display distinct antigenic variants in subsequent infections and therefore may be associated with protective immune responses.

3.3.2 Vector biology research and integrated vector management for malaria control—The CLAIM research agenda will address major gaps in understanding the ecology, behavior, vector potential, and control of *Anopheles* malaria vectors present in this region, to guide the development and implementation of more effective IVM strategies. Studies will be based on preliminary data and experience in each country. Successful malaria control will be focused on effective control of *Anopheles* mosquitoes confirmed to be malaria vectors in each country. We will: 1) Investigate the ecology, behavior, and malaria parasite transmission potential of malaria vector species to identify key factors that would facilitate more effective targeted vector control, 2) Determine how known and suspected malaria vector species from each country in the CLAIM network differ in their innate vector competence for *P. falciparum* and *P. vivax*, 3) Assess the efficacy of current vector control operations of NMCPs and conduct multi-country field trials of new vector control products that may strengthen capacities of NMCPs to implement effective IVM strategies for vector control. Based on this approach, IVM in CLAIM would include the use of treated nets, indoor residual spray and mosquito traps, control and management of breeding sites, biological control, improvement of housing quality, and possibly the use of new repellents. It would also include better diagnosis, opportunities which altogether would allow a more rational decision-making process and optimal use of resources for vector control.

In partnership with NMCPs, CLAIM will demonstrate the translational value of research outcomes for improving vector control in ecologically diverse areas of the non-Amazonian region through an interactive process of strengthening and evaluating IVM components of NMCPs.

3.3.3 Studies on malaria immunopathogenesis in Latin America—Due to the limited information on the most frequent malaria clinical manifestations and on their overall impact in the affected communities in LA, CLAIM activities will focus on the study of the prevalence, clinical spectrum and pathophysiology of malaria infection and its association with parasite and human host factors. Like in other regions of low endemicity and easy access to health services, severe and complicated malaria cases are rare, however, the prevalence of clinical manifestations such as anemia or gestational malaria are critically unknown. Moreover, few studies have been carried out in LA looking at the impact of

malaria infection in pregnant women, and on neonatal health and child development (Gonzalez et al., 2005; Pineros-Jimenez et al., 2008; Rodriguez-Morales et al., 2006). The CLAIM activities will be conducted through the following specific aims: 1) Establishment of the clinical profiles of malaria in different epidemiological settings and their association with the parasite and host immunological status, 2) Assessing the prevalence of malaria mixed infections and their influence in the clinical outcomes of the disease, 3) Determining the prevalence of hematological manifestations related to malaria infection and their association with concomitant immune status nutritional factors, and helminthes co-infections, and 4) Assessing the prevalence of placental malaria and its impact on neonatal health and child development.

Malaria and pregnancy studies will be built up on an ongoing multi-site center study sponsored by the European Community (Pregvax/CRESIB personal communication) aimed to determine the burden of *P. vivax* infection in pregnant women. Parasitological, hematological, and immunological evaluations and concomitant non-malaria infections will be evaluated. These studies will not only provide a better understanding of the immunopathogenesis of malaria in LA but will also generate useful information for malaria case management, control strategies including anti-malaria therapy, future use of malaria vaccines, and points of intervention to improve developmental outcomes of children.

3.3.4 Current perspectives for malaria vaccines and their use in elimination programs in LA—Another valuable tool for malaria elimination/eradication programs would be a polyvalent multi-species and multi-stage malaria vaccine. During the last two decades, significant progress has been made in the assessment of a first vaccine candidate directed to prevent infection by *P. falciparum* sporozoites (Crompton et al., 2010; Plowe et al., 2009). The first generation sporozoite-based *P. falciparum* RTS-S vaccine currently being tested in Phase III studies in Africa (Cohen et al., 2010a), and although it has formerly shown some incomplete protective effect against infection and clinical complications in Africa (Cohen et al., 2010b), it is opening the path for a faster development of other vaccine against both *P. falciparum* and *P. vivax* (Sacarlal et al., 2009).

