Malaria remains endemic in 17 countries in the Americas, where 723,000 cases were reported in 2019. The majority (> 90%) of the regional malaria burden is found within the Amazon Basin, which includes nine countries and territories in South America. Locally generated evidence is critical to provide information to public health decision makers upon which the design of efficient and regionally directed malaria control and elimination programs can be built. Plasmodium vivax is the predominant malaria parasite in the Amazon Basin. This parasite species appears to be more resilient to malaria control strategies worldwide. Asymptomatic Plasmodium infections constitute a potentially infectious reservoir that is typically missed by routine microscopy-based surveillance and often remains untreated. The primary Amazonian malaria vector, Nyssorhynchus (formerly Anopheles) darlingi, has changed its behavior to feed and rest predominantly outdoors, reducing the efficiency of core vector control measures such as indoor residual spraying and distribution of long-lasting insecticide-treated bed nets. We review public health implications of recent field-based research carried out by the Amazonia International Center of Excellence in Malaria Research in Peru and Brazil. We discuss the relative role of traditional and novel tools and
strategies for better malaria control and elimination across the Amazon, including improved diagnostic methods, new anti-relapse medicines, and biological larvicides, and emphasize the need to integrate research and public health policymaking.

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The 1990s saw the rapid reemergence of malaria in Amazonia, where it remains an important public health priority in South America. The Amazonian International Center of Excellence in Malaria Research (ICEMR) was designed to take a multidisciplinary approach toward identifying novel malaria control and elimination strategies. Based on geographically and epidemiologically distinct sites in the Northeastern Peruvian and Western Brazilian Amazon regions, synergistic projects integrate malaria epidemiology, vector biology, and immunology. The Amazonian ICEMR's overarching goal is to understand how human behavior and other sociodemographic features of human reservoirs of transmission—predominantly asymptomatically parasitemic people—interact with the major Amazonian malaria vector, Nyssorhynchus (formerly Anopheles)
darlingi, and with human immune responses to maintain malaria resilience and continued endemicity in a hypoendemic setting. Here, we will review Amazonian ICEMR's achievements on the synergies among malaria epidemiology, Plasmodium-vector interactions, and immune response, and how those provide a roadmap for further research, and, most importantly, point toward how to achieve malaria control and elimination in the Americas.

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Malaria is a major health problem in Peru despite substantial progress achieved by the ongoing malaria elimination program. This study explored the population genetics of 63 Plasmodium falciparum and 170 P. vivax cases collected in the Peruvian Amazon Basin between 2015 and 2019. Microscopy and PCR were used for malaria detection and positive samples were genotyped at neutral and drug resistance-associated regions. The P. falciparum population exhibited a low nucleotide diversity (\(\pi = 0.02\)) whereas the P. vivax population presented a higher genetic diversity (\(\pi = 0.34\)). All P. falciparum samples (\(n = 63\)) carried chloroquine (CQ) resistant mutations on Pfcrt. Most P. falciparum samples (53 out of 54) carried sulfadoxine (SD) resistant mutations on Pfdhfr and Pfdhps. No evidence was found of artemisinin resistance mutations on kelch13.

Population structure showed that a single cluster accounted for 93.4% of the P. falciparum samples whereas three clusters were found for P. vivax.
Our study shows a low genetic diversity for both species with significant differences in genetic sub-structuring. The high prevalence of CQ-resistance mutations could be a result of indirect selection pressures driven by the P. vivax treatment scheme. These results could be useful for public health authorities to safeguard the progress that Peru has achieved towards malaria elimination.

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Introduction: Herein, we tested the hypothesis that asymptomatic P. vivax (Pv) infected individuals (Asym) feature different epidemiological, clinical and biochemical characteristics, as well as hematological parameters, potentially predictive of clinical immunity in comparison to symptomatic Pv infected individuals (Sym). Methodology: Between 2018 – 2021, we conducted 11 population screenings (PS, Day 0 (D0)) in 13 different riverine communities around Iquitos city, in the Peruvian Amazon, to identify Pv Sym and Asym individuals. A group of these individuals agreed to participate in a nested case – control study to evaluate biochemical and hematological parameters. Pv Asym
individuals did not present common malaria symptoms (fever, headache, and chills), had a positive/negative microscopy result, a positive qPCR result, reported no history of antimalarial treatment during the last month, and were followed-up weekly until Day 21 (D21). Control individuals, had a negative malaria microscopy and qPCR result, no history of antimalarial treatment or malaria infections during the last three years, and no history of comorbidities or chronic infections. Results: From the 2159 individuals screened during PS, data revealed a low but heterogeneous Pv prevalence across the communities (11.4%), where most infections were Asym (66.7%) and submicroscopic (82.9%). A total of 29 Asym, 49 Sym, and 30 control individuals participated in the nested case-control study (n=78). Ten of the individuals that were initially Asym at D0, experienced malaria symptoms during follow up and therefore, were included in the Sym group. 29 individuals remained Asym throughout all follow-ups. High levels of eosinophils were found in Asym individuals in comparison to Sym and controls. Conclusion: For the first-time, key epidemiological, hematological, and biochemical features are reported from Pv Asym infections from the Peruvian Amazon. These results should be considered for the design and reshaping of malaria control measures as the country moves toward malaria elimination.

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A more sensitive surveillance tool is needed to identify Plasmodium vivax infections for treatment and to accelerate malaria elimination efforts.

To address this challenge, our laboratory has developed an eight-antigen panel that detects total IgG as serological markers of P. vivax exposure within the prior 9 months. The value of these markers has been established for use in areas with low transmission. In moderate-high transmission areas, there is evidence that total IgG is more long-lived than in areas with low transmission, resulting in poorer performance of these markers in these settings. Antibodies that are shorter-lived may be better markers of recent infection for use in moderate-high transmission areas. Using a multiplex assay, the antibody temporal kinetics of total IgG, IgG1, IgG3, and IgM against 29 P. vivax antigens were
measured over 36 weeks following asymptomatic P. vivax infection in Papua New Guinean children (n = 31), from an area with moderate-high transmission intensity. IgG3 declined faster to background than total IgG, IgG1, and IgM. Based on these kinetics, IgG3 performance was then assessed for classifying recent exposure in a cohort of Peruvian individuals (n = 590; age 3–85 years) from an area of moderate transmission intensity. Using antibody responses against individual antigens, the highest performance of IgG3 in classifying recent P. vivax infections in the prior 9 months was to one of the Pv-fam-a proteins assessed (PVX_125728) (AUC = 0.764). Surprisingly, total IgG was overall a better marker of recent P. vivax infection, with the highest individual classification performance to RBP2b1986–2653 (PVX_094255) (AUC = 0.838). To understand the acquisition of IgG3 in this Peruvian cohort, relevant epidemiological factors were explored using a regression model. IgG3 levels were positively associated with increasing age, living in an area with (relatively) higher transmission intensity, and having three or more PCR-detected blood-stage P. vivax infections within the prior 13 months. Overall, we found that IgG3 did not have high accuracy for detecting recent exposure to P. vivax in the Peruvian cohort, with our data suggesting that this is due to the high levels of prior exposure required to acquire high IgG3 antibody levels.

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PMID - 35895359
OWN - NLM
STAT - MEDLINE
DCOM - 20220729
LR - 20220802
IS - 1476-1645 (Electronic)
IS - 0002-9637 (Linking)
VI - 107
IP - 1
DP - 2022 Jul 13
TI - Insights into Plasmodium vivax Asymptomatic Malaria Infections and Direct Skin-Feeding Assays to Assess Onward Malaria Transmission in the Amazon.
Understanding the reservoir and infectivity of Plasmodium gametocytes to vector mosquitoes is crucial to align strategies aimed at malaria transmission elimination. Yet, experimental information is scarce regarding the infectivity of Plasmodium vivax for mosquitoes in diverse epidemiological settings where the proportion of asymptomatically infected individuals varies at a microgeographic scale. We measured the transmissibility of clinical and subclinical P. vivax malaria parasite carriers to the major mosquito vector in the Amazon Basin, Nyssorhynchus darlingi (formerly Anopheles). A total of 105 participants with natural P. vivax malaria infection were recruited from a cohort study in Loreto Department, Peruvian Amazon. Four of 18 asymptomatic individuals with P. vivax positivity by blood smear infected colony-grown Ny. darlingi (22%), with 2.6% (19 of 728) mosquitoes infected. In contrast, 77% (44/57) of symptomatic participants were infectious to mosquitoes with 51% (890 of 1,753) mosquitoes infected. Infection intensity was greater in symptomatic infections (mean, 17.8 oocysts/mosquito) compared with asymptomatic infections (mean, 0.28 oocysts/mosquito), attributed to parasitemia/gametocytemia level. Paired experiments (N = 27) using direct skin-feeding assays and direct membrane mosquito-feeding assays showed that infectivity to mosquitoes was similar for both methods. Longitudinal studies with longer follow-up of symptomatic and asymptomatic parasite infections are needed to determine the natural variations of disease transmissibility.

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BACKGROUND: The landscape of malaria transmission in the Peruvian Amazon is temporally and spatially heterogeneous, presenting different micro-

antibody signatures to Plasmodium vivax.
geographies with particular epidemiologies. Most cases are asymptomatic and escape routine malaria surveillance based on light microscopy (LM).

Following the implementation of control programs in this region, new approaches to stratify transmission and direct efforts at an individual and community level are needed. Antibody responses to serological exposure markers (SEM) to Plasmodium vivax have proven diagnostic performance to identify people exposed in the previous 9 months.

METHODOLOGY: We measured antibody responses against 8 SEM to identify recently exposed people and determine the transmission dynamics of P. vivax in peri-urban (Iquitos) and riverine (Mazan) communities of Loreto, communities that have seen significant recent reductions in malaria transmission. Socio-demographic, geo-reference, LM and qPCR diagnosis data were collected from two cross-sectional surveys. Spatial and multilevel analyses were implemented to describe the distribution of seropositive cases and the risk factors associated with exposure to P. vivax. PRINCIPAL FINDINGS: Low local transmission was detected by qPCR in both Iquitos (5.3%) and Mazan (2.7%); however, seroprevalence indicated a higher level of (past) exposure to P. vivax in Mazan (56.5%) than Iquitos (38.2%). Age and being male were factors associated with high odds of being seropositive in both sites. Higher antibody levels were found in individuals >15 years old. The persistence of long-lived antibodies in these individuals could overestimate the detection of recent exposure. Antibody levels in younger populations (<15 years old) could be a better indicator of recent exposure to P. vivax. CONCLUSIONS: The large number of current and past infections detected by SEMs allows for detailed local epidemiological analyses, in contrast to data from qPCR prevalence surveys which did not produce statistically significant associations.
Serological surveillance will be increasingly important in the Peruvian Amazon as malaria transmission is reduced by continued control and elimination efforts.

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Relative contribution of low-density and asymptomatic infections to Plasmodium vivax transmission in the Amazon: pooled analysis of individual participant data from population-based cross-sectional surveys.

Background: Low-density and asymptomatic Plasmodium vivax infections remain largely undetected and untreated and may contribute significantly to malaria transmission in the Amazon. Methods: We analysed individual participant data from population-based surveys that measured P. vivax prevalence by microscopy and polymerase chain reaction (PCR) between 2002 and 2015 and modelled the relationship between parasite density and infectiousness to vectors using membrane feeding assay data. We estimated the proportion of sub-patent (i.e., missed by microscopy) and asymptomatic P. vivax infections and examined how parasite density relates to clinical manifestations and mosquito infection in Amazonian settings. Findings: We pooled 24,986 observations from six sites in Brazil and Peru. P. vivax was detected in 6.8% and 2.1% of them by PCR and microscopy, respectively. 58.5% to 92.6% of P. vivax infections were asymptomatic and 61.2% to 96.3% were sub-patent across study sites. P. vivax density thresholds associated with clinical symptoms were one order of magnitude higher in children than in adults. We estimate that sub-patent parasite carriers are minimally infectious and contribute 12.7% to 24.9% of the community-wide P. vivax transmission, while asymptomatic carriers are the source of 28.2% to 79.2% of mosquito infections.

Interpretation: Asymptomatic P. vivax carriers constitute a vast infectious reservoir that, if targeted by malaria elimination strategies, could substantially reduce malaria transmission in the Amazon. Infected
children may remain asymptomatic despite high parasite densities that elicit clinical manifestations in adults. Funding: US National Institutes of Health, Fundacao de Amparo a Pesquisa do Estado de Sao Paulo, and Belgium Development Cooperation.

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Nyssorhynchus darlingi genome-wide studies related to microgeographic dispersion and blood-seeking behavior.

BACKGROUND: In Brazil, malaria is concentrated in the Amazon Basin, where more than 99% of the annual cases are reported. The main goal of this study was to investigate the population structure and genetic association of the biting behavior of Nyssorhynchus (also known as Anopheles) darlingi, the major malaria vector in the Amazon region of Brazil, using low-coverage genomic sequencing data. METHODS: Samples were collected in the municipality of Mancio Lima, Acre state, Brazil between 2016 and 2017. Different approaches using genotype imputation and no gene imputation for data treatment and low-coverage sequencing genotyping were performed. After the samples were genotyped, population stratification analysis was performed. RESULTS: Weak but statistically significant stratification signatures were identified between subpopulations separated by distances of approximately 2-3 km. Genome-wide association studies (GWAS) were performed to compare indoor/outdoor biting behavior and blood-seeking at dusk/dawn. A statistically significant association was observed between biting behavior and single nucleotide polymorphism (SNP) markers adjacent to the gene associated with cytochrome P450 (CYP) 4H14, which is associated with insecticide resistance. A statistically
significant association between blood-seeking periodicity and SNP markers adjacent to genes associated with the circadian cycle was also observed.

CONCLUSION: The data presented here suggest that low-coverage whole-genome sequencing with adequate processing is a powerful tool to genetically characterize vector populations at a microgeographic scale in malaria transmission areas, as well as for use in GWAS. Female mosquitoes entering houses to take a blood meal may be related to a specific CYP4H14 allele, and female timing of blood-seeking is related to circadian rhythm genes.

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Dried blood spots (DBS) typically prepared on filter papers are an ideal sample type for malaria surveillance by offering easy and cost-effective methods in terms of sample collection, storage, and transport. The objective of this study was to evaluate the applicability of DBS with a commercial multiplex malaria assay, developed to concurrently
measure Plasmodium antigens, histidine-rich protein 2 (HRP2), Plasmodium lactate dehydrogenase (pLDH), and a host inflammatory biomarker, C-reactive protein (CRP), in whole blood. The assay conditions were optimized for DBS, and thermal stability for measurement of Plasmodium antigens and CRP in dried blood were determined. Performance of the multiplex assay on matched DBS and whole blood pellet samples was also evaluated using the clinical samples. The results indicate the acceptable performance in multiplex antigen detection using DBS samples. At cutoff levels for DBS, with a diagnostic specificity with a lower 95% confidence bound > 92%, diagnostic sensitivities against polymerase chain reaction (PCR)-confirmed malaria for HRP2, Pf LDH, Pv LDH, and Pan LDH were 93.5%, 80.4%, 21.3%, and 55.6%, respectively. The half-life of pLDH was significantly less than that of HRP2 in thermal stability studies.

Results with DBS samples collected from Peru indicate that the uncontrolled storage conditions of DBS can result in inaccurate reporting for infection with P. falciparum parasites with hrp2/3 deletions. With careful consideration that minimizing the unfavorable DBS storage environment is essential for ensuring integrity of heat-labile Plasmodium antigens, DBS samples can be used as an alternative to liquid whole blood to detect P. falciparum with hrp2/3 deletions in malaria surveillance.

SUPPLEMENTARY INFORMATION: The online version of this article (10.1007/s12639-020-01325-2) contains supplementary material, which is available to authorized users.

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Multicopy targets for Plasmodium vivax and Plasmodium falciparum detection by colorimetric LAMP.

BACKGROUND: Loop-mediated isothermal amplification (LAMP) for malaria diagnosis at the point of care (POC) depends on the detection capacity of synthesized nucleic acids and the specificity of the amplification target. To improve malaria diagnosis, new colorimetric LAMP tests were developed using multicopy targets for Plasmodium vivax and Plasmodium falciparum detection. METHODS: The cytochrome oxidase I (COX1) mitochondrial gene and the non-coding sequence Pvr47 for P. vivax, and the sub-telomeric sequence of erythrocyte membrane protein 1 (EMP1) and the non-coding sequence Pfr364 for P. falciparum were targeted to design new LAMP primers. The limit of detection (LOD) of each colorimetric LAMP was established and assessed with DNA extracted by mini spin column kit and the Boil & Spin method from 28 microscopy infections, 101 malaria submicroscopic infections detected by real-time PCR only, and
negatives infections by both microscopy and PCR. RESULTS: The LODs for the colorimetric LAMPs were estimated between 2.4 to 3.7 parasites/microL of whole blood. For P. vivax detection, the colorimetric LAMP using the COX1 target showed a better performance than the Pvr47 target, whereas the Pfr364 target was the most specific for P. falciparum detection. All microscopic infections of P. vivax were detected by PvCOX1-LAMP using the mini spin column kit DNA extraction method and 81% (17/21) were detected using Boil & Spin sample preparation. Moreover, all microscopic infections of P. falciparum were detected by Pfr364-LAMP using both sample preparation methods. In total, PvCOX1-LAMP and Pfr364-LAMP detected 80.2% (81 samples) of the submicroscopic infections using the DNA extraction method by mini spin column kit, while 36.6% (37 samples) were detected using the Boil & Spin sample preparation method. CONCLUSION: The colorimetric LAMPs with multicopy targets using the COX1 target for P. vivax and the Pfr364 for P. falciparum have a high potential to improve POC malaria diagnosis detecting a greater number of submicroscopic Plasmodium infections.

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BACKGROUND: Remote rural riverine villages account for most of the reported malaria cases in the Peruvian Amazon. As transmission decreases due to intensive standard control efforts, malaria strategies in these villages will need to be more focused and adapted to local epidemiology.

METHODS: By integrating parasitological, entomological, and environmental observations between January 2016 and June 2017, we provided an in-depth characterization of malaria transmission dynamics in 4 riverine villages of the Mazan district, Loreto department. RESULTS: Despite variation across villages, malaria prevalence by polymerase chain reaction in March 2016 was high (>25% in 3 villages), caused by Plasmodium vivax mainly and composed of mostly submicroscopic infections. Housing without complete walls was the main malaria risk factor, while households close to forest edges were more commonly identified as spatial clusters of malaria.
prevalence. Villages in the basin of the Mazan River had a higher density of adult Anopheles darlingi mosquitoes, and retained higher prevalence and incidence rates compared to villages in the basin of the Napo River despite test-and-treat interventions. CONCLUSIONS: High heterogeneity in malaria transmission was found across and within riverine villages, resulting from interactions between the microgeographic landscape driving diverse conditions for vector development, housing structure, and human behavior.

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GR - U19 AI089681/AI/NIAID NIH HHS/United States
GR - UL1 TR001863/TR/NCATS NIH HHS/United States
PT - Journal Article
PT - Research Support, N.I.H., Extramural
PT - Research Support, Non-U.S. Gov't
PL - United States
TA - J Infect Dis
JT - The Journal of infectious diseases
JID - 0413675
SB - IM
MH - Adult
MH - Animals
MH - Anopheles/*parasitology
MH - *Bites and Stings
MH - Humans
Temporal and Microspatial Heterogeneity in Transmission Dynamics of Coendemic Plasmodium vivax and Plasmodium falciparum in Two Rural Cohort Populations in the Peruvian Amazon.

BACKGROUND: Malaria is highly heterogeneous: its changing microepidemiology needs to be addressed to support malaria elimination efforts at the regional level. METHODS: A 3-year, population-
based cohort study in 2 settings in the Peruvian Amazon (Lupuna, Cahuide) followed participants by passive and active case detection from January 2013 to December 2015. Incidence and prevalence rates were estimated using microscopy and polymerase chain reaction (PCR). RESULTS: Lupuna registered 1828 infections (1708 Plasmodium vivax, 120 Plasmodium falciparum; incidence was 80.7 infections/100 person-years (95% confidence interval [CI], 77.1-84.5). Cahuide detected 1046 infections (1024 P. vivax, 20 P. falciparum, 2 mixed); incidence was 40.2 infections/100 person-years (95% CI, 37.9-42.7). Recurrent P. vivax infections predominated onwards from 2013. According to PCR data, submicroscopic predominated over microscopic infections, especially in periods of low transmission. The integration of parasitological, entomological, and environmental observations evidenced an intense and seasonal transmission resilient to standard control measures in Lupuna and a persistent residual transmission after severe outbreaks were intensively handled in Cahuide. CONCLUSIONS: In 2 exemplars of complex local malaria transmission, standard control strategies failed to eliminate submicroscopic and hypnozoite reservoirs, enabling persistent transmission.

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GR - UL1 TR001863/TR/NCATS NIH HHS/United States
PT - Journal Article
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PL - United States
TA - J Infect Dis
JT - The Journal of infectious diseases
JID - 0413675
SB - IM
MH - Cohort Studies
MH - Humans
MH - *Malaria, Falciparum/epidemiology/transmission
MH - *Malaria, Vivax/epidemiology/transmission
MH - Peru/epidemiology
MH - Plasmodium falciparum
MH - Plasmodium vivax
MH - Prevalence
PMC - PMC8064053
OTO - NOTNLML
OT - Amazon
OT - Malaria
OT - Peru
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OT - transmission
EDAT- 2020/08/22 06:00
MHDA- 2022/02/11 06:00
CRDT- 2020/08/22 06:00
PHST- 2020/05/05 00:00 [received]
PHST- 2020/08/17 00:00 [accepted]
PHST- 2020/08/22 06:00 [pubmed]
PHST- 2022/02/11 06:00 [medline]
PHST- 2020/08/22 06:00 [entrez]
AID - 5895494 [pii]
AID - 10.1093/infdis/jiaa526 [doi]
PST - ppublish
PMID- 33831004
OWN - NLM
STAT- MEDLINE
DCOM- 20210913
LR - 20210920
IS - 1932-6203 (Electronic)
IS - 1932-6203 (Linking)
VI - 16
IP - 4
DP - 2021
TI - Ecology and larval population dynamics of the primary malaria
Nyssorhynchus darlingi in a high transmission setting dominated by fish farming in western Amazonian Brazil.

Vale do Rio Jurua in western Acre, Brazil, is a persistent malaria transmission hotspot partly due to fish farming development that was encouraged to improve local standards of living. Fish ponds can be productive breeding sites for Amazonian malaria vector species, including Nyssorhynchus darlingi, which, combined with high human density and mobility, add to the local malaria burden. This study reports entomological profile of immature and adult Ny. darlingi at three sites in Mancio Lima, Acre, during the rainy and dry season (February to September, 2017). From 63 fishponds, 10,859 larvae were collected, including 5,512 first-instar Anophelinae larvae and 4,927 second, third and fourth-instars, of which 8.5% (n = 420) were Ny. darlingi. This species was most abundant in not-abandoned fishponds and in the presence of emerging aquatic vegetation. Seasonal analysis of immatures in urban landscapes found no significant difference in the numbers of Ny. darlingi, corresponding to equivalent population density during the rainy to dry transition period. However, in the rural landscape, significantly higher numbers of Ny. darlingi larvae were collected in August (IRR = 5.80, p = 0.037) and September (IRR = 6.62, p = 0.023) (dry season), compared to February (rainy season), suggesting important role of fishponds for vector population maintenance during the seasonal transition in this landscape type. Adult sampling detected mainly Ny. darlingi (~93%), with similar outdoor feeding behavior, but different abundance according to landscape profile: urban site 1 showed higher peaks of human biting rate in May (46 bites/person/hour), than February (4) and September (15), while rural site 3 shows similar HBR
during the same sampling period (22, 24 and 21, respectively). This study contributes to a better understanding of the larvae biology of the main malaria vector in the Vale do Rio Jurua region and, ultimately will support vector control efforts.

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Towards one standard treatment for uncomplicated Plasmodium falciparum and Plasmodium vivax malaria: Perspectives from and for the Peruvian Amazon.

Lengthy research efforts have brought important lessons on its particular epidemiology:
the heterogeneous levels of transmission, the large reservoir of both asymptomatic and submicroscopic infections, the co-transmission of Plasmodium vivax and Plasmodium falciparum in the same areas, and the limitations of current diagnostics. Based on these features, the national elimination program could greatly benefit from simplified standard treatment, with the use of artemisinin-based combination
therapy and even shorter schemes of primaquine maintaining the total dosing. It is acknowledged that there is some uncertainty regarding the true prevalence of glucose-6-phosphate dehydrogenase deficiency (G6PD) and genetic polymorphisms related to cytochrome P-450 isozyme 2D6 functioning. Once we have a better understanding, tafenoquine, whether or not in combination with a rapid G6PD enzyme test, may become a future pathway to eliminate the otherwise hidden reservoir of the P. vivax hypnozoite through one standard Plasmodium treatment.
PvMSP8 as a Novel Plasmodium vivax Malaria Sero-Marker for the Peruvian Amazon.

The measurement of recent malaria exposure can support malaria control efforts. This study evaluated serological responses to an in-house Plasmodium vivax Merozoite Surface Protein 8 (PvMSP8) expressed in a Baculovirus system as sero-marker of recent exposure to P. vivax (Pv) in the Peruvian Amazon. In a first evaluation, IgGs against PvMSP8 and PvMSP10 proteins were measured by Luminex in a cohort of 422 Amazonian individuals with known history of Pv exposure (monthly data of infection status by qPCR and/or microscopy over five months). Both serological responses were able to discriminate between exposed and non-exposed individuals in a good manner, with slightly higher performance of anti-PvMSP10 IgGs (area under the curve AUC = 0.78 [95% CI = 0.72–0.83]) than anti-PvMSP8 IgGs (AUC = 0.72 [95% CI = 0.67–0.78]) (p = 0.01). In a second evaluation, the analysis by ELISA of 1251 plasma samples, collected during a population-based cross-sectional survey, confirmed the good performance of anti-PvMSP8 IgGs for discriminating between
individuals with Pv infection at the time of survey and/or with antecedent of Pv in the past month (AUC = 0.79 [95% CI = 0.74–0.83]). Anti-PvMSP8 IgG antibodies can be considered as a good biomarker of recent Pv exposure in low-moderate transmission settings of the Peruvian Amazon.

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LA - eng
GR - UL1 TR001863/TR/NCATS NIH HHS/United States
GR - Contract 218-2015-FONDECYT/Fondo Nacional de Desarrollo Cientifico,
Tecnologico y de Innovacion Tecnologica" (FONDECYT/CONCYTEC)
GR - U19AI089681/NH/NIH HHS/United States
GR - D43TW007120/TW/FIC NIH HHS/United States
PT - Journal Article
DEP - 20210302
PL - Switzerland
TA - Pathogens
JT - Pathogens (Basel, Switzerland)
JID - 101596317
PMC - PMC7999794
OTO - NOTNLM
OT - ELISA
OT - Luminex
OT - P. vivax
OT - PvMSP8
OT - antibodies
OT - malaria
EDAT- 2021/04/04 06:00
MHDA- 2021/04/04 06:01
CRDT- 2021/04/03 01:08
PHST- 2021/01/30 00:00 [received]
PHST- 2021/02/24 00:00 [revised]
PHST- 2021/02/24 00:00 [accepted]
PHST- 2021/04/03 01:08 [entrez]
PHST- 2021/04/04 06:00 [pubmed]
PHST- 2021/04/04 06:01 [medline]
AID - pathogens10030282 [pii]
AID - 10.3390/pathogens10030282 [doi]
PST - epublish
PMID- 33632222
OWN - NLM
STAT- MEDLINE
DCOM- 20210813
BACKGROUND: Manual microscopy remains a widely-used tool for malaria diagnosis and clinical studies, but it has inconsistent quality in the field due to variability in training and field practices. Automated diagnostic systems based on machine learning hold promise to improve quality and reproducibility of field microscopy. The World Health Organization (WHO) has designed a 55-slide set (WHO 55) for their External Competence Assessment of Malaria Microscopists (ECAMM) programme, which can also serve as a valuable benchmark for automated systems. The performance of a fully-automated malaria diagnostic system, EasyScan GO, on a WHO 55 slide set was evaluated. METHODS: The WHO 55 slide set is designed to evaluate microscopist competence in three areas of malaria diagnosis using Giemsa-stained blood films, focused on crucial field needs: malaria parasite detection, malaria parasite species identification (ID), and malaria parasite quantitation. The EasyScan GO is a fully-automated system that combines scanning of Giemsa-stained blood films with assessment algorithms to deliver malaria diagnoses. This system was tested on a WHO 55 slide set. RESULTS: The EasyScan GO achieved 94.3% detection accuracy, 82.9% species ID accuracy, and 50% quantitation accuracy, corresponding to WHO microscopy competence Levels 1, 2, and 1, respectively. This is, to our knowledge, the best performance of a fully-automated system on a WHO 55 set. CONCLUSIONS: EasyScan GO's expert ratings in detection and quantitation on the WHO 55
slide set point towards its potential value in drug efficacy
use-cases, as well as in some case management situations with less
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Heterogeneity in response to serological exposure markers of recent Plasmodium vivax infections in contrasting epidemiological contexts.

BACKGROUND: Antibody responses as serological markers of Plasmodium vivax infection have been shown to correlate with exposure, but little is known about the other factors that affect antibody responses in naturally infected people from endemic settings. To address this question, we studied IgG responses to novel serological exposure markers (SEMs) of P. vivax in three settings with different transmission intensity.

METHODOLOGY: We validated a panel of 34 SEMs in a Peruvian cohort with up to three years' longitudinal follow-up using a multiplex platform and compared results to data from cohorts in Thailand and Brazil. Linear regression models were used to characterize the association
between antibody responses and age, the number of detected blood-stage infections during follow-up, and time since previous infection. Receiver Operating Characteristic (ROC) analysis was used to test the performance of SEMs to identify P. vivax infections in the previous 9 months.

PRINCIPAL FINDINGS: Antibody titers were associated with age, the number of blood-stage infections, and time since previous P. vivax infection in all three study sites. The association between antibody titers and time since previous P. vivax infection was stronger in the low transmission settings of Thailand and Brazil compared to the higher transmission setting in Peru. Of the SEMs tested, antibody responses to RBP2b had the highest performance for classifying recent exposure in all sites, with area under the ROC curve (AUC) = 0.83 in Thailand, AUC = 0.79 in Brazil, and AUC = 0.68 in Peru. CONCLUSIONS: In low transmission settings, P. vivax SEMs can accurately identify individuals with recent blood-stage infections. In higher transmission settings, the accuracy of this approach diminishes substantially. We recommend using P. vivax SEMs in low transmission settings pursuing malaria elimination, but they are likely to be less effective in high transmission settings focused on malaria control.

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GR - U19 AI089681/AI/NIAID NIH HHS/United States
GR - U19 AI129392/AI/NIAID NIH HHS/United States
GR - UL1 TR001863/TR/NCATS NIH HHS/United States
PT - Journal Article
PT - Research Support, N.I.H., Extramural
PT - Research Support, Non-U.S. Gov't
DEP - 20210216
PL - United States
TA - PLoS Negl Trop Dis
JT - PLoS neglected tropical diseases
JID - 101291488
RN - 0 (Biomarkers)
RN - 0 (Immunoglobulin G)
SB - IM
MH - Antibody Formation
MH - Biomarkers/*blood
MH - Brazil/epidemiology
MH - Cohort Studies
MH - Humans
MH - Immunoglobulin G/blood
MH - Longitudinal Studies
MH - Malaria, Vivax/blood/*diagnosis/epidemiology/immunology
MH - Peru/epidemiology
MH - Plasmodium vivax
MH - Prevalence
MH - Serologic Tests/*methods/standards
MH - Thailand/epidemiology
PMC - PMC7909627
COIS- I have read the journal's policy and the authors of this
manuscript have
the following competing interests: RJL, MTW, Takafumi Tsuboi
and IM are
inventors on patent PCT/US17/67926 on a system, method,
apparatus and
diagnostic test for Plasmodium vivax. No other authors declare
a conflict
of interest.
EDAT- 2021/02/17 06:00
MHDA- 2021/06/11 06:00
CRDT- 2021/02/16 17:10
PHST- 2020/08/31 00:00 [received]
PHST- 2021/01/21 00:00 [accepted]
PHST- 2021/02/26 00:00 [revised]
PHST- 2021/02/17 06:00 [pubmed]
PHST- 2021/06/11 06:00 [medline]
PHST- 2021/02/16 17:10 [entrez]
AID - 10.1371/journal.pntd.0009165 [doi]
AID - PNTD-D-20-01535 [pii]
PST - epublish
10.1371/journal.pntd.0009165. eCollection 2021 Feb.

PMID- 32885776
OWN - NLM
STAT- MEDLINE
DCOM- 20201123
LR - 20210920
IS - 1476-1645 (Electronic)
IS - 0002-9637 (Linking)
VI - 103
IP - 5
DP - 2020 Nov
TI - Malaria Situation in the Peruvian Amazon during the COVID-19
Pandemic.
PG - 1773-1776
LID - 10.4269/ajtmh.20-0889 [doi]
AB - The Peruvian Ministry of Health reports a near absence of
malaria cases
in the Amazon region during the COVID-19 pandemic. However,
the rapid
increase in SARS-CoV-2 infections has overwhelmed the Peruvian
health
system, leading to national panic and closure of public
medical
facilities, casting doubt on how accurately malaria cases'numbers
reflect reality. In the Amazon region of Loreto, where malaria
cases are
concentrated, COVID-19 has led to near-complete closure of the
primary
healthcare system, and diagnosis and treatment of acute
febrile
illnesses, including malaria, has plummeted. Here, we describe
the potential association of COVID-19 with a markedly reduced number of reported malaria cases due to the reduced control activities carried out by the Peruvian Malaria Zero Program, which could lead to malaria resurgence and an excess of morbidity and mortality.
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GR  - UL1 TR001863/TR/NCATS NIH HHS/United States
PT  - Journal Article
PT  - Research Support, N.I.H., Extramural
PL  - United States
TA  - Am J Trop Med Hyg
JT  - The American journal of tropical medicine and hygiene

JID  - 0370507
SB  - IM
MH  - Betacoronavirus
MH  - COVID-19
MH  - Coronavirus Infections/*epidemiology
MH  - Humans
MH  - Malaria/*epidemiology/prevention & control
MH  - Pandemics
MH  - Peru/epidemiology
MH  - Pneumonia, Viral/*epidemiology
MH  - SARS-CoV-2

PM  - PMC7646770
EDAT- 2020/09/05 06:00
MHDA- 2020/11/24 06:00
CRDT- 2020/09/05 06:00
PHST- 2020/09/05 06:00 [pubmed]
PHST- 2020/11/24 06:00 [medline]
PHST- 2020/09/05 06:00 [entrez]
AID  - 10.4269/ajtmh.20-0889 [doi]
PST - ppublish

PMID- 32748776
OWN  - NLM
STAT- MEDLINE
DCOM- 20201123
LR  - 20220902
IS  - 1476-1645 (Electronic)
IS  - 0002-9637 (Linking)
VI  - 103
IP  - 4
DP  - 2020 Oct
TI  - Diagnosis of Plasmodium vivax by Loop-Mediated Isothermal
    Amplification
    in Febrile Patient Samples from Loreto, Peru.
PG  - 1549-1552
Plasmodium vivax is co-endemic with Plasmodium falciparum in Peru, and optimum management requires distinguishing these two species in the blood of patients. For the differential identification of P. vivax and other Plasmodium spp., the Loopamp(TM) Malaria Pan Detection Kit in combination with the Loopamp Malaria Pv Detection Kit (Eiken Chemical Co. Ltd., Tokyo, Japan) was used to evaluate 559 whole blood samples collected in 2017 from febrile patients with suspected malaria attending different health facilities in the Loreto region. The Loopamp Malaria Pan Detection Kit showed a sensitivity of 87.7% (95% CI: 83.5-91.9) and a specificity of 94.4% (95% CI: 91.9-96.9) and good agreement with PCR (Cohen's kappa: 0.8266, 95% CI: 0.7792-0.874). By comparison, the Loopamp Malaria Pv Detection Kit showed a similar sensitivity (84.4%, 95% CI: 79.0-89.7) and specificity (92.4%, 95% CI: 89.7-95.0) and substantial agreement with PCR (Cohen's kappa: 0.7661, 95% CI: 0.7088-0.8234).
Human movement affects malaria epidemiology at multiple geographical levels; however, few studies measure the role of human movement in the Amazon Region due to the challenging conditions and cost of movement tracking technologies. We developed an open-source low-cost 3D printable GPS-tracker and used this technology in a cohort study to characterize the role of human population movement in malaria epidemiology in a rural riverine village in the Peruvian Amazon. In this pilot study of 20 participants (mean age = 40 years old), 45,980 GPS coordinates were recorded over 1 month. Characteristic movement patterns were observed relative to the infection status and occupation of the participants. Applying two analytical animal movement ecology methods, utilization distributions (UDs) and integrated step selection functions (iSSF), we showed contrasting environmental selection and space use patterns according to infection status. These data suggested an important role of human movement in the epidemiology of malaria in the Peruvian Amazon due to high connectivity between villages of the same riverine network, suggesting limitations of current community-based control strategies. We additionally demonstrate the utility of this low-cost technology with movement ecology analysis to characterize human movement in resource-poor environments.
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Multiplex Human Malaria Array: Quantifying Antigens for Malaria Rapid Diagnostics.