Due to the great epidemiological importance of *P. vivax* in LA, CLAIM will also focus efforts on: 1) A comprehensive study on the immune responses to *P. vivax* antigen arrays, 2) Studies directed at understanding how clinical immunity as well as transmission blocking immunity develops in endemic communities, 3) The selection and establishment of field sites for Phase II and Phase III vaccine studies, which will provide support to current efforts being made in Colombia on the identification and clinical development of a *P. vivax* malaria vaccine (Arevalo-Herrera et al., 2010; Arevalo-Herrera and Herrera, 2001; Herrera et al., 2007; Herrera et al., 2011). The simultaneous transmission of both parasite species in LA will facilitate the evaluation of vaccines to both, *P. falciparum* and *P. vivax* as well as their combination.

3.4 Interrelationships of the specific projects and cooperative activities with other projects and organizations

The CLAIM has established an interdisciplinary research team composed of a broad group of scientists from multiple public and private research centers from CLAIM's partner countries (Colombia, Guatemala, Panama and Peru) including centers and organizations depending from, or associated to the MOH from all participant countries, as well as consultants/collaborators from the Pan American Health Organization and/or the US Centers for Disease Control and Prevention. It also involves a group of prominent and experienced scientists from other endemic countries like Brazil and Ecuador, as well as from the United States (USA), Europe (EU) and Africa. CLAIM profits from the valuable experience in

malaria surveillance and control, anti-malarial drug resistance, sero-epidemiology and molecular epidemiology, vector bionomics, public health, and social determinants of the interdisciplinary group and is currently making efforts to closely articulate its research agenda to malaria control/elimination activities initiated by the governments of the region.

In close partnership with the NMCPs in each country, this research will provide a strong scientific basis for strengthening national surveillance programs, targeting and intensifying integrated malaria control operations in focal areas of significant malaria transmission, and improving evidence-based evaluations of NMCP operations. Overall, these investigations will address the interaction between epidemiological endpoints and disease ecology while translating into NMCP concepts and tools derived from evolutionary biology, ecology, sero-epidemiology, and social epidemiology. As a proof of principle, CLAIM is currently joining efforts with a large malaria control initiative directed to intensify malaria control in the five departments with highest malaria transmission (Antioquia, Chocó, Cordoba, and Valle del Cauca). The CLAIM will contribute its research component to this five-year project recently initiated by the Colombian MOH with support from the GFATM: The articulation of this GFATM project titled, INTEMAL, will provide valuable experience to be transferred to other countries of the region. Moreover, an integrative approach is also being established with the SM2015 as at least three of the countries covered by that initiative are originally included as CLAIM partners.

3.6 Data management plan

Data produced as a result of the research activities undertaken by the CLAIM is heterogeneous with respect to origin, format, and spatio-temporal scale. The data management plan for this operation consists of a federation of several information systems, and the procedures to enforce its correct use. There are several challenges in dealing with this type of scenario (Kashyap et al., 2006; Wright and Sittig, 2008), such as: 1) Ethical practices when dealing with personal information, 2) Quality control of data capture and annotation, 3) The need of structured procedures, such as data standards, for collecting and managing data, 4) Availability, e.g. the proportion of time a system is in a functioning condition, 5) Scalability, e.g. the ability of a system to handle growing amounts of data and use, 6) Maintainability, e.g. the ability of a system to make future maintenance and adaptability easier, 7) Appropriate IT-security procedures that ensures correct data access only by appropriate parties. Correct data capture, organization, and processing make it productive beyond the context of their collection when a controlled flow of data is channeled though the appropriate devices (Bauer, 2008).

There are a number of traditional and non-traditional analytical tools that can be used to extract information from the data. Ecological models can produce significant insights into the ways in which density and distribution of human populations affect *P. falciparum* and *P. vivax* in the zone studied and vice versa. Beyond the mathematical significance and challenge of constructing such a modeling regime lays the necessity of connecting the mathematical structure to test cases in such a way that prediction and prevention become meaningful possibilities. Such an enterprise requires expertise to: 1) Construct a mathematical framework via complex systems theory capable of conceptualizing simultaneously the aims of CLAIM, 2) bridge the divide between mathematical theory on the one hand and empirical data on the other by means of careful parameterization of analytic models via simulation, GIS mapping, advanced sensing techniques, spatial statistics, and biostatistics, 3) bridge models with field practice.