Malaria antigen detection through rapid diagnostic tests (RDTs) is widely used to diagnose malaria and estimate prevalence. To support more sensitive next-generation RDT development and screen asymptomatic malaria, we developed and evaluated the Q-Plex() Human Malaria Array (Quansys Biosciences, Logan, UT), which quantifies the antigens commonly used in RDTs—Plasmodium falciparum-specific histidine-rich protein 2 (HRP2), P. falciparum-specific lactate dehydrogenase (Pf LDH), Plasmodium vivax-specific LDH (Pv LDH), and Pan malaria lactate dehydrogenase (Pan LDH), and human C-reactive protein (CRP), a biomarker of severity in malaria. At threshold levels yielding 99.5% or more diagnostic specificity, diagnostic sensitivities against polymerase chain reaction-confirmed malaria for HRP2, Pf LDH, Pv LDH, and Pan LDH were 92.7%, 71.5%, 46.1%, and 83.8%, respectively. P. falciparum culture strains and samples from Peru indicated that HRP2 and Pf LDH combined improves detection of P. falciparum parasites with hrp2 and hrp3 deletions. This array can be used for antigen-based malaria screening and detecting hrp2/3 deletion mutants of P. falciparum.

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GR - U19 AI089674/AI/NIAID NIH HHS/United States
PT - Journal Article
PL - United States
TA - Am J Trop Med Hyg
JT - The American journal of tropical medicine and hygiene
JID - 0370507
RN - 0 (Antigens, Protozoan)
RN - 0 (DNA, Protozoan)
SB - IM
MH - Antigens, Protozoan/genetics
MH - DNA, Protozoan/*genetics
MH - Diagnostic Tests, Routine
MH - Humans
MH - Malaria/*diagnosis
MH - Multiplex Polymerase Chain Reaction/*methods
MH - Plasmodium/*genetics
MH - Sensitivity and Specificity
MH - Species Specificity
PMC - PMC7253106
EDAT- 2020/03/20 06:00
MHDA- 2020/08/15 06:00
CRDT- 2020/03/20 06:00
PHST- 2020/03/20 06:00 [pubmed]
PHST- 2020/08/15 06:00 [medline]
PHST- 2020/03/20 06:00 [entrez]
AID - 10.4269/ajtmh.19-0763 [doi]
PST - ppublish
AB - BACKGROUND: Case management is one of the principal strategies for malaria control. This study aimed to estimate the economic costs of uncomplicated malaria case management and explore the influence of health-seeking behaviours on those costs. METHODS: A knowledge, attitudes and practices (KAP) survey was applied to 680 households of fifteen communities in Mazan-Loreto in March 2017, then a socio-economic survey was conducted in September 2017 among 161 individuals with confirmed uncomplicated malaria in the past 3 months. Total costs per episode were estimated from both provider (Ministry of Health, MoH) and patient perspectives. Direct costs were estimated using a standard costing estimation procedure, while the indirect costs considered the loss of incomes among patients, substitute labourers and companions due to illness in terms of the monthly minimum wage. Sensitivity analysis evaluated the uncertainty of the average cost per episode. RESULTS: The KAP survey showed that most individuals (79.3%) that had malaria went to a health facility for a diagnosis and treatment, 2.7% received those services from community health workers, and 8% went to a drugstore or were self-treated at home. The average total cost per episode in the Mazan district was US$ 161. The cost from the provider's perspective was
US$ 30.85 per episode while from the patient's perspective the estimated cost was US$ 131 per episode. The average costs per Plasmodium falciparum episode (US$ 180) were higher than those per Plasmodium vivax episode (US$ 156) due to longer time lost from work by patients with P. falciparum infections (22.2 days) than by patients with P. vivax infections (17.0 days). The delayed malaria diagnosis (after 48 h of the onset of symptoms) was associated with the time lost from work due to illness (adjusted mean ratio 1.8; 95% CI 1.3, 2.6). The average cost per malaria episode was most sensitive to the uncertainty around the lost productivity cost due to malaria. CONCLUSIONS: Despite the provision of free malaria case management by MoH, there is delay in seeking care and the costs of uncomplicated malaria are mainly borne by the families. These costs are not well perceived by the society and the substantial financial impact of the disease can be frequently undervalued in public policy planning.

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Human Plasmodium vivax diversity, population structure and evolutionary origin.

More than 200 million malaria clinical cases are reported each year due to Plasmodium vivax, the most widespread Plasmodium species in the world. This species has been neglected and understudied for a long time, due to its lower mortality in comparison with Plasmodium falciparum. A renewed interest has emerged in the past decade with the discovery of antimalarial drug resistance and of severe and even fatal human cases. Nonetheless, today there are still significant gaps in our understanding of the population genetics and evolutionary history of P. vivax, particularly because of a lack of genetic data from Africa. To address these gaps, we genotyped 14 microsatellite loci in 834 samples obtained from 28 locations in 20 countries from around the world. We discuss the worldwide population genetic structure and diversity and the evolutionary origin of P. vivax in the world and its introduction into the Americas. This study demonstrates the importance of conducting genome-
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Anti-MSP-10 IgG indicates recent exposure to Plasmodium vivax infection in the Peruvian Amazon.

BACKGROUND Serological tools for the accurate detection of recent malaria exposure are needed to guide and monitor malaria control efforts. IgG responses against Plasmodium vivax and P. falciparum merozoite surface protein-10 (MSP10) were measured as a potential way to identify recent malaria exposure in the Peruvian Amazon.

METHODS A field-based study included 470 participants in a longitudinal cohort who completed a comprehensive evaluation: light microscopy and PCR on enrollment, at least 1 monthly follow-up by light microscopy, a second PCR, and serum and dried blood spots for serological analysis at the end of the follow-up. IgG titers against novel mammalian cell-produced recombinant PvMSP10 and PfMSP10 were determined by ELISA.

RESULTS During the follow-up period, 205 participants were infected, including 171 with P. vivax, 26 with P. falciparum, 6 with infections by both species but at different times, and 2 with mixed infections. Exposure to P. vivax was more accurately identified when serological responses to PvMSP10 were obtained from serum (sensitivity, 58.1%; specificity, 81.8%; AUC: 0.76) than from dried blood spots (sensitivity, 35.2%; specificity, 83.5%; AUC: 0.64) (PAUC < 0.001). Sensitivity was highest (serum, 82.9%; dried blood spot,
45.7%) with confirmed P. vivax infections occurring 7–30 days before sample collection; sensitivity decreased significantly in relation to time since last documented infection. PvMSP10 serological data did not show evidence of interspecies cross-reactivity. Anti-PfMSP10 responses poorly discriminated between P. falciparum-exposed and nonexposed individuals (AUC = 0.59; P > 0.05).

CONCLUSION Anti-PvMSP10 IgG indicates recent exposure to P. vivax at the population level in the Amazon region. Serum, not dried blood spots, should be used for such serological tests.

FUNDING Cooperative agreement U19AI089681 from the United States Public Health Service, NIH/National Institute of Allergy and Infectious Diseases, as the Amazonian International Center of Excellence in Malaria Research.

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BACKGROUND: Malaria diagnostics by rapid diagnostic test (RDT) relies primarily on the qualitative detection of Plasmodium falciparum histidine-rich protein 2 (PfHRP2) and Plasmodium spp lactate dehydrogenase (pLDH). As novel RDTs with increased sensitivity are being developed and implemented as point of care diagnostics, highly sensitive laboratory-based assays are needed for evaluating RDT performance. Here, a quantitative suspension array technology (qSAT) was developed, validated and applied for the simultaneous detection of PfHRP2 and pLDH.
in a variety of biological samples (whole blood, plasma and dried blood spots) from individuals living in different endemic countries.

RESULTS:
The qSAT was specific for the target antigens, with analytical ranges of 6.8 to 762.8 pg/ml for PfHRP2 and 78.1 to 17076.6 pg/ml for P. falciparum LDH (Pf-LDH). The assay detected Plasmodium vivax LDH (Pv-LDH) at a lower sensitivity than Pf-LDH (analytical range of 1093.20 to 187288.5 pg/ml).

Both PfHRP2 and pLDH levels determined using the qSAT showed to positively correlate with parasite densities determined by quantitative PCR (Spearman r = 0.59 and 0.75, respectively) as well as microscopy (Spearman r = 0.40 and 0.75, respectively), suggesting the assay to be a good predictor of parasite density. CONCLUSION: This immunoassay can be used as a reference test for the detection and quantification of PfHRP2 and pLDH, and could serve for external validation of RDT performance, to determine antigen persistence after parasite clearance, as well as a complementary tool to assess malaria burden in endemic settings.

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A pilot evaluation of alternative procedures to simplify LAMP-based malaria diagnosis in field conditions.

Highly-sensitive and field-friendly diagnostic tools are needed for accurate detection of low-density malaria infections. Although loop-mediated isothermal amplification (LAMP) fulfills these conditions, operational challenges are still encountered during pilot population screenings in remote settings when employing Loopamp MALARIA Pan/Pf detection kit (Eiken Chemical Co.). This study evaluates different procedures for the simplification of sample preparation and result reading steps of current LAMP protocols. The reference 'Boil & Spin' (B&S) pre-amplification procedure was compared to three alternative methods, along with a colorimetric staining protocol based on malachite green. Results suggested that the B&S supernatant transference step may be omitted without an impact on test performance, even when colorimetry was incorporated to facilitate results visualization.
centrifugation and/or heat-incubation were proved to be compatible with LAMP-based malaria DNA detection, but resulted in a low-to-moderate decrease in sensitivity and ambiguous result interpretation for the most straightforward protocol. Nevertheless, all simplified LAMP methods could still reach lower limits of detection than the currently used tools for malaria mass-screening (i.e. microscopy and rapid tests), indicating that these alternative strategies may deserve further consideration. This evaluation, therefore, demonstrates the feasibility of skipping some of the main procedural bottlenecks of LAMP-malaria protocols, a much-needed achievement to make point-of-care implementation of molecular diagnostics a reality.

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Microsatellite analysis reveals connectivity among geographically distant transmission zones of Plasmodium vivax in the Peruvian Amazon: A critical barrier to regional malaria elimination.
Despite efforts made over decades by the Peruvian government to eliminate malaria, Plasmodium vivax remains a challenge for public health decision-makers in the country. The uneven distribution of its incidence, plus its complex pattern of dispersion, has made ineffective control measures based on global information that lack the necessary detail to understand transmission fully. In this sense, population genetic tools can complement current surveillance. This study describes the genetic diversity and population structure from September 2012 to March 2015 in three geographically distant settlements, Cahuide (CAH), Lupuna (LUP) and Santa Emilia (STE), located in the Peruvian Amazon. A total of 777 P. vivax mono-infections, out of 3264, were genotyped. Among study areas, LUP showed 19.7% of polyclonal infections, and its genetic diversity (Hexp) was 0.544. Temporal analysis showed a significant increment of polyclonal infections and Hexp, and the introduction and persistence of a new parasite population since March 2013. In STE, 40.1% of infections were polyclonal, with Hexp = 0.596. The presence of four genetic clusters without signals of clonal expansion and infections with lower parasite densities compared against the other two areas were also found. At least four parasite populations were present in CAH in 2012, where, after June 2014, malaria cases decreased from 213 to 61, concomitant with a decrease in polyclonal infections (from 0.286 to 0.18), and expectedly variable Hexp. Strong signals of gene flow were present in the study areas and wide geographic distribution of highly diverse parasite populations were found. This study suggests that movement of malaria parasites by human reservoirs connects geographically distant malaria transmission areas in the Peruvian Amazon. The maintenance of high levels of parasite genetic
diversity through human mobility is a critical barrier to malaria elimination in this region.

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BACKGROUND: Different antigens are needed to characterize Plasmodium falciparum infection in terms of seroreactivity and targets for invasion inhibition, in order to guide and identify the proper use of such proteins as tools for the development of serological markers and/or as vaccine candidates. METHODS: IgG responses in 84 serum samples from individuals with P. falciparum infection [classified as symptomatic (Sym) or asymptomatic (Asym)], or acute Plasmodium vivax infection, from the Peruvian Amazon region, were evaluated by enzyme-linked immunosorbent assays specific for a baculovirus-produced recombinant protein P. falciparum Merozoite Surface Protein 10 (rMSP10) and for non-EGF region selected peptides of PfMSP10 selected by a bioinformatics tool (PfMSP10-1, PfMSP10-2 and PfMSP10-3). Monoclonal antibodies against the selected peptides were evaluated by western blotting, confocal microscopy and inhibition invasion assays. RESULTS: Seroreactivity analysis of the P. falciparum Sym- and Asym-infected individuals against rMSP10 showed a higher response as compared to the individuals with P. vivax acute infection. IgG responses against peptide PfMSP10-1 were weak. Interestingly high IgG response was found against peptide PfMSP10-2 and the combination of peptides PfMSP10-1 + PfMSP10-2. Monoclonal antibodies
were capable of detecting native PfMSP10 on purified schizonts by western blot and confocal microscopy. A low percentage of inhibition of merozoite invasion of erythrocytes in vitro was observed when the monoclonal antibodies were compared with the control antibody against AMA-1 antigen.

Further studies are needed to evaluate the role of PfMSP10 in the merozoite invasion. CONCLUSIONS: The rMSP10 and the PfMSP10-2 peptide synthesized for this study may be useful antigens for evaluation of P. falciparum malaria exposure in Sym and Asym individuals from the Peruvian Amazon region. Moreover, these antigens can be used for further investigation of the role of this protein in other malaria-endemic areas.

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A multiplex qPCR approach for detection of pfhrp2 and pfhrp3 gene deletions in multiple strain infections of Plasmodium falciparum.

The rapid and accurate diagnosis of Plasmodium falciparum malaria is an essential factor in malaria control.
Currently, malaria diagnosis in the field depends heavily on using rapid diagnostic tests (RDTs) many of which detect circulating parasite-derived histidine-rich protein 2 antigen (PfHRP2) in capillary blood. P. falciparum strains lacking PfHRP2, due to pfhrp2 gene deletions, are an emerging threat to malaria control programs. The novel assay described here, named qHRP2/3-del, is well suited for high-throughput screening of P. falciparum isolates to identify these gene deletions. The qHRP2/3-del assay identified pfhrp2 and pfhrp3 deletion status correctly in 93.4% of samples with parasitemia levels higher than 5 parasites/microL when compared to nested PCR. The qHRP2/3-del assay can correctly identify pfhrp2 and pfhrp3 gene deletions in multiple strain co-infections, particularly prevalent in Sub-Saharan countries. Deployment of this qHRP2/3-del assay will provide rapid insight into the prevalence and potential spread of P. falciparum isolates that escape surveillance by RDTs.

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LA - eng
GR - U19 AI089681/AI/NIAID NIH HHS/United States
GR - U19 AI110820/AI/NIAID NIH HHS/United States
PT - Journal Article
PT - Research Support, N.I.H., Extramural
PT - Research Support, Non-U.S. Gov't
DEP - 20190911
PL - England
TA - Sci Rep
JT - Scientific reports
JID - 101563288
RN - 0 (Antigens, Protozoan)
RN - 0 (HRP-2 antigen, Plasmodium falciparum)
RN - 0 (HRP3 protein, Plasmodium falciparum)
RN - 0 (Protozoan Proteins)
SB - IM
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MH - *Gene Deletion
MH - Plasmodium falciparum/*genetics/physiology
MH - Polymerase Chain Reaction/*methods
MH - Protozoan Proteins/*genetics/*metabolism
PMC - PMC6739368
EDAT- 2019/09/13 06:00
MHDA- 2020/10/29 06:00
Higher risk of malaria transmission outdoors than indoors by Nyssorhynchus darlingi in riverine communities in the Peruvian Amazon.

BACKGROUND: Malaria remains an important public health problem in Peru where incidence has been increasing since 2011. Of over 55,000 cases reported in 2017, Plasmodium vivax was the predominant species (76%), with P. falciparum responsible for the remaining 24%. Nyssorhynchus darlingi (previously Anopheles darlingi) is the main vector in Amazonian Peru, where hyperendemic Plasmodium transmission pockets have been found. Mazan district has pronounced spatial heterogeneity of P. vivax malaria. However, little is known about behavior, ecology or seasonal dynamics of Ny. darlingi in Mazan. This study aimed to gather baseline information about bionomics of malaria vectors and transmission risk factors in a hyperendemic malaria area of Amazonian Peru. METHODS: To assess vector biology metrics, five surveys (two in the dry and three in the rainy season), including collection of sociodemographic information, were conducted in four communities in 2016–2017 on the Napo (Urco
Mirano, URC; Salvador, SAL and Mazan Rivers (Visto Bueno, VIB; Libertad, LIB). Human-biting rate (HBR), entomological inoculation rate (EIR) and human blood index (HBI) were measured to test the hypothesis of differences in entomological indices of Ny. darlingi between watersheds. A generalized linear mixed effect model (GLMM) was constructed to model the relationship between household risk factors and the EIR.

**RESULTS:**
Nyssorhynchus darlingi comprised 95% of 7117 Anophelinae collected and its abundance was significantly higher along the Mazan River. The highest EIRs (3.03–4.54) were detected in March and June in URC, LIB and VIB, and significantly more Ny. darlingi were infected outdoors than indoors. Multivariate analysis indicated that the EIR was >12 times higher in URC compared with SAL. The HBI ranged from 0.42–0.75; humans were the most common blood source, followed by Galliformes and cows. There were dramatic differences in peak biting time and malaria incidence with similar bednet coverage in the villages. **CONCLUSIONS:**
Nyssorhynchus darlingi is the predominant contributor to malaria transmission in the Mazan District, Peru. Malaria risk in these villages is higher in the peridomestic area, with pronounced heterogeneities between and within villages on the Mazan and the Napo Rivers. Spatiotemporal identification and quantification of the prevailing malaria transmission would provide new evidence to orient specific control measures for vulnerable or at high risk populations.

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Plasmodium vivax parasites preferentially invade reticulocyte cells in a multistep process that is still poorly understood. In this study, we used ex vivo invasion assays and population genetic analyses to investigate the involvement of complement receptor 1 (CR1) in P. vivax invasion. First, we observed that P. vivax invasion of reticulocytes was consistently reduced when CR1 surface expression was reduced through enzymatic cleavage, in the presence of naturally low-CR1-expressing cells compared with high-CR1-expressing cells, and with the addition of soluble CR1, a known inhibitor of P. falciparum invasion. Immuno-precipitation experiments with P. vivax Reticulocyte Binding Proteins showed no evidence of complex formation. In addition, analysis of CR1 genetic data for worldwide human populations with different exposure to malaria parasites show significantly higher frequency of CR1 alleles associated with low receptor expression on the surface of RBCs and higher linkage disequilibrium in human populations exposed to P. vivax malaria compared with unexposed populations. These results are consistent with a positive selection of low-CR1-expressing alleles in vivax-endemic areas. Collectively, our findings demonstrate that CR1 availability on the surface of RBCs modulates P. vivax invasion. The identification of new molecular interactions is crucial to guiding the rational development of new therapeutic interventions against vivax malaria.
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In Amazonian Peru, the primary malaria vector, Nyssorhynchus...
Darlingi (formerly Anopheles darlingi), is difficult to target using standard vector control methods because it mainly feeds and rests outdoors. Larval source management could be a useful supplementary intervention, but to determine its feasibility, more detailed studies on the larval ecology of Ny. darlingi are essential. We conducted a multi-level study of the larval ecology of Anophelinae mosquitoes in the peri-Iquitos region of Amazonian Peru, examining the environmental characteristics of the larval habitats of four species, comparing the larval microbiota among species and habitats, and placing Ny. darlingi larval habitats in the context of spatial heterogeneity in human malaria transmission. We collected Ny. darlingi, Nyssorhynchus rangeli (formerly Anopheles rangeli), Nyssorhynchus triannulatus s.l. (formerly Anopheles triannulatus s.l.), and Nyssorhynchus sp. nr. konderi (formerly Anopheles sp. nr. konderi) from natural and artificial water bodies throughout the rainy and dry seasons. We found that, consistent with previous studies in this region and in Brazil, the presence of Ny. darlingi was significantly associated with water bodies in landscapes with more recent deforestation and lower light intensity. Nyssorhynchus darlingi presence was also significantly associated with a lower vegetation index, other Anophelinae species, and emergent vegetation. Though they were collected in the same water bodies, the microbial communities of Ny. darlingi larvae were distinct from those of Ny. rangeli and Ny. triannulatus s.l., providing evidence either for a species-specific larval microbiome or for segregation of these species in distinct microhabitats within each water body. We demonstrated that houses with more reported malaria cases were located closer to Ny. darlingi larval habitats; thus, targeted control of these sites could help ameliorate malaria risk. The co-occurrence of Ny. darlingi larvae in
water bodies with other putative malaria vectors increases the potential impact of larval source management in this region.

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Infectious disease dynamics are affected by human mobility more powerfully than previously thought, and thus reliable traceability data are essential. In rural riverine settings, lack of infrastructure and dense tree coverage deter the implementation of cutting-edge technology to collect human mobility data. To overcome this challenge, this study proposed the use of a novel open mobile mapping tool, GeoODK. This study consists of a purposive sampling of 33 participants in six villages with contrasting patterns of malaria transmission that demonstrates a feasible approach to map human mobility. The self-reported traceability data
allowed the construction of the first human mobility framework in rural riverine villages in the Peruvian Amazon. The mobility spectrum in these areas resulted in travel profiles ranging from 2 hours to 19 days; and distances between 10 to 167 km. Most Importantly, occupational-related mobility profiles with the highest displacements (in terms of time and distance) were observed in commercial, logging, and hunting activities. These data are consistent with malaria transmission studies in the area that show villages in watersheds with higher human movement are concurrently those with greater malaria risk. The approach we describe represents a potential tool to gather critical information that can facilitate malaria control activities.

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LA - eng
SI - figshare/10.6084/m9.figshare.7091075.v1
PT - Journal Article
DEP - 20190122
PL - United States
TA - PeerJ
JT - PeerJ
JID - 101603425
PMC - PMC6346981
OTO - NOTNLM
OT - Amazon
OT - Contact network
OT - Epidemics
OT - Human mobility
OT - Infectious diseases
OT - Malaria
OT - Network
COIS - The authors declare there are no competing interests.
EDAT- 2019/01/31 06:00
MHDA- 2019/01/31 06:01
CRDT- 2019/01/31 06:00
PHST- 2018/10/23 00:00 [received]
PHST- 2018/12/18 00:00 [accepted]
PMST- 2019/01/31 06:00 [entrez]
PHST- 2019/01/31 06:00 [pubmed]
PHST- 2019/01/31 06:01 [medline]
AID - 10.7717/peerj.6298 [doi]
AID - 6298 [pii]
PST - epublish
AB - Interest in larval source management (LSM) as an adjunct intervention to control and eliminate malaria transmission has recently increased mainly because long-lasting insecticidal nets (LLINs) and indoor residual spray (IRS) are ineffective against exophagic and exophilic mosquitoes. In Amazonian Peru, the identification of the most productive, positive water bodies would increase the impact of targeted mosquito control on aquatic life stages. The present study explores the use of unmanned aerial vehicles (drones) for identifying Nyssorhynchus darlingi (formerly Anopheles darlingi) breeding sites with high-resolution imagery (~0.02m/pixel) and their multispectral profile in Amazonian Peru. Our results show that high-resolution multispectral imagery can discriminate a profile of water bodies where Ny. darlingi is most likely to breed (overall accuracy 86.73%-96.98%) with a moderate differentiation of spectral bands. This work provides proof-of-concept of the use of high-resolution images to detect malaria vector breeding sites in Amazonian Peru and such innovative methodology could be crucial for LSM malaria integrated interventions.

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LA - eng
GR - R01 AI110112/AI/NIAID NIH HHS/United States
GR - U19 AI089681/AI/NIAID NIH HHS/United States
PT - Journal Article
PT - Research Support, N.I.H., Extramural
PT - Research Support, Non-U.S. Gov't
DEP - 20190117
PL - United States
TA - PLoS Negl Trop Dis
JT - PLoS neglected tropical diseases
JID - 101291488
SB - IM
MH - Animals
MH - Anopheles/*growth & development
MH - *Ecosystem
MH - Entomology/*methods
MH - Female
MH - Image Processing, Computer-Assisted/*methods
MH - Mosquito Vectors/*growth & development
MH - Optical Imaging/*methods
MH - Peru
MH - Proof of Concept Study
PMC - PMC6353212
Nyssorhynchus dunhami: bionomics and natural infection by Plasmodium falciparum and P. vivax in the Peruvian Amazon.

BACKGROUND Nyssorhynchus dunhami, a member of the Nuneztovari Complex, has been collected in Brazil, Colombia, and Peru and described as zoophilic. Although to date Ny. dunhami has not been documented to be naturally infected by Plasmodium, it is frequently misidentified as other Oswaldoi subgroup species that are local or regional malaria vectors.

OBJECTIVES The current study seeks to verify the morphological identification of Nuneztovari Complex species collected in the peri-Iquitos region of Amazonian Peru, to determine their Plasmodium infection status, and to describe ecological characteristics of their larval habitats. METHODS We collected Ny. nuneztovari s.l. adults in
2011-2012, and Ny. nuneztovari s.l. larvae and adults in 2016-2017. When possible, samples were identified molecularly using cytochrome c oxidase subunit I (COI) barcode sequencing. Adult Ny. nuneztovari s.l. from 2011-2012 were tested for Plasmodium using real-time PCR. Environmental characteristics associated with Ny. nuneztovari s.l. larvae-positive water bodies were evaluated. FINDINGS We collected 590 Ny. nuneztovari s.l. adults and 116 larvae from eight villages in peri-Iquitos. Of these, 191 adults and 111 larvae were identified by COI sequencing; all were Ny. dunhami. Three Ny. dunhami were infected with P. falciparum, and one with P. vivax, all collected from one village on one night. Ny. dunhami larvae were collected from natural and artificial water bodies, and their presence was positively associated with other Anophelinae larvae and amphibians, and negatively associated with people living within 250m. MAIN CONCLUSIONS Of Nuneztovari Complex species, we identified only Ny. dunhami across multiple years in eight peri-Iquitos localities. This study is, to our knowledge, the first report of natural infection of molecularly identified Ny. dunhami with Plasmodium. We advocate the use of molecular identification methods in this region to monitor Ny. dunhami and other putative secondary malaria vectors to more precisely evaluate their importance in malaria transmission.
Background: Faced with the resurgence of malaria, malaria surveillance in the Peruvian Amazon incorporated consecutive active case detection (ACD) interventions using light microscopy (LM) as reactive measure in communities with an unusual high number of cases during high transmission season (HTS). We assessed the effectiveness in malaria detection of this local ACD-based strategy. Methods: A cohort study was conducted in
June(-)July 2015 in Mazan, Loreto. Four consecutive ACD interventions at intervals of 10 days were conducted in four riverine communities (Gamitanacocha, Primero de Enero, Libertad and Urco Mirano). In each intervention, all inhabitants were visited at home, and finger-prick blood samples collected for immediate diagnosis by LM and on filter paper for later analysis by quantitative real-time polymerase chain reaction (qPCR). Effectiveness was calculated by dividing the number of malaria infections detected using LM by the number of malaria infections detected by delayed qPCR. Results: Most community inhabitants (88.1%, 822/933) were present in at least one of the four ACD interventions. A total of 451 infections were detected by qPCR in 446 participants (54.3% of total participants); five individuals had two infections. Plasmodium vivax was the predominant species (79.8%), followed by P. falciparum (15.3%) and P. vivax-P. falciparum co-infections (4.9%). Most qPCR-positive infections were asymptomatic (255/448, 56.9%). The ACD-strategy using LM had an effectiveness of 22.8% (detection of 103 of the total qPCR-positive infections). Children aged 5(-)14 years, and farming as main economic activity were associated with P. vivax infections.

Conclusions: Although the ACD-strategy using LM increased the opportunity of detecting and treating malaria infections during HTS, the number of detected infections was considerably lower than the real burden of infections (those detected by qPCR).

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BACKGROUND: Microscopic examination of Giemsa-stained blood films remains a major form of diagnosis in malaria case management, and is a reference standard for research. However, as with other visualization-based diagnoses, accuracy depends on individual technician performance, making standardization difficult and reliability poor. Automated image recognition based on machine-learning, utilizing convolutional neural networks, offers potential to overcome these drawbacks. A prototype digital microscope device employing an algorithm based on machine-learning, the Autoscope, was assessed for its potential in malaria microscopy. Autoscope was tested in the Iquitos region of Peru in 2016 at two peripheral health facilities, with routine microscopy and PCR as reference standards. The main outcome measures include sensitivity and specificity of diagnosis of malaria from Giemsa-stained blood films, using PCR as reference. METHODS: A cross-sectional, observational trial was conducted at two peripheral primary health facilities in Peru. 700 participants were enrolled with the criteria: (1) age between 5 and 75 years, (2) history of fever in the last 3 days or elevated temperature on admission, (3) informed consent. The main outcome measures included sensitivity and specificity of diagnosis of malaria from Giemsa-stained blood films, using PCR as reference. RESULTS: At the San Juan clinic, sensitivity of Autoscope for diagnosing malaria was 72% (95% CI 64-80%), and specificity was 85% (95% CI 79-90%). Microscopy performance was similar to Autoscope, with sensitivity 68% (95% CI 59-76%) and specificity 100% (95% CI 98-100%). At San Juan, 85% of prepared slides had a minimum of 600 WBCs imaged, thus meeting Autoscope's design
assumptions. At the second clinic, Santa Clara, the sensitivity of Autoscope was 52% (95% CI 44–60%) and specificity was 70% (95% CI 64–76%). Microscopy performance at Santa Clara was 42% (95% CI 34–51) and specificity was 97% (95% CI 94–99). Only 39% of slides from Santa Clara met Autoscope's design assumptions regarding WBCs imaged.

CONCLUSIONS: Autoscope's diagnostic performance was on par with routine microscopy when slides had adequate blood volume to meet its design assumptions, as represented by results from the San Juan clinic. Autoscope's diagnostic performance was poorer than routine microscopy on slides from the Santa Clara clinic, which generated slides with lower blood volumes. Results of the study reflect both the potential for artificial intelligence to perform tasks currently conducted by highly-trained experts, and the challenges of replicating the adaptiveness of human thought processes.

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LA - eng
PT - Comparative Study
PT - Journal Article
DEP - 20180925
PL - England
TA - Malar J
JT - Malaria journal
JID - 101139802
SB - IM
MH - Adolescent
Acceptability of a herd immunity-focused, transmission-blocking malaria vaccine in malaria-endemic communities in the Peruvian Amazon: an exploratory study.
BACKGROUND: A transmission-blocking vaccine (TBV) to prevent malaria-infected humans from infecting mosquitoes has been increasingly considered as a tool for malaria control and elimination. This study tested the hypothesis that a malaria TBV would be acceptable among residents of a malaria-hypoendemic region. METHODS: The study was carried out in six Spanish-speaking rural villages in the Department of Loreto in the Peruvian Amazon. These villages comprise a cohort of 430 households associated with the Peru-Brazil International Centre for Excellence in Malaria Research. Individuals from one-third (143) of enrolled households in an ongoing longitudinal, prospective cohort study in 6 communities in Loreto, Peru, were randomly selected to participate by answering a pre-validated questionnaire. RESULTS: All 143 participants expressed desire for a malaria vaccine in general; only 1 (0.7%) expressed unwillingness to receive a transmission-blocking malaria vaccine. Injection was considered most acceptable for adults (97.2%); for children drops in the mouth were preferred (96.8%). Acceptability waned marginally with the prospect of multiple injections (83.8%) and different projected efficacies at 70 and 50% (90.1 and 71.8%, respectively). Respondents demonstrated clear understanding that the vaccine was for community, rather than personal, protection against malaria infection.

DISCUSSION: In this setting of the Peruvian Amazon, a transmission-blocking malaria vaccine was found to be almost universally acceptable. This study is the first to report that residents of a malaria-endemic region have been queried regarding a malaria vaccine strategy that policymakers in the industrialized world often dismiss as altruistic.
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In vitro culture of Plasmodium vivax liver stages underlies key understandings of the fundamental biology of this parasite, particularly the latent, hypnozoite stage, toward drug and vaccine development. Here, we report systematic production of Plasmodium vivax sporozoites in colonized Anopheles darlingi mosquitoes in the Peruvian Amazon. Human subject-derived P. vivax-infected blood was fed to Anopheles darlingi females using standard membrane feedings assays. Optimizing A. darlingi infection and sporozoite production included replacement of infected patient donor serum with naive donor serum, comparing anticoagulants in processing blood samples, and addition of penicillin-streptomycin and ATP to infectious blood meals. Replacement of donor serum by naive serum in the P. vivax donor blood increased oocysts in the mosquito midgut, and heparin, as anticoagulant, was associated with the highest sporozoite yields. Maintaining blood-fed mosquitoes on penicillin-streptomycin in sugar significantly extended mosquito survival which enabled greater sporozoite yield. In this study, we have shown that a robust P. vivax
sporozoite production is feasible in a malaria-endemic setting where infected subjects and a stable A. darlingi colony are brought together, with optimized laboratory conditions.

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AB - BACKGROUND: In Loreto Department, Peru, a successful 2005-2010 malaria control programme (known as PAMAFRO) included massive distribution of long-lasting insecticidal nets (LLINs). Additional local distribution of LLINs occurred in individual villages, but not between 2012 and 2015. A 2011-2012 study of the primary regional malaria vector Anopheles darlingi detected a trend of increased exophagy compared with pre-PAMAFRO behaviour. For the present study, An. darlingi were collected in three villages in Loreto in 2013-2015 to test two hypotheses: (1) that between LLIN distributions, An. darlingi reverted to pre-intervention biting behaviour; and, (2) that there are separate sub-populations of An. darlingi in Loreto with distinct biting behaviour. RESULTS: In 2013-2015 An. darlingi were collected by human landing catch during the rainy and dry seasons in the villages of Lupuna and Cahuide. The abundance of An. darlingi varied substantially across years, villages and time periods, and there was a twofold decrease in the ratio of
An. darlingi over the study period. Unexpectedly, there was evidence of a rainy season population decline in An. darlingi. Plasmodium-infected An. darlingi were detected indoors and outdoors throughout the night, and the monthly An. darlingi human biting rate was correlated with the number of malaria cases. Using nextRAD genotyping-by-sequencing, 162 exophagic and endophagic An. darlingi collected at different times during the night were genotyped at 1021 loci. Based on model-based and non-model-based analyses, all genotyped An. darlingi belonged to a homogeneous population, with no evidence for genetic differentiation by biting location or time. CONCLUSIONS: This study identified a decreasing proportion of exophagic An. darlingi in two villages in the years between LLIN distributions. As there was no evidence for genetic differentiation between endophagic and exophagic An. darlingi, this shift in biting behaviour may be the result of behavioural plasticity in An. darlingi, which shifted towards increased exophagy due to repellence by insecticides used to impregnate LLINs and subsequently reverted to increased endophagy as the nets aged. This study highlights the need to target vector control interventions to the biting behaviour of local vectors, which, like malaria risk, shows high temporal and spatial heterogeneity.