Spatial models driven by epidemic and environmental data have shown increasing promise to reduce the burden of infectious diseases (Riley, 2007). In particular, distance-transmission modeling may employ buffers and a distance decay functions based on vector and case data

where the spatial coordinates are known. Such distance-transmission modeling was used successfully to predict the effects of different culling strategies based on infection status (infected or susceptible), species compositions and farm size during the 2001 foot-and-mouth epidemic in the UK, for example (Keeling et al., 2001). Recent studies that utilize spatial data on anopheline vectors in concert with environmental data have successfully identified vector habitats with a high probability of supporting transmission at a variety of scales (Sinka et al., 2010; Zeilhofer et al., 2007). The resultant maps that depict probabilities of vector occurrence can significantly streamline implementation of IVM strategies by targeting priority regions and habitats that have high risk for malaria transmission.

As anthropogenically induced environmental changes (e.g., deforestation and climate change), progress into the 21st century other modeling tools originating from ecology hold significant promise to predict future distributions of malaria parasites and vectors. For example, ecological niche models (ENMs) have been used to predict future distribution of different members of the medically important *An. minimus* complex found in Southeast Asia (Foley et al., 2008). Because EMNs are driven largely by information on vector presence data, climate, land cover and landscape properties, projected changes in the independent covariates can provide powerful inferences into likely future distribution of *Plasmodium* and *Anopheline* species. Global warming, in particular, is likely to counteract to some extent the successful elimination measures that have resulted in a marked decline in malaria incidence worldwide (Gething et al., 2010). Moreover, the Intergovernmental Panel on Climate Change (IPCC) syntheses suggest warming of 3–4°C throughout many parts of the Americas by 2099 (Parry and Intergovernmental Panel on Climate Change. Working Group II., 2007). In this light, ENMs could play a vital role in predicting future malaria risk maps based on current and projected environmental co-variants. However, despite the potential of ENMs to map malaria risk, a survey of the malaria risk-mapping literature using the ISI Web of Science databases suggests that ENMs have rarely been employed to model vector or pathogen distributions in the Central or South American contexts (Levine et al., 2004).

Data and information flow is facilitated at CLAIM by the use of tools such as MS Sharepoint (document repository), Elluminate (webinar management), and OpenClinica (open source information system for clinical form management). A website has been established at CLAIM (www.caucaseco.org) that serves as the centralized gateway for data management. This web site provides information in real time to all CLAIM members, allowing controlled access to information to all parties involved.

3.7 Overall CLAIM vision and perspectives

In conclusion, CLAIM will closely interact with the NMCPs of the associated countries as well as with major control/elimination projects being developed in the region with multilateral funding in order to update or set the baseline of important variables such as: 1) Age-specific attack rates, 2) asymptomatic parasitemia rates, 3) distribution of *P. falciparum vs P. vivax* in space and time, among others.

The formidable array of competences covered jointly by the interdisciplinary research groups of CLAIM and the experience staff of the NMCPs is likely to significantly contribute to the continuous decrease in malaria incidence in the regions, to bring several countries into eliminations phases, and, hopefully, the certification as malaria free of, some of the currently most advanced countries in the region. The articulation of efforts being made in the region among the BMGF, CARSO, PAHO, CDC, IDRC, the Global Fund, the local governments and communities, and several others with this initiative from NIAID/NIH, is likely to become a model for other malaria endemic regions.

Acknowledgments

This work has been supported by the US National Institute of Allergy and Infectious Diseases (NIAID/NIH) (Grant number U19AI089702).

References

Alonso PL, Brown G, Herrera-Arevalo M, Binka F, Chitnis C, Collins F, Doumbo O, Hall L, Levine M, Mendis K, Newman RD, Plowe C, Rodriguez MH, Sinden R, Slutsker L, Tanner M. A research agenda to underpin malaria erradication. PLoS Med. 2011; 8:e1000406. [PubMed: 21311579]

Alvarado B, Alzate A, Mateus J, Carvajal R. Efectos de una intervención educativa y de participación comunitaria en el control de la malaria en Buenaventura, Colombia. Biomédica. 2006; 26:366–378.