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Evolutionary structure of Plasmodium falciparum major variant surface antigen genes in South America: Implications for epidemic transmission and surveillance.

Strong founder effects resulting from human migration out of...
Africa have led to geographic variation in single nucleotide polymorphisms (SNPs) and microsatellites (MS) of the malaria parasite, Plasmodium falciparum. This is particularly striking in South America where two major founder populations of P. falciparum have been identified that are presumed to have arisen from the transatlantic slave trade. Given the importance of the major variant surface antigen of the blood stages of P. falciparum as both a virulence factor and target of immunity, we decided to investigate the population genetics of the genes encoding "Plasmodium falciparum Erythrocyte Membrane Protein 1" (Pf EMP1) among several countries in South America, in order to evaluate the transmission patterns of malaria in this continent. Deep sequencing of the DBLalpha domain of var genes from 128 P. falciparum isolates from five locations in South America was completed using a 454 high throughput sequencing protocol. Striking geographic variation in var DBLalpha sequences, similar to that seen for SNPs and MS markers, was observed. Colombia and French Guiana had distinct var DBLalpha sequences, whereas Peru and Venezuela showed an admixture. The importance of such geographic variation to herd immunity and malaria vaccination is discussed.
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BACKGROUND: The incidence of malaria due both to Plasmodium falciparum and Plasmodium vivax in the Peruvian Amazon has risen in the past 5 years. This study tested the hypothesis that the maintenance and emergence of malaria in hypoendemic regions such as Amazonia is determined by submicroscopic and asymptomatic Plasmodium parasitaemia carriers. The present study aimed to precisely quantify the rate of very-low parasitaemia carriers in two sites of the Peruvian Amazon in relation to transmission patterns of P. vivax and P. falciparum in this area.

METHODS: This study was carried out within the Amazonian-ICEMR longitudinal cohort. Blood samples were collected for light microscopy diagnosis and packed red blood cell (PRBC) samples were analysed by qPCR. Plasma samples were tested for total IgG reactivity against recombinant PvMSP-10 and PfMSP-10 antigens by ELISA. Occupation and age 10 years and greater were considered surrogates of occupation-related mobility. Risk factors for P. falciparum and P. vivax infections detected by PRBC-qPCR were assessed by multilevel logistic regression models.

RESULTS: Among 450 subjects, the prevalence of P. vivax by PRBC-PCR (25.1%) was sixfold higher than that determined by microscopy (3.6%). The prevalence of P. falciparum infection was 4.9% by PRBC-PCR and 0.2% by microscopy. More than 40% of infections had parasitaemia under 5 parasites/µL. Multivariate analysis for infections detected by PRBC-PCR showed that
participants with recent settlement in the study area (AOR 2.1; 95% CI 1.03:4.2), age \( \geq 30 \) years (AOR 3.3; 95% CI 1.6:6.9) and seropositivity to P. vivax (AOR 1.8; 95% CI 1.0:3.2) had significantly higher likelihood of P. vivax infection, while the odds of P. falciparum infection was higher for participants between 10 and 29 years (AOR 10.7; 95% CI 1.3:91.1) and with a previous P. falciparum infection (AOR 10.4; 95% CI 1.5:71.1). CONCLUSIONS: This study confirms the contrasting transmission patterns of P. vivax and P. falciparum in the Peruvian Amazon, with stable local transmission for P. vivax and the source of P. falciparum to the study villages dominated by very low parasitaemia carriers, age 10 years and older, who had travelled away from home for work and brought P. falciparum infection with them.

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GR - U19 AI089681/AI/NIAID NIH HHS/United States
PT - Journal Article
PT - Research Support, N.I.H., Extramural
PT - Research Support, Non-U.S. Gov't
DEP - 20171016
PL - England
TA - Malar J
JT - Malaria journal
JID - 101139802
SB - IM
MH - Adolescent
MH - Adult
MH - Asymptomatic Infections/*epidemiology
MH - Child
MH - Cross-Sectional Studies
MH - Female
MH - Humans
MH - Malaria, Falciparum/*epidemiology/parasitology
MH - Malaria, Vivax/*epidemiology/parasitology
MH - Male
MH - Multivariate Analysis
MH - Parasitemia/*epidemiology/parasitology
MH - Peru/epidemiology
MH - Plasmodium falciparum/*isolation & purification
MH - Plasmodium vivax/*isolation & purification
MH - Prevalence
MH - Seroepidemiologic Studies
MH - Young Adult
PMC - PMC5644076
OTO - NOTNLM
OT - Human mobility
OT - MSP10
OT - Malaria
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OT - Molecular epidemiology
OT - Plasmodium falciparum
OT - Plasmodium vivax
OT - Sensitivity
OT - Serology
OT - Specificity
OT - Sub-microscopic
EDAT- 2017/10/19 06:00
MHDA- 2018/05/15 06:00
CRDT- 2017/10/18 06:00
PHST- 2017/06/30 00:00 [received]
PHST- 2017/10/11 00:00 [accepted]
PHST- 2017/10/18 06:00 [entrez]
PHST- 2017/10/19 06:00 [pubmed]
PHST- 2018/05/15 06:00 [medline]
AID - 10.1186/s12936-017-2063-x [doi]
AID - 10.1186/s12936-017-2063-x [pii]
PST - epublish
BACKGROUND: Loop-mediated isothermal DNA amplification (LAMP) methodology offers an opportunity for point-of-care (POC) molecular detection of asymptomatic malaria infections. However, there is still little evidence on the feasibility of implementing this technique for population screenings in isolated field settings. METHODS: Overall, we recruited 1167 individuals from terrestrial ('road') and hydric ('riverine') communities of the Peruvian Amazon for a cross-sectional survey to detect asymptomatic malaria infections. The technical performance of LAMP was evaluated in a subgroup of 503 samples, using real-time Polymerase Chain Reaction (qPCR) as reference standard. The operational feasibility of introducing LAMP testing in the mobile screening campaigns was assessed based on field-suitability parameters, along with a pilot POC-LAMP assay in a riverine community without laboratory infrastructure. RESULTS: LAMP had a sensitivity of 91.8% (87.7–94.9) and specificity of 91.9% (87.8–95.0), and the overall accuracy was significantly better among samples collected during road screenings than riverine communities (p<0.004). LAMP–based diagnostic strategy was successfully implemented within the field-team logistics and the POC–LAMP pilot in the
Riverine community allowed for a reduction in the turnaround time for case management, from 12-24 hours to less than 5 hours. Specimens with haemolytic appearance were regularly observed in riverine screenings and could help explaining the hindered performance/interpretation of the LAMP reaction in these communities. CONCLUSIONS: LAMP-based molecular malaria diagnosis can be deployed outside of reference laboratories, providing similar performance as qPCR. However, scale-up in remote field settings such as riverine communities needs to consider a number of logistical challenges (e.g. environmental conditions, labour-intensiveness in large population screenings) that can influence its optimal implementation.
Micro-epidemiology and spatial heterogeneity of P. vivax parasitaemia in riverine communities of the Peruvian Amazon: A multilevel analysis.

Malaria has steadily increased in the Peruvian Amazon over the last five years. This study aimed to determine the parasite prevalence and micro-geographical heterogeneity of Plasmodium vivax parasitaemia in communities of the Peruvian Amazon. Four cross-sectional active case detection surveys were conducted between May and July 2015 in four riverine communities in Mazan district. Analysis of 2785 samples of 820 individuals nested within 154 households for Plasmodium parasitaemia was carried out using light microscopy and qPCR. The spatio-temporal distribution of Plasmodium parasitaemia, dominated by P. vivax, was shown...
to cluster at both household and community levels. Of enrolled individuals, 47% had at least one P. vivax parasitaemia and 10% P. falciparum, by qPCR, both of which were predominantly sub-microscopic and asymptomatic. Spatial analysis detected significant clustering in three communities. Our findings showed that communities at small-to-moderate spatial scales differed in P. vivax parasite prevalence, and multilevel Poisson regression models showed that such differences were influenced by factors such as age, education, and location of households within high-risk clusters, as well as factors linked to a local micro-geographic context, such as travel and occupation. Complex transmission patterns were found to be related to human mobility among communities in the same micro-basin.

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BACKGROUND: Understanding the dynamics of malaria transmission in diverse endemic settings is key for designing and implementing locally adapted and sustainable control and elimination strategies. A parasitological and epidemiological survey was conducted in September–October 2012, as a baseline underlying a 3-year population-based longitudinal cohort study. The aim was to characterize malaria transmission patterns in two contrasting ecological rural sites in the Peruvian Amazon, Lupuna (LUP), a riverine environment, and Cahuide (CAH), associated with road-linked deforestation. METHODS: After a full population census, 1941 individuals 3 years and older (829 in LUP, 1112 in CAH) were interviewed, clinically examined and had a blood sample taken for the detection of malaria parasites by microscopy and PCR. Species-specific parasite prevalence was estimated overall and by site. Multivariate logistic regression models assessed risk factors for parasite infection by PCR, while SaTScan detected spatial clusters of PCR-positive individuals within each site. In addition, data from routine malaria surveillance in the period 2009–2012 were obtained. RESULTS: Parasite prevalence by PCR was higher in CAH than in LUP for Plasmodium vivax (6.2% vs. 3.9%) and for Plasmodium falciparum (2.6% vs. 1.2%). Among PCR-confirmed infections, asymptomatic (Asy) parasite carriers were always more common than symptomatic (Sy) infections for P. vivax (Asy/Sy ratio: 2/1 in LUP and 3.7/1 in CAH) and for P. falciparum (Asy/Sy ratio: 1.3/1 in
Sub-patent (Spat) infections also predominated over patent (Pat) infections for both species: P. vivax (Spat/Pat ratio: 2.8/1 in LUP and 3.7/1 in CAH) and P. falciparum malaria (Spat/Pat ratio: 1.9/1 in LUP and 26/0 in CAH). For CAH, age, gender and living in a household without electricity were significantly associated with P. vivax infection, while only age and living in a household with electricity was associated with P. falciparum infection. For LUP, only household overcrowding was associated with P. falciparum infection. The spatial analysis only identified well-defined clusters of P. vivax and P. falciparum infected individuals in CAH. Reported malaria incidence indicated that malaria transmission has long occurred in LUP with primarily seasonal patterns, and confirmed a malaria outbreak in CAH since May 2012.

CONCLUSIONS: This parasitological and epidemiological baseline assessment demonstrates that malaria transmission and parasite prevalence is heterogeneous in the Peruvian Amazon, and influenced by local socio-demographics and ecological contexts. Riverine and road construction/deforestation contexts must be taken into account in order to carry out effective anti-malaria control and elimination efforts.

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Predominance of asymptomatic and sub-microscopic infections characterizes the Plasmodium gametocyte reservoir in the Peruvian Amazon.

Malaria transmission requires that Anopheles mosquitoes ingest Plasmodium gametocyte stages circulating in the human bloodstream. In the context of malaria elimination, understanding the epidemiology of gametocytes relative to all Plasmodium infections and the contribution of asymptomatic and sub-microscopic parasite carriers to the gametocyte reservoir is necessary, especially in low endemic settings.
with predominance of P. vivax. A 13-month longitudinal study was conducted in two communities (n = 1935 individuals) of Loreto Department, Peru, with five active screenings for Plasmodium infections and gametocyte stages by quantitative real-time PCR (qPCR) and reverse transcription (RT)-qPCR, respectively. Parasite prevalence by qPCR was 7.2% for P. vivax (n = 520/7235; range by survey 6.0%-8.1%) and 3.2% for P. falciparum (n = 235/7235; range by survey 0.4%-7.7%). Sub-microscopic infections accounted for 73.5% of P. vivax (range by survey 60%-89%) and almost the totality of P. falciparum cases. Gametocytes were found in 28.4% P. vivax infections (range by survey 18.7%-34.1%), with a peak of 61.5% in one community at the start of the transmission season. About 59.8% of all P. vivax gametocyte carriers were asymptomatic and 31.9% were sub-microscopic. Age patterns for gametocyte prevalence paralleled asexual stage infections and peaked among >15-25 year old individuals. Asexual parasite density was found to be the strongest predictor for P. vivax gametocyte presence in longitudinal multivariate analysis (odds ratio 2.33 [95% confidence interval 1.96, 2.78]; P<0.001). Despite significant differences in seasonality patterns and P. vivax prevalence found at the local scale, sub-microscopic and asymptomatic infections predominate and contribute significantly to the gametocyte reservoir in different communities of the Peruvian Amazon. Control and elimination campaigns need sensitive tools to detect all infections that escape routine malaria surveillance, which may contribute to maintain transmission in the region.

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Defining the next generation of Plasmodium vivax diagnostic tests for control and elimination: Target product profiles.
The global prevalence of malaria has decreased over the past fifteen years, but similar gains have not been realized against *Plasmodium vivax* because this species is less responsive to conventional malaria control interventions aimed principally at *P. falciparum*. Approximately half of all malaria cases outside of Africa are caused by *P. vivax*. This species places dormant forms in human liver that cause repeated clinical attacks without involving another mosquito bite. The diagnosis of acute patent *P. vivax* malaria relies primarily on light microscopy. Specific rapid diagnostic tests exist but typically perform relatively poorly compared to those for *P. falciparum*. Better diagnostic tests are needed for *P. vivax*. To guide their development, FIND, in collaboration with *P. vivax* experts, identified the specific diagnostic needs associated with this species and defined a series of three distinct target product profiles, each aimed at a particular diagnostic application: (i) point-of-care of acutely ill patients for clinical care purposes; (ii) point-of-care asymptomatic and otherwise sub-patent residents for public health purposes, e.g., mass screen and treat campaigns; and (iii) ultra-sensitive not point-of-care diagnosis for epidemiological research/surveillance purposes. This report presents and discusses the rationale for these *P. vivax*-specific diagnostic target product profiles. These contribute to the rational development of fit-for-purpose diagnostic tests suitable for the clinical management, control and elimination of *P. vivax* malaria.

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PT - Journal Article
PT - Research Support, Non-U.S. Gov't
DEP - 20170403
PL - United States
TA - PLoS Negl Trop Dis
JT - PLoS neglected tropical diseases
JID - 101291488
SB - IM
MH - Diagnostic Tests, Routine
AB - BACKGROUND: Rapid diagnostic tests (RDTs) are today the most widely used method for malaria diagnosis and are recommended, alongside microscopy, for the confirmation of suspected cases before the administration of anti-malarial treatment. The diagnostic performance of RDTs, as compared to microscopy or PCR is well described but the actual analytical sensitivity of current best-in-class tests is poorly documented. This value is however a key performance indicator and a benchmark value needed to developed new RDTs of improved sensitivity. METHODS:
Thirteen RDTs detecting either the Plasmodium falciparum histidine rich protein 2 (HRP2) or the plasmodial lactate dehydrogenase (pLDH) antigens were selected from the best performing RDTs according to the WHO-FIND product testing programme. The analytical sensitivity of these products was evaluated using a range of reference materials including P. falciparum and Plasmodium vivax whole parasite samples as well as recombinant proteins. RESULTS: The best performing HRP2-based RDTs could detect all P. falciparum cultured samples at concentrations as low as 0.8 ng/mL of HRP2. The limit of detection of the best performing pLDH-based RDT specifically detecting P. vivax was 25 ng/mL of pLDH. CONCLUSION: The analytical sensitivity of P. vivax and Pan pLDH-based RDTs appears to vary considerably from product to product, and improvement of the limit-of-detection for P. vivax detecting RDTs is needed to match the performance of HRP2 and Pf pLDH-based RDTs for P. falciparum. Different assays using different reference materials produce different values for antigen concentration in a given specimen, highlighting the need to establish universal reference assays.

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Spatio-temporal analysis of malaria incidence in the Peruvian Amazon Region between 2002 and 2013.

Malaria remains a major public health problem in the Peruvian Amazon where the persistence of high-risk transmission areas (hotspots) challenges the current malaria control strategies. This study aimed at identifying significant space-time clusters of malaria incidence in Loreto region 2002–2013 and to determine significant changes across years in relation to the control measures applied. Poisson regression and purely temporal, spatial, and space–time analyses were conducted. Three significantly different periods in terms of annual incidence rates (AIR) were identified, overlapping respectively with the pre-, during, and post- implementation control activities supported by PAMAFRO project. The most likely space-time clusters of malaria incidence for P. vivax and P. falciparum corresponded to the pre- and first two years of the PAMAFRO project and were situated in the northern districts of Loreto, while secondary clusters were identified in eastern and southern districts with
the latest onset and the shortest duration of PAMAFRO interventions.

Malaria in Loreto was highly heterogeneous at geographical level and over time. Importantly, the excellent achievements obtained during 5 years of intensified control efforts totally vanished in only 2 to 3 years after the end of the program, calling for sustained political and financial commitment for the success of malaria elimination as ultimate goal.

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Malaria in Peru, dominated by Plasmodium vivax, remains a public health problem. The 1990s saw newly epidemic malaria emerge, primarily in the Loreto Department in the Amazon region, including areas near to Iquitos, the capital city, but sporadic malaria transmission also occurred in the 1990s-2000s in both north-coastal Peru and the gold mining regions of southeastern Peru. Although a Global Fund-supported intervention (PAMAFRO, 2005-2010) was temporally associated with a decrease of malaria transmission, from 2012 to the present, both P. vivax and Plasmodium falciparum malaria cases have rapidly increased. The Peruvian Ministry of Health continues to provide artemisinin-based combination therapy for microscopy-confirmed cases of P. falciparum and chloroquine-primaquine for P. vivax. Malaria transmission continues in remote areas nonetheless, where the mobility of humans and parasites facilitates reintroduction outside of ongoing surveillance activities, which is critical to address for future malaria control and elimination efforts. Ongoing P. vivax research gaps in Peru include the following: identification of asymptomatic parasitemics, quantification of the contribution of patent and subpatent parasitemics to mosquito transmission, diagnosis of nonparasitemic hypnozoite carriers, and implementation of surveillance for potential emergence of
chloroquine- and 8-aminoquinoline-resistant P. vivax Clinical trials of tafenoquine in Peru have been promising, and glucose-6-phosphate dehydrogenase deficiency in the region has not been observed to be a limitation to its use. Larger-scale challenges for P. vivax (and malaria in general) in Peru include logistical difficulties in accessing remote riverine populations, consequences of government policy and poverty trends, and obtaining international funding for malaria control and elimination.

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Correction: Colorimetric Detection of Plasmodium vivax in Urine Using MSP10 Oligonucleotides and Gold Nanoparticles.

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Colorimetric Detection of Plasmodium vivax in Urine Using MSP10 Oligonucleotides and Gold Nanoparticles.
specificity (97%), and only mild cross-reactivity with P. falciparum (21%). It is simple to use, with a visible color change that negates the need for a spectrometer, making it suitable for use in austere conditions. Using urine eliminates the need for finger-prick, increasing both the safety profile and patient acceptance of this model.

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GR - U19 AI0895681/AI/NIAID NIH HHS/United States
GR - U19 AI089702/AI/NIAID NIH HHS/United States
PT - Journal Article
DEP - 20161005
PL - United States
TA - PLoS Negl Trop Dis
JT - PLoS neglected tropical diseases
JID - 101291488
RN - 0 (Antigens, Protozoan)
RN - 0 (DNA, Protozoan)
RN - 0 (Oligonucleotides)
RN - 0 (Protozoan Proteins)
RN - 7440-57-5 (Gold)
SB - IM
MH - Antigens, Protozoan/genetics
MH - Colorimetry/economics/*methods/standards
MH - Cross Reactions
MH - DNA, Protozoan/urine
MH - Gold
MH - Humans
MH - Malaria, Vivax/*diagnosis/parasitology/urine
MH - Mass Screening
MH - *Metal Nanoparticles
MH - Microscopy
MH - *Oligonucleotides
MH - Parasitemia/diagnosis/parasitology
MH - Pilot Projects
MH - Plasmodium vivax/genetics/*isolation & purification/ultrastructure
MH - Protozoan Proteins/genetics
MH - Sensitivity and Specificity
MH - Urine/*parasitology
PMC - PMC5051960
COI - The authors have declared that no competing interests exist.
EDAT - 2016/10/06 06:00
MHDA - 2017/05/26 06:00
CRDT - 2016/10/06 06:00
Population genomics studies identify signatures of global dispersal and drug resistance in Plasmodium vivax.

Plasmodium vivax is a major public health burden, responsible for the majority of malaria infections outside Africa. We explored the impact of demographic history and selective pressures on the P. vivax genome by sequencing 182 clinical isolates sampled from 11 countries across the globe, using hybrid selection to overcome human DNA contamination. We confirmed previous reports of high genomic diversity in P. vivax relative to the more virulent Plasmodium falciparum species; regional populations of P. vivax exhibited greater diversity than the global P. falciparum population, indicating a large and/or stable population. Signals of natural selection suggest that P. vivax is evolving in response to antimalarial drugs and is adapting to regional differences in the human host and the mosquito vector. These findings underline the variable epidemiology of this parasite species and highlight the breadth of approaches that may be required to eliminate P. vivax globally.
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ABSTRACT: Characterizing the parasite dynamics and population structure provides useful information to understand the dynamic of transmission and to better target control interventions. Despite considerable efforts for its control, vivax malaria remains a major health problem in Peru. In this study, we have explored the population genetics of Plasmodium vivax isolates from Iquitos, the main city in the Peruvian Amazon, and 25 neighbouring peri-urban as well as rural villages along the Iquitos-Nauta Road. METHODOLOGY/ RESULTS: From April to December 2008, 292 P. vivax isolates were collected and successfully genotyped using 14 neutral microsatellites. Analysis of the molecular data revealed a similar proportion of monoclonal and polyclonal infections in urban areas, while in rural areas monoclonal infections were predominant (p = 0.002). Multiplicity of infection was higher in urban (MOI = 1.5-2) compared to rural areas (MOI = 1) (p = 0.003). The level of genetic
diversity was similar in all areas (He = 0.66–0.76, p = 0.32) though genetic differentiation between areas was substantial (PHIPT = 0.17, p<0.0001).

Principal coordinate analysis showed a marked differentiation between parasites from urban and rural areas. Linkage disequilibrium was detected in all the areas ([Formula: see text] = 0.08–0.49, for all p<0.0001).

Gene flow among the areas was established through Bayesian analysis of migration models. Recent bottleneck events were detected in 4 areas and a recent parasite expansion in one of the isolated areas. In total, 87 unique haplotypes grouped in 2 or 3 genetic clusters described a sub-structured parasite population. CONCLUSION/SIGNIFICANCE: Our study shows a sub-structured parasite population with clonal propagation, with most of its components recently affected by bottleneck events.

Iquitos city is the main source of parasite spreading for all the peripheral study areas. The routes of transmission and gene flow and the reduction of the parasite population described are important from the public health perspective as well for the formulation of future control policies.

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AB - BACKGROUND: With low and markedly seasonal malaria transmission, increasingly sensitive tools for better stratifying the risk of infection and targeting control interventions are needed. A cross-sectional survey to characterize the current malaria transmission patterns, identify hotspots, and detect recent changes using parasitological and serological measures was conducted in three sites of the Peruvian Amazon.

MATERIAL AND METHODS: After full census of the study population, 651 participants were interviewed, clinically examined and had a blood sample taken for
the detection of malaria parasites (microscopy and PCR) and antibodies against P. vivax (PvMSP119, PvAMA1) and P. falciparum (PfGLURP, PfAMA1) antigens by ELISA. Risk factors for malaria infection (positive PCR) and malaria exposure (seropositivity) were assessed by multivariate survey logistic regression models. Age-specific seroprevalence was analyzed using a reversible catalytic conversion model based on maximum likelihood for generating seroconversion rates (SCR, lambda). SaTScan was used to detect spatial clusters of serology-positive individuals within each site. RESULTS: The overall parasite prevalence by PCR was low, i.e. 3.9% for P. vivax and 6.7% for P. falciparum, while the seroprevalence was substantially higher, 33.6% for P. vivax and 22.0% for P. falciparum, with major differences between study sites. Age and location (site) were significantly associated with P. vivax exposure; while location, age and outdoor occupation were associated with P. falciparum exposure. P. falciparum seroprevalence curves showed a stable transmission throughout time, while for P. vivax transmission was better described by a model with two SCRs. The spatial analysis identified well-defined clusters of P. falciparum seropositive individuals in two sites, while it detected only a very small cluster of P. vivax exposure. CONCLUSION: The use of a single parasitological and serological malaria survey has proven to be an efficient and accurate method to characterize the species specific heterogeneity in malaria transmission at micro-geographical level as well as to identify recent changes in transmission.

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LA  - eng
PT  - Journal Article
PT  - Research Support, Non-U.S. Gov't
DEP - 20150910
PL  - United States
TA  - PLoS One
JID - 101285081
SB  - IM
MH  - Adolescent
MH  - Adult
MH  - Child
MH  - Factor Analysis, Statistical
MH  - Geography
MH  - Humans
MH  - Incidence
MH  - Malaria, Falciparum/*blood/epidemiology/parasitology/*transmission
MH  - Malaria, Vivax/*blood/epidemiology/parasitology/*transmission
MH  - Multivariate Analysis
MH  - Peru/epidemiology
MH  - Plasmodium falciparum
MH  - Plasmodium vivax
MH  - Prevalence
MH  - Risk Factors
MH  - Seroepidemiologic Studies
MH  - Species Specificity
MH  - Young Adult
PMC - PMC4565712
EDAT- 2015/09/12 06:00
MHDA- 2016/05/24 06:00
CRDT- 2015/09/11 06:00
PHST- 2015/04/21 00:00 [received]
PHST- 2015/08/17 00:00 [accepted]
PHST- 2015/09/11 06:00 [entrez]
PHST- 2015/09/12 06:00 [pubmed]
PHST- 2016/05/24 06:00 [medline]
AID - 10.1371/journal.pone.0137458 [doi]
AID - PONE-D-15-17351 [pii]
PST - epublish
       eCollection 2015.
Diagnosis is "the act of identifying a disease, illness, or problem by examining someone or something." When an individual with acute fever presents for clinical attention, accurate diagnosis leading to specific, prompt treatment often saves lives. As applied to malaria, not only individual patient diagnosis is important but also assessing population-level malaria prevalence using appropriate diagnostic methods is essential for public health purposes. Similarly, identifying (diagnosing) fake antimalarial medications prevents the use of counterfeit drugs that can have disastrous effects. Therefore, accurate diagnosis in broad areas related to malaria is fundamental to improving health-care delivery, informing funding agencies of current malaria situations, and aiding in the prioritization of regional and national control efforts. The International Centers of Excellence for Malaria Research (ICEMR), supported by the U.S. National Institute of Allergy and Infectious Diseases, has collaborated on global efforts to improve malaria diagnostics by working to harmonize and systematize procedures across different regions where endemicity and financial resources vary. In this article, the different diagnostic methods used across each ICEMR are reviewed and challenges are discussed.
Malaria Molecular Epidemiology: Lessons from the International Centers of Excellence for Malaria Research Network.

Molecular epidemiology leverages genetic information to study the risk factors that affect the frequency and distribution of malaria cases. This article describes molecular epidemiologic investigations currently being carried out by the International Centers of Excellence for Malaria Research (ICEMR) network in a variety of malaria-endemic settings. First, we discuss various novel approaches to understand malaria incidence and gametocytemia, focusing on Plasmodium falciparum and Plasmodium vivax. Second, we describe and compare different parasite genotyping methods commonly used in malaria epidemiology and population genetics. Finally, we discuss potential applications of molecular epidemiological tools and methods toward malaria control and elimination efforts.

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BACKGROUND: Several platforms have been used to generate the primary data for microsatellite analysis of malaria parasite genotypes. Each has relative advantages but share a limitation of being time- and cost-intensive. A commercially available automated capillary gel cartridge system was assessed in the microsatellite analysis of Plasmodium vivax diversity in the Peruvian Amazon. METHODS: The reproducibility and accuracy of a commercially-available automated capillary system, QIAxcel, was assessed using a sequenced PCR product of 227 base pairs. This product was measured 42 times, then 27 P. vivax samples from Peruvian Amazon subjects were analyzed with this instrument using five informative microsatellites. Results from the QIAxcel system were compared with a Sanger-type sequencing machine, the ABI PRISM((R)) 3100.
Genetic Analyzer.

RESULTS: Significant differences were seen between the sequenced amplicons and the results from the QIAxcel instrument. Different runs, plates and cartridges yielded significantly different results. Additionally, allele size decreased with each run by 0.045, or 1 bp, every three plates. QIAxcel and ABI PRISM systems differed in giving different values than those obtained by ABI PRISM, and too many (i.e. inaccurate) alleles per locus were also seen with the automated instrument. CONCLUSIONS: While P. vivax diversity could generally be estimated using an automated capillary gel cartridge system, the data demonstrate that this system is not sufficiently precise for reliably identifying parasite strains via microsatellite analysis. This conclusion reached after systematic analysis was due both to inadequate precision and poor reproducibility in measuring PCR product size.

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Plasmodium vivax Diversity and Population Structure across Four Continents.

Plasmodium vivax is the geographically most widespread human malaria parasite. To analyze patterns of microsatellite diversity and population structure across countries of different transmission intensity, genotyping data from 11 microsatellite markers was either generated or compiled from 841 isolates from four continents collected in 1999–2008.

Diversity was highest in South-East Asia (mean allelic richness 10.0–12.8), intermediate in the South Pacific (8.1–9.9) Madagascar and Sudan (7.9–8.4), and lowest in South America and Central Asia (5.5–7.2).

A reduced panel of only 3 markers was sufficient to identify approx. 90% of all haplotypes in South Pacific, African and SE-Asian
populations, but only 60–80% in Latin American populations, suggesting that typing of 2–6 markers, depending on the level of endemicity, is sufficient for epidemiological studies. Clustering analysis showed distinct clusters in Peru and Brazil, but little sub-structuring was observed within Africa, SE-Asia or the South Pacific. Isolates from Uzbekistan were exceptional, as a near-clonal parasite population was observed that was clearly separated from all other populations (FST>0.2). Outside Central Asia FST values were highest (0.11–0.16) between South American and all other populations, and lowest (0.04–0.07) between populations from South-East Asia and the South Pacific. These comparisons between P. vivax populations from four continents indicated that not only transmission intensity, but also geographical isolation affect diversity and population structure. However, the high effective population size results in slow changes of these parameters. This persistency must be taken into account when assessing the impact of control programs on the genetic structure of parasite populations.
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AB - BACKGROUND: Focal screening and treatment (FSAT) of malaria infections has recently been introduced in Peru to overcome the inherent limitations of passive case detection (PCD) and further decrease the malaria burden.

Here, we used a relatively straightforward mathematical model to assess the potential of FSAT as elimination strategy for Plasmodium falciparum malaria in the Peruvian Amazon Region. METHODS: A baseline model was developed to simulate a scenario with seasonal malaria transmission and the effect of PCD and treatment of symptomatic infections on the P. falciparum malaria transmission in a low endemic area of the Peruvian Amazon. The model was then adjusted to simulate intervention scenarios for predicting the long term additional impact of FSAT on P. falciparum malaria prevalence and incidence. Model parameterization was done using data from a cohort study in a rural Amazonian community as
well as published transmission parameters from previous studies in similar areas.

The effect of FSAT timing and frequency, using either microscopy or a supposed field PCR, was assessed on both predicted incidence and prevalence rates. RESULTS: The intervention model indicated that the addition of FSAT to PCD significantly reduced the predicted P. falciparum incidence and prevalence. The strongest reduction was observed when three consecutive FSAT were implemented at the beginning of the low transmission season, and if malaria diagnosis was done with PCR. Repeated interventions for consecutive years (10 years with microscopy or 5 years with PCR), would allow reaching near to zero incidence and prevalence rates. CONCLUSIONS: The addition of FSAT interventions to PCD may enable to reach P. falciparum elimination levels in low endemic areas of the Amazon Region, yet the progression rates to those levels may vary substantially according to the operational criteria used for the intervention.
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During 2010–2012, an outbreak of 210 cases of malaria occurred in Tumbes, in the northern coast of Peru, where no Plasmodium falciparum malaria case had been reported since 2006. To identify the source of the parasite causing this outbreak, we conducted a molecular epidemiology investigation. Microsatellite typing showed an identical genotype in all 54 available isolates. This genotype was also identical to that of parasites isolated in 2010 in the Loreto region of the Peruvian Amazon and closely related to clonet B, a parasite lineage previously reported in the Amazon during 1998–2000. These findings are consistent with travel history of index case-patients. DNA sequencing revealed mutations in the Pfdhfr, Pfdhps, Pfcrt, and Pfmdr1 loci, which are strongly associated with resistance to chloroquine and sulfadoxine/pyrimethamine, and deletion of the Pfhrp2 gene. These results highlight the need for timely molecular epidemiology investigations to trace the parasite source during malaria reintroduction events.

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BACKGROUND: Peru has presented a decreasing malaria trend during the last decade, particularly in areas on northwestern coast; however, a limited number of cases continues to be reported yearly mainly in malaria hotspots. METHODS: A two-phase study was conducted to identify spatial and temporal clusters of incident Plasmodium vivax malaria, as well as to determine risk factors associated with households (HH) presenting P. vivax malaria episodes in an urban area of the northwestern Peruvian Coast from June 2008 to May 2010. In the first stage, a full census of the study population was conducted, including geo-referencing of reported P. vivax episodes. In the second stage, a population-based case-control study allowed the identification of risk factors associated with HHs reporting episodes. A total of 117 case HHs with reported P. vivax and 117 control HHs without malaria episodes were assessed. A semi-structured questionnaire was used to interview the head of households and to collect data on HH location and structure, availability of public services, preventive malaria measures, family member with outdoor
occupation (farmer, moto-taxi driver), and other HH characteristics. Univariate and multivariate logistic regression analyses were performed to determine case-HH risk factors. SaTScan was used to detect spatial and temporal P. vivax malaria clusters. RESULTS: The most likely spatial cluster of malaria incidence included 1,040 people (22.4% of total population) in 245 HHs (24.6% of total HHs) accounting for 283 malaria episodes (40.1% of total episodes) during the study period (RR = 2.3, p < 0.001). A temporal cluster was also identified from April 12, 2009 to July 4, 2009 accounting for 355 malaria episodes (50.4% of total episodes) (RR = 7.2, p = 0.001). Factors significantly associated with case HHs compared with control HHs were: proximity to water drain < 200 metres (OR = 2.3, 95% CI: 1.3, 4.0); HH size >5 individuals (OR = 1.8, 95% CI: 1.0, 3.2); lack of potable water (OR = 1.8, 95% CI: 1.1, 3.2); and having domestic and peridomestic animals (OR = 3.6, 95% CI: 1.3, 9.5). CONCLUSION: Plasmodium vivax malaria incidence is highly heterogeneous in space and time in the urban study area with important geographical and housing risk factors associated with symptomatic episodes.