Alvarez G, Pineros JG, Tobon A, Rios A, Maestre A, Blair S, Carmona-Fonseca J. Efficacy of three chloroquine-primaquine regimens for treatment of Plasmodium vivax malaria in Colombia. Am J Trop Med Hyg. 2006; 75:605–609. [PubMed: 17038680]

Anderson, TJ.; Haubold, B.; Williams, JT.; Estrada-Franco, JG.; Richardson, L.; Mollinedo, R.; Bockarie, M.; Mokili, J.; Mharakurwa, S.; French, N.; Whitworth, J.; Velez, ID.; Brockman, AH.; Nosten, F.; Ferreira, MU.; Day, KP. Microsatellite markers reveal a spectrum of population structures in the malaria parasite Plasmodium falciparum; Molecular Biology and Evolution. 2000. p. 1467-1482.%U http://www.ncbi.nlm.nih.gov/pubmed/11018154

Arevalo-Herrera M, Chitnis C, Herrera S. Current status of Plasmodium vivax vaccine. Hum Vaccin. 2010; 6:124–132. [PubMed: 20009526]

Arevalo-Herrera M, Herrera S. Plasmodium vivax malaria vaccine development. Mol Immunol. 2001; 38:443–455. [PubMed: 11741694]

Artavanis-Tsakonas K, Tongren JE, Riley EM. The war between the malaria parasite and the immune system: immunity, immunoregulation and immunopathology. Clin Exp Immunol. 2003; 133:145–152. [PubMed: 12869017]

Bacon DJ, McCollum AM, Griffing SM, Salas C, Soberon V, Santolalla M, Haley R, Tsukayama P, Lucas C, Escalante AA, Udhayakumar V. Dynamics of malaria drug resistance patterns in the Amazon basin region following changes in Peruvian national treatment policy for uncomplicated malaria. Antimicrob Agents Chemother. 2009; 53:2042–2051. [PubMed: 19258269]

Bauer S. Mining data, gathering variables and recombining information: the flexible architecture of epidemiological studies. Stud Hist Philos Biol Biomed Sci. 2008; 39:415–428. [PubMed: 19026973]

Bosman A, Mendis KN. A major transition in malaria treatment: the adoption and deployment of artemisinin-based combination therapies. Am J Trop Med Hyg. 2007; 77:193–197. [PubMed: 18165492]

Carrasquilla, G. Descentralización, reforma sectorial y control de la malaria en Colombia. In: Yadón, Z.; Grtler, R.; Tobar, F.; Medici, A., editors. Desce ntralización y gestión del control de las enfermedades transmisibles en América Latina. PAHO; Buenos Aires: 2006. p. 320

Carvajal R, Mosquera J, Carrasquilla G. The world of malaria: a health educational experience in the Colombian Pacific coast. Colomb Med. 2010; 41:240–247.

Cohen J, Benns S, Vekemans J, Leach A. The malaria vaccine candidate RTS, S/AS is in phase III clinical trials. Ann Pharm Fr. 2010a; 68:370–379. [PubMed: 21073995]

Cohen J, Nussenzweig V, Nussenzweig R, Vekemans J, Leach A. From the circumsporozoite protein to the RTS, S/AS candidate vaccine. Hum Vaccin. 2010b; 6:90–96. [PubMed: 19806009]

Coleman RE, Maneechai N, Ponlawat A, Kumpitak C, Rachapaew N, Miller RS, Sattabongkot J. Short report: Failure of the OptiMAL rapid malaria test as a tool for the detection of asymptomatic malaria in an area of Thailand endemic for Plasmodium falciparum and P. vivax. Am J Trop Med Hyg. 2002a; 67:563–565. [PubMed: 12518844]

Coleman RE, Maneechai N, Rachapaew N, Kumpitak C, Soyseng V, Miller RS, Thimasarn K, Sattabongkot J. Field evaluation of the ICT Malaria Pf/Pv immunochromatographic test for the detection of asymptomatic malaria in a Plasmodium falciparum/vivax endemic area in Thailand. Am J Trop Med Hyg. 2002b; 66:379–383. [PubMed: 12164291]

Corredor V, Murillo C, Echeverry DF, Benavides J, Pearce RJ, Roper C, Guerra AP, Osorio L. Origin and dissemination across the Colombian Andes mountain range of sulfadoxine-pyrimethamine resistance in Plasmodium falciparum. Antimicrob Agents Chemother. 2010; 54:3121–3125. [PubMed: 20498318]