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AB - BACKGROUND: Persons with blood-stage Plasmodium falciparum parasitemia in the absence of symptoms are considered to be clinically immune. We hypothesized that asymptomatic subjects with P. falciparum parasitemia would differentially recognize a subset of P. falciparum proteins on a genomic scale. METHODS AND FINDINGS: Compared with symptomatic subjects, sera from clinically immune, asymptotically infected individuals differentially recognized 51 P. falciparum proteins, including the established vaccine candidate PfMSP1. Novel, hitherto unstudied hypothetical proteins and other proteins not previously recognized as potential vaccine candidates were also differentially recognized. Genes encoding the proteins differentially recognized by the Peruvian clinically immune individuals exhibited a significant
enrichment of
nonsynonymous nucleotide variation, an observation consistent
with these
genes undergoing immune selection. CONCLUSIONS: A limited set
of P.
falciparum protein antigens was associated with the
development of
naturally acquired clinical immunity in the low-transmission
setting of
the Peruvian Amazon. These results imply that, even in a low-
transmission
setting, an asexual blood-stage vaccine designed to reduce
clinical
malaria symptoms will likely need to contain large numbers of
often-
polymorphic proteins, a finding at odds with many current
efforts in the
design of vaccines against asexual blood-stage P. falciparum.
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 Genetic diversity of VAR2CSA ID1-DBL2Xb in worldwide Plasmodium falciparum populations: impact on vaccine design for placental malaria.
In placental malaria (PM), sequestration of infected erythrocytes in the placenta is mediated by an interaction between VAR2CSA, a Plasmodium falciparum protein expressed on erythrocytes, and chondroitin sulfate A (CSA) on syncytiotrophoblasts. Recent works have identified ID1-DBL2Xb as the minimal CSA-binding region within VAR2CSA able to induce strong protective immunity, making it the leading candidate for the development of a vaccine against PM. Assessing the existence of population differences in the distribution of ID1-DBL2Xb polymorphisms is of paramount importance to determine whether geographic diversity must be considered when designing a candidate vaccine based on this fragment. In this study, we examined patterns of sequence variation of ID1-DBL2Xb in a large collection of P. falciparum field isolates (n=247) from different malaria-endemic areas, including Africa (Benin, Senegal, Cameroon and Madagascar), Asia (Cambodia), Oceania (Papua New Guinea), and Latin America (Peru). Detection of variants and estimation of their allele frequencies were performed using next-generation sequencing of DNA pools. A considerable amount of variation was detected along the whole gene segment, suggesting that several allelic variants may need to be included in a candidate vaccine to achieve broad population coverage. However, most sequence variants were common and extensively shared among worldwide parasite populations, demonstrating long term persistence of those polymorphisms, probably maintained through balancing selection. Therefore, a vaccine mixture including such stable antigen variants will be putatively applicable and efficacious in all world regions where malaria occurs. Despite similarity in ID1-DBL2Xb allele repertoire across geographic areas, several peaks of strong population
differentiation were observed at specific polymorphic loci, pointing out putative targets of humoral immunity subject to positive immune selection.
Anopheles darlingi Root is the most important malaria vector in the Amazonia region of South America. However, continuous propagation of An. darlingi in the laboratory has been elusive, limiting entomological, genetic/genomic, and vector-pathogen interaction studies of this mosquito species. Here, we report the establishment of an An. darlingi colony derived from wild-caught mosquitoes obtained in the northeastern Peruvian Amazon region of Iquitos in the Loreto Department. We show that the numbers of eggs, larvae, pupae, and adults continue to rise at least to the F6 generation. Comparison of feeding Plasmodium vivax ex vivo of F4 and F5 to F1 generation mosquitoes showed the comparable presence of oocysts and sporozoites, with numbers that corresponded to blood-stage asexual parasitemia and gametocytemia, confirming P. vivax vectorial capacity in the colonized mosquitoes. These results provide new avenues for research on An. darlingi biology and study of An. darlingi-Plasmodium interactions.
Patterns of selection on Plasmodium falciparum erythrocyte-binding
antigens after the colonization of the New World.

AB - Pathogens, which have recently colonized a new host species or new populations of the same host, are interesting models for understanding how populations may evolve in response to novel environments. During its colonization of South America from Africa, Plasmodium falciparum, the main agent of malaria, has been exposed to new conditions in distinctive new human populations (Amerindian and populations of mixed origins) that likely exerted new selective pressures on the parasite's genome. Among the genes that might have experienced strong selective pressures in response to these environmental changes, the eba genes (erythrocyte-binding antigens genes), which are involved in the invasion of the human red blood cells, constitute good candidates. In this study, we analysed, in South America, the polymorphism of three eba genes (eba-140, eba-175, eba-181) and compared it to the polymorphism observed in African populations. The aim was to determine whether these genes faced selective pressures in South America distinct from what they experienced in Africa. Patterns of genetic variability of these genes were compared to the patterns observed at two housekeeping genes (adsl and serca) and 272 SNPs to separate adaptive effects from demographic effects. We show that, conversely to Africa, eba-140 seemed to be under stronger diversifying selection in South America than eba-175. In contrast, eba-181 did not show any sign of departure from neutrality. These changes in the patterns of selection on the eba genes could be the consequence of changes in the host immune response, the host receptor polymorphisms and/or the ability of the parasite to silence or express differentially its invasion proteins.

CI - (c) 2014 John Wiley & Sons Ltd.
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AB - BACKGROUND: Previous data have suggested that regulatory T cells (Tregs) balance protective immune responses with immune mediated pathology in malaria. This study aimed to determine to test the hypothesis that Treg proportions or absolute levels are associated with parasitaemia and malaria symptoms. METHODS: Treg cells were quantified by flow cytometry as CD4+ CD25+, Foxp3+, CD127(low) T cells. Three patient groups were assessed: patients with symptomatic Plasmodium falciparum malaria (S), subjects with asymptomatic P. falciparum parasitaemia (AS) and uninfected control individuals (C). RESULTS: S, AS and C groups had similar absolute numbers and percentage of Tregs (3.9%, 3.5% and 3.5% respectively). Levels of parasitaemia were not associated with Treg percentage (p = 0.47). CONCLUSION: Neither relative nor absolute regulatory T cell numbers were found to be associated with malaria-related symptomatology in this study. Immune mechanisms other than Tregs are likely to be responsible for the state of asymptomatic P. falciparum parasitaemia in the Peruvian Amazon; but further study to explore these mechanisms is needed.
Population structure and spatio-temporal transmission dynamics of Plasmodium vivax after radical cure treatment in a rural village of the Peruvian Amazon.

BACKGROUND: Despite the large burden of Plasmodium vivax, little is known about its transmission dynamics. This study explored the population structure and spatio-temporal dynamics of P. vivax recurrent infections after radical cure in a two-year cohort study carried out in a rural community of the Peruvian Amazon.

METHODS: A total of 37 P. vivax participants recruited in San Carlos community (Peru) between April and December 2008 were treated radically with chloroquine and primaquine and followed up monthly for two years with systematic blood sampling. All samples were screened for malaria parasites and subsequently all P. vivax infections genotyped using 15 microsatellites. Parasite population structure and dynamics were determined by computing different genetic indices and using spatio-temporal statistics.

RESULTS: After radical cure, 76% of the study participants experienced one or more recurrent P. vivax infections, most of them sub-patent and asymptomatic. The parasite population displayed limited genetic diversity (He = 0.49) and clonal structure, with most infections (84%) being monoclonal.

Spatio-temporal
Clusters of specific haplotypes were found throughout the study and persistence of highly frequent haplotypes were observed over several months within the same participants/households. CONCLUSIONS: In San Carlos community, P. vivax recurrences were commonly observed after radical treatment, and characterized by asymptomatic, sub-patent and clustered infections (within and between individuals from a few neighbouring households). Moreover low genetic diversity as well as parasite inbreeding are likely to define a clonal parasite population which has important implications on the malaria epidemiology of the study area.

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PT - Journal Article
PT - Research Support, Non-U.S. Gov't
DEP - 20140106
PL - England
TA - Malar J
JT - Malaria journal
JID - 101139802
AB - The majority of malaria rapid diagnostic tests (RDTs) detect
Plasmodium falciparum histidine-rich protein 2 (PfHRP2), encoded by the pfhrp2 gene. Recently, P. falciparum isolates from Peru were found to lack pfhrp2 leading to false-negative RDT results. We hypothesized that pfhrp2-deleted parasites in Peru derived from a single genetic event. We evaluated the parasite population structure and pfhrp2 haplotype of samples collected between 1998 and 2005 using seven neutral and seven chromosome 8 microsatellite markers, respectively. Five distinct pfhrp2 haplotypes, corresponding to five neutral microsatellite-based clonal lineages, were detected in 1998-2001; pfhrp2 deletions occurred within four haplotypes. In 2003-2005, outcrossing among the parasite lineages resulted in eight population clusters that inherited the five pfhrp2 haplotypes seen previously and a new haplotype; pfhrp2 deletions occurred within four of these haplotypes. These findings indicate that the genetic origin of pfhrp2 deletion in Peru was not a single event, but likely occurred multiple times.

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BACKGROUND: Where malaria endemicity is low, control programmes need increasingly sensitive tools for monitoring malaria transmission intensity (MTI) and to better define health priorities. A cross-sectional survey was conducted in a low endemicity area of the Peruvian north-western coast to assess the MTI using both molecular and serological tools. METHODS: Epidemiological, parasitological and serological data were collected from 2,667 individuals in three settlements of Bellavista district, in May 2010. Parasite infection was detected using microscopy and polymerase chain reaction (PCR). Antibodies to Plasmodium vivax merozoite surface protein-119 (PvMSP1(1)(9)) and to Plasmodium falciparum glutamate-rich protein (PfGLURP) were detected by ELISA. Risk factors for exposure to malaria (seropositivity) were assessed by multivariate survey logistic regression models. Age-specific antibody prevalence of both P. falciparum and P. vivax were analysed using a previously published catalytic conversion model based on maximum likelihood for generating seroconversion rates (SCR). RESULTS: The overall parasite prevalence by microscopy and PCR were extremely low: 0.3 and 0.9%, respectively for P. vivax, and 0 and 0.04%, respectively for P. falciparum, while seroprevalence was much higher, 13.6% for P. vivax and 9.8% for P. falciparum. Settlement, age and occupation as moto-taxi driver...
During the previous year were significantly associated with P. falciparum exposure, while age and distance to the water drain were associated with P. vivax exposure. Likelihood ratio tests supported age seroprevalence curves with two SCR for both P. vivax and P. falciparum indicating significant changes in the MTI over time. The SCR for PfGLURP was 19-fold lower after 2002 as compared to before (lambda1 = 0.022 versus lambda2 = 0.431), and the SCR for PvMSP1(1)(9) was four-fold higher after 2006 as compared to before (lambda1 = 0.024 versus lambda2 = 0.006). CONCLUSION: Combining molecular and serological tools considerably enhanced the capacity of detecting current and past exposure to malaria infections and related risks factors in this very low endemicity area. This allowed for an improved characterization of the current human reservoir of infections, largely hidden and heterogeneous, as well as providing insights into recent changes in species specific MTIs. This approach will be of key importance for evaluating and monitoring future malaria elimination strategies.

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Malaria has been part of Peruvian life since at least the 1500s. While Peru gave the world quinine, one of the first treatments for malaria, its history is pockmarked with endemic malaria and occasional epidemics. In this review, major increases in Peruvian malaria incidence over the past hundred years are described, as well as the human factors that have facilitated these events, and concerted private and governmental efforts to control malaria. Political support for malaria control has varied and unexpected events like vector and parasite resistance have adversely impacted morbidity and mortality. Though the ready availability of novel insecticides like DDT and efficacious medications reduced malaria to very low levels for a decade after the post eradication era, malaria reemerged as an important modern day challenge to Peruvian public health. Its reemergence sparked collaboration between domestic and international partners towards the elimination of malaria in Peru.
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.
BACKGROUND: While coverage of long-lasting insecticide-treated nets (LLIN) has steadily increased, a growing number of studies report gaps between net ownership and use. We conducted a mixed-methods social science study assessing the importance of net preference and use after Olyset(R) LLINs were distributed through a mass campaign in rural communities surrounding Iquitos, the capital city of the Amazonian region of Peru. METHODS: The study was conducted in the catchment area of the Paujil and Cahuide Health Centres (San Juan district) between July 2007 and November 2008. During a first qualitative phase, participant observation and in-depth interviews collected information on key determinants for net preference and use. In a second quantitative phase, a survey among recently confirmed malaria patients evaluated the acceptability and use of both LLINs and traditional nets, and a case control study assessed the association between net preference/use and housing structure (open vs. closed houses). RESULTS: A total of 10 communities were selected for the anthropological fieldwork and 228 households participated in the quantitative studies. In the study area, bed nets are considered part of the housing structure and are therefore required to fulfil specific architectural and social functions, such as providing privacy and shelter, which the newly distributed Olyset(R) LLINs ultimately did not. The LLINs' failure to meet these criteria could mainly be attributed to their large mesh size, transparency and perceived ineffectiveness to protect against mosquitoes and other insects, resulting in 63.3% of households not using any of the distributed LLINs. Notably, LLIN usage was significantly lower in houses with no interior or exterior walls (35.2%) than in those with walls (73.8%) (OR = 5.2, 95CI [2.2; 12.3], p<0.001). CONCLUSION: Net preference can interfere with
optimal LLIN use. In order to improve the number of effective days of LLIN protection per dollar spent, appropriate quantitative and qualitative methods for collecting information on net preference should be developed before any LLIN procurement decision is made.

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PT - Journal Article
PT - Research Support, Non-U.S. Gov't
DEP - 20130102
PL - United States
TA - PLoS One
JT - PloS one
JID - 101285081
SB - IM
MH - Attitude to Health
MH - Choice Behavior
MH - Climate
MH - Family Characteristics
MH - Housing
MH - Humans
MH - Insecticide-Treated Bednets/*statistics & numerical data
MH - Malaria/*prevention & control
MH - Mosquito Control/*instrumentation/methods
MH - Patient Acceptance of Health Care/statistics & numerical data
MH - Peru
Plasmodium falciparum field isolates from South America use an atypical red blood cell invasion pathway associated with invasion ligand polymorphisms.

Studies of Plasmodium falciparum invasion pathways in field isolates have been limited. Red blood cell (RBC) invasion is a complex process involving two invasion protein families; Erythrocyte Binding-Like (EBL) and the Reticulocyte Binding-Like (PfRh) proteins, which are polymorphic and not fully characterized in field isolates. To determine the various P. falciparum invasion pathways used by parasite isolates from South America, we studied the invasion phenotypes in three regions: Colombia, Peru and Brazil. Additionally, polymorphisms in three members of the EBL (EBA-181, EBA-175 and EBL-1) and five members of the PfRh (PfRh1, PfRh2a,
PfRh2b, PfRh4, PfRh5) families were determined. We found that most P. falciparum field isolates from Colombia and Peru invade RBCs through an atypical invasion pathway phenotypically characterized as resistant to all enzyme treatments (NrTrCr). Moreover, the invasion pathways and the ligand polymorphisms differed substantially among the Colombian and Brazilian isolates while the Peruvian isolates represent an amalgam of those present in the Colombian and Brazilian field isolates. The NrTrCr invasion profile was associated with the presence of the PfRh2a pepC variant, the PfRh5 variant 1 and EBA-181 RVKKN variant. The ebl and Pfrh expression levels in a field isolate displaying the NrTrCr profile also pointed to PfRh2a, PfRh5 and EBA-181 as being possibly the major players in this invasion pathway. Notably, our studies demonstrate the uniqueness of the Peruvian P. falciparum field isolates in terms of their invasion profiles and ligand polymorphisms, and present a unique opportunity for studying the ability of P. falciparum parasites to expand their invasion repertoire after being reintroduced to human populations. The present study is directly relevant to asexual blood stage vaccine design focused on invasion pathway proteins, suggesting that regional invasion variants and global geographical variation are likely to preclude a simple one size fits all type of vaccine.

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BACKGROUND: Erythrocyte invasion by Plasmodium falciparum is a complex process that involves two families; Erythrocyte Binding-Like (EBL) and the Reticulocyte Binding-Like (PfRh) proteins. Antibodies that inhibit merozoite attachment and invasion are believed to be important in mediating naturally acquired immunity and immunity generated by parasite blood stage vaccine candidates. The hypotheses tested in this study were 1) that antibody responses against specific P. falciparum invasion ligands (EBL and PfRh) differ between symptomatic and asymptomatic individuals living in the low-transmission region of the Peruvian Amazon and 2), such antibody responses might have an association, either direct or indirect, with clinical immunity observed in asymptotically parasitaemic individuals.

METHODS: ELISA was used to assess antibody responses (IgG, IgG1 and IgG3) against recombinant P. falciparum invasion ligands of the EBL (EBA-175, EBA-181, EBA-140) and PfRh families (PfRh1, PfRh2a, PfRh2b, PfRh4 and PfRh5) in 45 individuals infected with P. falciparum from Peruvian Amazon. Individuals were classified as having symptomatic malaria (N=37) or asymptomatic infection (N=8).

RESULTS: Antibody responses against both EBL and PfRh family proteins were significantly higher in asymptomatic compared to symptomatic individuals, demonstrating an association with clinical immunity.
IgG1 responses against EBA-181, PfRh2a and PfRh2b were significantly higher in the asymptomatic individuals. Total IgG antibody responses against PfRh1, PfRh2a, PfRh2b, PfRh5, EBA-175, EBA-181 and MSP119 proteins were negatively correlated with level of parasitaemia. IgG1 responses against EBA-181, PfRh2a and PfRh2b and IgG3 response for PfRh2a were also negatively correlated with parasitaemia. CONCLUSIONS: These data suggest that falciparum malaria patients who develop clinical immunity (asymptomatic parasitaemia) in a low transmission setting such as the Peruvian Amazon have antibody responses to defined P. falciparum invasion ligand proteins higher than those found in symptomatic (non-immune) patients. While these findings will have to be confirmed by larger studies, these results are consistent with a potential role for one or more of these invasion ligands as a component of an anti-P. falciparum vaccine in low-transmission malaria-endemic regions.
AB - BACKGROUND: In the Peruvian Amazon, Plasmodium falciparum and Plasmodium vivax malaria are endemic in rural areas, where microscopy is not available. Malaria rapid diagnostic tests (RDTs) provide quick and accurate diagnosis. However, pfhrp2 gene deletions may limit the use of histidine-rich protein-2 (PfHRP2) detecting RDTs. Further, cross-reactions of P. falciparum with P. vivax-specific test lines and vice versa may impair diagnostic specificity. METHODS: Thirteen RDT products were evaluated on 179 prospectively collected malaria positive samples. Species diagnosis was performed by microscopy and confirmed by PCR. Pfhrp2 gene deletions were assessed by PCR. RESULTS: Sensitivity for P. falciparum diagnosis was lower for PfHRP2 compared to P. falciparum-specific Plasmodium lactate dehydrogenase (Pf-pLDH)-detecting RDTs (71.6% vs. 98.7%, p<0.001). Most (19/21) false negative PfHRP2 results were associated with pfhrp2 gene deletions (25.7% of 74 P. falciparum samples). Diagnostic sensitivity for P. vivax (101 samples) was excellent, except for two products. In 10/12 P. vivax-detecting RDT products, cross-reactions with the PfHRP2 or Pf-pLDH line occurred at a median frequency of 2.5% (range 0%-10.9%) of P. vivax samples assessed. In two RDT products, two and one P. falciparum samples respectively cross-reacted with the Pv-pLDH line. Two Pf-pLDH/pan-pLDH-detecting RDTs showed excellent sensitivity with few (1.0%) cross-reactions but showed faint Pf-pLDH lines in 24.7% and 38.9% of P. falciparum
samples.