Crompton PD, Pierce SK, Miller LH. Advances and challenges in malaria vaccine development. J Clin Invest. 2010; 120:4168–4178. [PubMed: 21123952]

Dondorp AM, Yeung S, White L, Nguon C, Day NP, Socheat D, von Seidlein L. Artemisinin resistance: current status and scenarios for containment. Nat Rev Microbiol. 2010; 8:272–280. [PubMed: 20208550]

Feachem RG, Phillips AA, Targett GA, Snow RW. Call to action: priorities for malaria elimination. Lancet. 2010; 376:1517–1521. [PubMed: 21035844]

Feachem, RGA.; Phillips, AA.; Targett, GA. Shrinking the Malaria Map: A Prospectus on Malaria Elimination. The Global Health Group; San Francisco: 2009.

Foley DH, Rueda LM, Peterson AT, Wilkerson RC. Potential distribution of two species in the medically important Anopheles minimus complex (Diptera: Culicidae). J Med Entomol. 2008; 45:852–860. [PubMed: 18826026]

Gabaldon A. Malaria eradication in Venezuela: doctrine, practice, and achievements after twenty years. Am J Trop Med Hyg. 1983; 32:203–211. [PubMed: 6340536]

Gabaldon A, Berti LA, Guerrero L, Garcia Martin G. Eradication of malaria in Venezuela. Program, progress and present status. Rev Sanid Asist Soc Suppl. 1961; 3:290–336.

Gething PW, Smith DL, Patil AP, Tatem AJ, Snow RW, Hay SI. Climate change and the global malaria recession. Nature. 2010; 465:342–345. [PubMed: 20485434]

Giron SL, Mateus JC, Castellar CE. Cost-effectiveness analysis of two strategies for malaria control in the urban area of Buenaventura, Colombia. Biomedica. 2006; 26:379–386. [PubMed: 17176001]

Gonzalez L, Ochoa J, Franco L, Arroyave M, Restrepo E, Blair S, Maestre A. Nosocomial Plasmodium falciparum infections confirmed by molecular typing in Medellin, Colombia. Malar J. 2005; 4:9. [PubMed: 15703072]

Good MF, Doolan DL. Malaria vaccine design: immunological considerations. Immunity. 2010; 33:555–566. [PubMed: 21029965]

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. The international limits and population at risk of Plasmodium vivax transmission in 2009. PLoS Negl Trop Dis. 2010; 4:e774. [PubMed: 20689816]

Herrera S, Corradin G, Arevalo-Herrera M. An update on the search for a Plasmodium vivax vaccine. Trends Parasitol. 2007; 23:122–128. [PubMed: 17258937]

Herrera S, Fernández O, Vera O, Cárdenas W, Ramírez O, Palacios R, Chen-Mok M, Corradin G, Arévalo-Herrera M. Phase I safety and immunogenicity trial of Plasmodium vivax CS derived long synthetic peptides adjuvanted with Montanide ISA 720 or Montanide ISA 51. The American Journal of Tropical Medicine and Hygiene. 2011; 84:12–20. [PubMed: 21292873]

Kashyap V, Morales A, Hongsermeier T. On implementing clinical decision support: achieving scalability and maintainability by combining business rules and ontologies. AMIA Annu Symp Proc. 2006:414–418. [PubMed: 17238374]

Keeling MJ, Woolhouse ME, Shaw DJ, Matthews L, Chase-Topping M, Haydon DT, Cornell SJ, Kappey J, Wilesmith J, Grenfell BT. Dynamics of the 2001 UK foot and mouth epidemic: stochastic dispersal in a heterogeneous landscape. Science. 2001; 294:813–817. [PubMed: 11679661]

Kroeger A, Meyer R, Mancheno M, Gonzalez M. Health education for community-based malaria control: an intervention study in Ecuador, Colombia and Nicaragua. Trop Med Int Health. 1996; 1:836–846. [PubMed: 8980598]

Levine, RS.; Peterson, AT.; Benedict, MQ. Geographic and ecologic distributions of the Anopheles gambiae complex predicted using a genetic algorithm; The American Journal of Tropical Medicine and Hygiene. 2004. p. 105-109.%U http://www.ncbi.nlm.nih.gov/pubmed/14993618

Lopez Y, Arroyave A, Salazar A. Evaluacion de la resistencia in vivo a los medicamentos antimalaricos. El Bagre, Antonia. Rev Epidemiol Antioquia. 1999; 24:181–194.

Machado RL, Povoa MM, Calvosa VS, Ferreira MU, Rossit AR, dos Santos EJ, Conway DJ. Genetic structure of Plasmodium falciparum populations in the Brazilian Amazon region. J Infect Dis. 2004; 190:1547–1555. [PubMed: 15478058]

Marsh K. Research priorities for malaria elimination. Lancet. 2010; 376:1626–1627. [PubMed: 21035843]

Mendez F, Carrasquilla G, Munoz A. Risk factors associated with malaria infection in an urban setting. Trans R Soc Trop Med Hyg. 2000; 94:367–371. [PubMed: 11127234]

Moonen B, Cohen JM, Snow RW, Slutsker L, Drakeley C, Smith DL, Abeyasinghe RR, Rodriguez MH, Maharaj R, Tanner M, Targett G. Operational strategies to achieve and maintain malaria elimination. Lancet. 2010; 376:1592–1603. [PubMed: 21035841]

Moorthy VS, Reed Z, Smith PG. MALVAC 2008: Measures of efficacy of malaria vaccines in phase 2b and phase 3 trials--scientific, regulatory and public health perspectives. Vaccine. 2009; 27:624–628. [PubMed: 19061928]

Nieto T, Mendez F, Carrasquilla G. Knowledge, beliefs and practices relevant for malaria control in an endemic urban area of the Colombian Pacific. Soc Sci Med. 1999; 49:601–609. [PubMed: 10452416]

PAHO. Descentralización y gestión del control de las enfermedades transmisibles en América Latina. Buenos Aires: 2006.

PAHO, WHO. Integrated vector management: a comprehensive response to vector-borne diseases, 48th directing council 60th session of the regional committee. WHO; Washington, D.C.: 2008.

PAMAFRO. Reporte de Resultados Fase II. 2009.

Parry, ML. Intergovernmental Panel on Climate Change. Climate change 2007: impacts, adaptation and vulnerability. Published for the Intergovernmental Panel on Climate Change [by] Cambridge University Press; Cambridge: 2007. Working Group II.

Pineros-Jimenez JG, Arboleda M, Jaramillo JC, Blair S. Report of five cases of severe neonatal Plasmodium vivax malaria in Uraba, Colombia. Biomedica. 2008; 28:471–479. [PubMed: 19462553]

Plowe CV, Alonso P, Hoffman SL. The potential role of vaccines in the elimination of falciparum malaria and the eventual eradication of malaria. J Infect Dis. 2009; 200:1646–1649. [PubMed: 19877844]

Riley S. Large-scale spatial-transmission models of infectious disease. Science. 2007; 316:1298–1301. [PubMed: 17540894]

Roberts DR, Andre RG. Insecticide resistance issues in vector-borne disease control. Am J Trop Med Hyg. 1994; 50:21–34. [PubMed: 8024082]

Rodriguez-Morales AJ, Sanchez E, Vargas M, Piccolo C, Colina R, Arria M, Franco-Paredes C. Pregnancy outcomes associated with Plasmodium vivax malaria in northeastern Venezuela. Am J Trop Med Hyg. 2006; 74:755–757. [PubMed: 16687675]

Rodríguez A, Penilla R, Rodríguez H, Rodríguez M, Hemingway J, Betanzos A, Hernández-Avila J. Knowledge and beliefs about malaria transmission and practices for vector control in Southern Mexico. Salud Pblica de México. 2003; 45:7.

Roll Back Malaria. Organization, W.H. Roll Back Malaria Partnership: A Global Malaria Action Programme. Geneva: 2008.

Rubio-Palis Y, Zimmerman RH. Ecoregional classification of malaria vectors in the neotropics. J Med Entomol. 1997; 34:499–510. [PubMed: 9379453]

Ruebush TK 2nd, Godoy HA. Community participation in malaria surveillance and treatment. I. The Volunteer Collaborator Network of Guatemala. Am J Trop Med Hyg. 1992; 46:248–260. [PubMed: 1558264]

Sacarlal J, Aide P, Aponte JJ, Renom M, Leach A, Mandomando I, Lievens M, Bassat Q, Lafuente S, Macete E, Vekemans J, Guinovart C, Sigauque B, Sillman M, Milman J, Dubois MC, Demoitie MA, Thonnard J, Menendez C, Ballou WR, Cohen J, Alonso PL. Long-term safety and efficacy of the RTS, S/AS02A malaria vaccine in Mozambican children. J Infect Dis. 2009; 200:329–336. [PubMed: 19569964]

Schofield L, Mueller I. Clinical immunity to malaria. Curr Mol Med. 2006; 6:205–221. [PubMed: 16515511]

Shretta, R.; Adegoke, C.; Segbor, P. Global funds grands for malaria: lessons learned in the implementation of ACT poilices in Ghana. 2007.

Sinka ME, Rubio-Palis Y, Manguin S, Patil AP, Temperley WH, Gething PW, Van Boeckel T, Kabaria CW, Harbach RE, Hay SI. The dominant Anopheles vectors of human malaria in the Americas: occurrence data, distribution maps and bionomic precis. Parasit Vectors. 2010; 3:72. [PubMed: 20712879]

SM2015. Salud Mesoamerica 2015. 2010.

Stratton L, O'Neill MS, Kruk ME, Bell ML. The persistent problem of malaria: addressing the fundamental causes of a global killer. Soc Sci Med. 2008; 67:854–862. [PubMed: 18583009]

TDR/WHO. The Malaria Eradication Research Agenda Initiative. 2009.

Vittor AY, Pan W, Gilman RH, Tielsch J, Glass G, Shields T, Sanchez-Lozano W, Pinedo VV, Salas-Cobos E, Flores S, Patz JA. Linking deforestation to malaria in the Amazon: characterization of the breeding habitat of the principal malaria vector, Anopheles darlingi. Am J Trop Med Hyg. 2009; 81:5–12. [PubMed: 19556558]

Wells TN, Poll EM. When is enough enough? The need for a robust pipeline of high-quality antimalarials. Discov Med. 2010; 9:389–398. [PubMed: 20515606]

WHO. The use of artemisinin and its derivatives as anti-malarial drugs. 1998.

WHO. World Malaria Report 2005. World Health Organization, Roll Back Malaria, UNICEF; Geneva: 2005. p. 294

WHO. Malaria vector control and personal protection. World Health Organ Tech Rep Ser. 2006; 936:1–62. back cover. [PubMed: 16623084]

WHO. World Malaria report 2008. World Health Organization; Geneve: 2008. p. 215

WHO. World Malaria report 2009. World Health Organization; Geneve: 2009. p. 40

WHO. Global report on antimalaria drug efficacy and drug resistance: 2000 – 2010. World Health Organization; Geneva: 2010. p. 124

WHO. Global plan for artemisinin resistance containment (GPARC). 2011a.

WHO. Handbook on Integrated Vector Managment (IVM). World Health Organization; 2011b. In press

Wongsrichanalai C, Barcus MJ, Muth S, Sutamihardja A, Wernsdorfer WH. A review of malaria diagnostic tools: microscopy and rapid diagnostic test (RDT). Am J Trop Med Hyg. 2007; 77:119–127. [PubMed: 18165483]

World Bank, S. World Development Report 1993 Investing in Health. Oxford University Press, Incorporated %@ 9780195208900; New York: 1993.

Wright A, Sittig DF. SANDS: a service-oriented architecture for clinical decision support in a National Health Information Network. J Biomed Inform. 2008; 41:962–981. [PubMed: 18434256]

Zeilhofer P, dos Santos ES, Ribeiro AL, Miyazaki RD, dos Santos MA. Habitat suitability mapping of Anopheles darlingi in the surroundings of the Manso hydropower plant reservoir, Mato Grosso, Central Brazil. Int J Health Geogr. 2007; 6:7. [PubMed: 17343728]

Research Highlights

Important key gaps in malaria research in Latin America

Prospects for malaria elimination

Overall CLAIM plan for control/elimination

FIGURE 1.
CLAIM participating countries and selected study locations, in which a total of 21 sentinel sites will be studied.