CONCLUSION: PfHRP2-detecting RDTs are not suitable in the Peruvian Amazon due to pfhrp2 gene deletions. Two Pf-pLDH-detecting RDTs performed excellently and are promising RDTs for this region although faint test lines are of concern.

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GR - U19 AI089681/AI/NIAID NIH HHS/United States
PT - Journal Article
PT - Research Support, N.I.H., Extramural
PT - Research Support, Non-U.S. Gov't
DEP - 20120828
PL - United States
TA - PLoS One
JT - PloS one
JID - 101285081
RN - 0 (Antigens, Protozoan)
RN - 0 (HRP-2 antigen, Plasmodium falciparum)
RN - 0 (HRP3 protein, Plasmodium falciparum)
RN - 0 (Protozoan Proteins)
SB - IM
MH - Adolescent
MH - Adult
MH - Aged
MH - Antigens, Protozoan/*genetics/metabolism
MH - Child
MH - Child, Preschool
MH - Female
MH - Gene Deletion
MH - Geography
MH - Humans
MH - Infant
MH - Malaria/*diagnosis/*parasitology
MH - Male
MH - Microscopy/methods
Amazonian malaria: asymptomatic human reservoirs, diagnostic challenges, environmentally driven changes in mosquito vector populations, and the mandate for sustainable control strategies.

Across the Americas and the Caribbean, nearly 561,000 slide-confirmed malaria infections were reported officially in 2008. The nine Amazonian countries accounted for 89% of these infections; Brazil and Peru alone contributed 56% and 7% of them, respectively. Local populations of the relatively neglected parasite Plasmodium vivax, which currently accounts for 77% of the regional malaria burden, are extremely diverse genetically and geographically structured. At a time when malaria
elimination is placed on the public health agenda of several endemic countries, it remains unclear why malaria proved so difficult to control in areas of relatively low levels of transmission such as the Amazon Basin. We hypothesize that asymptomatic parasite carriage and massive environmental changes that affect vector abundance and behavior are major contributors to malaria transmission in epidemiologically diverse areas across the Amazon Basin. Here we review available data supporting this hypothesis and discuss their implications for current and future malaria intervention policies in the region. Given that locally generated scientific evidence is urgently required to support malaria control interventions in Amazonia, we briefly describe the aims of our current field-oriented malaria research in rural villages and gold-mining enclaves in Peru and a recently opened agricultural settlement in Brazil.

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PT - Journal Article
PT - Research Support, N.I.H., Extramural
PT - Review
DEP - 20111012
PL - Netherlands
TA - Acta Trop
Preliminary enquiry into the availability, price and quality of malaria rapid diagnostic tests in the private health sector of six malaria-endemic countries.
OBJECTIVES: This enquiry aimed to provide a snap-shot of availability, price and quality of malaria rapid diagnostic tests (RDTs) in private health facilities at selected sites in six malaria-endemic countries in Africa, South East Asia and South America. METHODS: In each study site, data collectors surveyed private healthcare facilities which were selected based on accessibility from their home institution. Using a questionnaire, information was recorded about the facility itself and the malaria RDT(s) available. Where possible, a small number of RDTs were procured and quality control tested using a standardized procedure.

RESULTS: Of the 324 private healthcare facilities visited, 35 outlets (mainly private clinics and hospitals) were found to supply 10 different types of RDTs products. RDT prices across the six countries ranged from US$1.00 to $16.81. Five of the 14 malaria RDTs collected failed quality control testing. CONCLUSIONS: In the private outlets sampled, the availability of RDTs was limited. Some of the RDTs whose quality we tested demonstrated inadequate sensitivity. This presents a number of risks. Given the more widespread distribution of antimalarials currently planned for private sector facilities, parasite-based diagnosis in this sector will be essential to adhere to the WHO guidelines for effective case management of malaria. Considerable regulation and quality control are also necessary to assure the availability of accurate and reliable RDTs, as well as adequate case management and provider adherence to RDT results. Public sector engagement is likely to be essential in this process.
Multiple independent introductions of Plasmodium falciparum in South America.

The origin of Plasmodium falciparum in South America is controversial. Some studies suggest a recent introduction during the European colonizations and the transatlantic slave trade. Other evidence---archeological and genetic---suggests a much older origin. We collected and analyzed P. falciparum isolates from different regions of the world, encompassing the distribution range of the parasite, including populations from sub-Saharan Africa, the Middle East, Southeast Asia, and South America. Analyses of microsatellite and SNP polymorphisms show that the populations of P. falciparum in South America are subdivided in two main genetic clusters (northern and southern). Phylogenetic analyses, as well as Approximate Bayesian Computation methods suggest independent introductions of the two clusters from African sources. Our estimates of divergence time between the South American populations and their likely sources favor a likely introduction from Africa during the transatlantic slave trade.

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Aims: To present a new approach for estimating the "true prevalence" of malaria and apply it to datasets from Peru, Vietnam, and Cambodia.

Methods: Bayesian models were developed for estimating both the malaria prevalence using different diagnostic tests (microscopy, PCR & ELISA), without the need of a gold standard, and the tests' characteristics. Several sources of information, i.e. data, expert opinions and other sources of knowledge can be integrated into the model. This approach resulting in an optimal and harmonized estimate of malaria infection prevalence, with no conflict between the different sources of information, was tested on data from Peru, Vietnam and Cambodia. Results: Malaria sero-prevalence was relatively low in all sites, with ELISA showing the highest estimates. The sensitivity of microscopy and ELISA were statistically lower in Vietnam than in the other sites. Similarly, the specificities of microscopy, ELISA and PCR were significantly lower in Vietnam than in the other sites. In Vietnam and Peru, microscopy was closer to the "true" estimate than the other 2 tests while as
ELISA, with its lower specificity, usually overestimated the prevalence.

CONCLUSIONS: Bayesian methods are useful for analyzing prevalence results when no gold standard diagnostic test is available. Though some results are expected, e.g. PCR more sensitive than microscopy, a standardized and context-independent quantification of the diagnostic tests' characteristics (sensitivity and specificity) and the underlying malaria prevalence may be useful for comparing different sites. Indeed, the use of a single diagnostic technique could strongly bias the prevalence estimation. This limitation can be circumvented by using a Bayesian framework taking into account the imperfect characteristics of the currently available diagnostic tests. As discussed in the paper, this approach may further support global malaria burden estimation initiatives.

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Plasmodium vivax sub-patent infections after radical treatment are common in Peruvian patients: results of a 1-year prospective cohort study.

BACKGROUND: There is an increasing body of literature reporting treatment failure of the currently recommended radical treatment of Plasmodium vivax infections. As P. vivax is the main malaria species outside the African continent, emerging tolerance to its radical treatment regime could have major consequences in countries like Peru, where 80% of malaria cases are due to P. vivax. Here we describe the results of a 1-year longitudinal follow up of 51 confirmed P. vivax patients living around Iquitos, Peruvian Amazon, and treated according to the Peruvian national guidelines. METHODOLOGY: Each month a blood sample for microscopy and later genotyping was systematically collected. Recent exposure to infection was estimated by detecting antibodies against the P. vivax circumsporozoite protein (CSP) and all PCR confirmed P. vivax infections were genotyped with 16 polymorphic microsatellites. RESULTS: During a 1-year period, 84 recurrent infections, 22 positive also by microscopy, were identified, with a median survival time to first recurrent infection of 203 days. Most of them (71%) were asymptomatic; in 13 patients the infection persisted undetected by microscopy for several consecutive months. The genotype of mostly recurrent infections differed from that at day 0 while fewer differences were seen between the recurrent infections. The average expected heterozygosity was 0.56. There was strong linkage disequilibrium (I(A)(s) = 0.29, p<1.10(-4)) that remained also when analyzing only the unique haplotypes, suggesting common inbreeding. CONCLUSION: In Peru, the P. vivax recurrent infections
were common and displayed a high turnover of parasite genotypes compared to day 0. Plasmodium vivax patients, even when treated according to the national guidelines, may still represent an important parasite reservoir that can maintain transmission. Any elimination effort should consider such a hidden reservoir.

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LA - eng
PT - Journal Article
PT - Research Support, Non-U.S. Gov't
DEP - 20110128
PL - United States
TA - PLoS One
JT - PloS one
JID - 101285081
RN - 0 (Antibodies, Protozoan)
SB - IM
MH - Antibodies, Protozoan/blood
MH - Cohort Studies
MH - Genotype
MH - Humans
MH - Longitudinal Studies
MH - Malaria, Vivax/*epidemiology/*therapy/transmission
MH - Peru/epidemiology
MH - *Plasmodium vivax/genetics
MH - Polymerase Chain Reaction
MH - Prospective Studies
MH - Recurrence
PMC - PMC3030575
Placental histopathologic changes associated with subclinical malaria infection and its impact on the fetal environment.

Microscopic examination of placental tissue can provide an accurate assessment of malaria infection during pregnancy. In this cross-sectional study of 193 women in Iquitos, Peru, 1.0% and 6.6% had parasites in the peripheral blood as detected by microscopy and polymerase chain reaction, respectively. However, 22% had placental malaria pigment indicating past, subclinical infections. Placental tissues with pigment from 24 cases were matched by gravidity and month of delivery to 24 controls and histopathologically examined. Cases had significantly higher number of monocytes in the intervillous space (44.7 versus 25.5; P = 0.012).

Pigmented monocytes in fetal vessels were present in 33.3% of cases. This study demonstrated that subclinical malarial infection occurred frequently in pregnant women and is associated with increased presence of monocytes in the placenta. Pigmented monocytes in fetal vessels suggest parasites can breach the placental barrier and enter the fetal
[Use of standardized blood smear slide sets for competency assessment in the malaria microscopic diagnosis in the Peruvian Amazon].

OBJECTIVES: To assess the competency of microscopists for malaria diagnosis using standardized slide sets in the Peruvian Amazon. MATERIAL AND METHODS: Cross-sectional study carried out in 122 first level health facilities of the Peruvian Amazon, between July and September 2007. Within the frame of the project "Control Malaria in the border areas of the Andean Region: A community approach" (PAMAFRO), we evaluated the malaria diagnosis performance in 68 microscopists without expertise (< 1 year of expertise) and 76 microscopists with expertise (> 1 year) using standardized sets of 20 blood smear slides according to the World Health Organization (WHO) recommendations. A correct diagnosis (correct species identification) was defined as "agreement", a microscopist was qualified as an "expert" if they have an agreement >/=90% (>/= 18 slides with correct diagnosis), as a "referent" with an agreement between 80% and <90%, "competent" if they are between 70 and <80% and "in training" if they have <70%. RESULTS: Microscopists with expertise (68.6%) had more agreement than those without expertise (48.2%). The competency
assessment was acceptable (competent, referent, or experts levels) in 11.8% of the microscopists without expertise and in 52.6% from those with expertise. The agreement was lower using blood smear slides with P. falciparum with low parasitaemia, with P. malariae and with mixed infections.

CONCLUSIONS: Is the first assessment, we found only one of three microscopists from the Peruvian Amazon is competent for malaria diagnosis according to the WHO standards. From this baseline data, we have to continue working in order to improve the competency assessment of the microscopists within the frame of a quality assurance system.

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PT - English Abstract
PT - Journal Article
PT - Research Support, Non-U.S. Gov't
TT - Uso de paneles de laminas estandarizadas para la evaluacion de competencias en el diagnostico microscopico de malaria en la Amazonia Peruana.
PL - Peru
TA - Rev Peru Med Exp Salud Publica
JT - Revista peruana de medicina experimental y salud publica
JID - 101227566
SB - IM
MH - Clinical Laboratory Techniques/standards
MH - Cross-Sectional Studies
MH - Humans
MH - Malaria/*blood/*diagnosis
MH - Microscopy/standards
MH - Parasitology/standards
MH - Peru
MH - Professional Competence/*standards
EDAT - 2011/02/11 06:00
Field evaluation of a rapid diagnostic test (Parascreen) for malaria diagnosis in the Peruvian Amazon.

BACKGROUND: The rapid diagnostic tests for malaria (RDT) constitute a fast and opportune alternative for non-complicated malaria diagnosis in areas where microscopy is not available. The objective of this study was to validate a RDT named Parascreen under field conditions in Iquitos, department of Loreto, Peru. Parascreen is a RDT that detects the histidine-rich protein 2 (HRP2) antigen from Plasmodium falciparum and lactate dehydrogenase from all Plasmodium species. METHODS: Parascreen was compared with microscopy performed by experts (EM) and polymerase chain reaction (PCR) using the following indicators: sensitivity (Se), specificity (Sp), positive (PV+) and negative predictive values (PV-), positive (LR+) and negative likelihood ratio (LR-). RESULTS: 332 patients with suspected non-complicated malaria who attended to the MOH health centres were enrolled between October and December 2006. For P. falciparum malaria, Parascreen in comparison with EM, had Se: 53.5%, Sp: 98.7%, PV+: 66.7%, PV-: 97.8%, LR+: 42.27 and LR-: 0.47; and
for non-P. falciparum malaria, Se: 77.1%, Sp: 97.6%, PV+: 91.4%, PV-: 92.7%, LR+: 32.0 and LR-: 0.22. The comparison of Parascreen with PCR showed, for P. falciparum malaria, Se: 81.8%, Sp: 99.1%, PV+: 75%, PV-: 99.4, LR+: 87.27 and LR-: 0.18; and for non-P. falciparum malaria Se: 76.1%, Sp: 99.2%, PV+: 97.1%, PV-: 92.0%, LR+: 92.51 and LR-: 0.24. CONCLUSIONS: The study results indicate that Parascreen is not a valid and acceptable test for malaria diagnosis under the field conditions found in the Peruvian Amazon. The relative proportion of Plasmodium species, in addition to the genetic characteristics of the parasites in the area, must be considered before applying any RDT, especially after the finding of P. falciparum malaria parasites lacking pfhrp2 gene in this region.

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PT - Evaluation Study
PT - Journal Article
PT - Research Support, N.I.H., Extramural
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PT - Validation Study
DEP - 20100607
PL - England
TA - Malar J
JT - Malaria journal
JID - 101139802
RN - 0 (Antigens, Protozoan)
RN - 0 (HRP-2 antigen, Plasmodium falciparum)
RN - 0 (Protozoan Proteins)
Multilocus genotyping reveals high heterogeneity and strong local population structure of the Plasmodium vivax population in the Peruvian Amazon.
BACKGROUND: Peru is one of the Latin American countries with the highest malaria burden, mainly due to Plasmodium vivax infections. However, little is known about P. vivax transmission dynamics in the Peruvian Amazon, where most malaria cases occur. The genetic diversity and population structure of P. vivax isolates collected in different communities around Iquitos city, the capital of the Peruvian Amazon, was determined. METHODS: Plasmodium vivax population structure was determined by multilocus genotyping with 16 microsatellites on 159 P. vivax infected blood samples (mono-infections) collected in four sites around Iquitos city. The population characteristics were assessed only in samples with monoclonal infections (n = 94), and the genetic diversity was determined by calculating the expected heterozygosity and allelic richness. Both linkage disequilibrium and the genetic differentiation (theta) were estimated. RESULTS: The proportion of polyclonal infections varied substantially by site (11% – 70%), with the expected heterozygosity ranging between 0.44 and 0.69; no haplotypes were shared between the different populations. Linkage disequilibrium was present in all populations (IAS 0.14 – 0.61) but was higher in those with fewer polyclonal infections, suggesting inbreeding and a clonal population structure. Strong population differentiation (theta = 0.45) was found and the Bayesian inference cluster analysis identified six clusters based on distinctive allele frequencies. CONCLUSION: The P. vivax populations circulating in the Peruvian Amazon basin are genetically diverse, strongly differentiated and they have a low effective recombination rate. These results are in line with the low and clustered pattern of malaria transmission observed in the region around Iquitos city.
Adherence to 7-day primaquine treatment for the radical cure of P. vivax in the Peruvian Amazon.

Despite being free of charge, treatment adherence to 7-day primaquine for the radical cure of Plasmodium vivax was estimated at 62.2% among patients along the Iquitos-Nauta road in the Peruvian Amazon. The principal reason for non-adherence was the perceived adverse effects related to local humoral illness conceptions that hold that malaria produces a hot state of body, which is further aggravated by the characteristically hot medical treatment. Notably, patients were willing to adhere to the first 3 days of treatment during which symptoms are most apparent and include the characteristic chills. Nevertheless, as symptoms abate, the perceived aggravating characteristics of the medication outweigh the perceived advantages of treatment adherence. Improving community awareness about the role of primaquine to prevent further malaria transmission and fostering a realistic system of direct observed treatment intake, organized at community level, can be expected to improve adherence to the radical cure of P. vivax in this
BACKGROUND: Accurate diagnosis is essential for prompt and appropriate treatment of malaria. While rapid diagnostic tests (RDTs) offer great potential to improve malaria diagnosis, the sensitivity of RDTs has been reported to be highly variable. One possible factor contributing to variable test performance is the diversity of parasite antigens. This is of particular concern for Plasmodium falciparum histidine-rich protein 2 (PfHRP2)-detecting RDTs since PfHRP2 has been reported to be highly variable in isolates of the Asia-Pacific region. METHODS: The pfhrp2 exon 2 fragment from 458 isolates of P. falciparum collected from 38 countries was amplified and sequenced. For a subset of 80 isolates, the
exon 2 fragment of histidine-rich protein 3 (pfhrp3) was also amplified and sequenced. DNA sequence and statistical analysis of the variation observed in these genes was conducted. The potential impact of the pfhrp2 variation on RDT detection rates was examined by analysing the relationship between sequence characteristics of this gene and the results of the WHO product testing of malaria RDTs: Round 1 (2008), for 34 PfHRP2-detecting RDTs. RESULTS: Sequence analysis revealed extensive variations in the number and arrangement of various repeats encoded by the genes in parasite populations world-wide. However, no statistically robust correlation between gene structure and RDT detection rate for P. falciparum parasites at 200 parasites per microlitre was identified. CONCLUSIONS: The results suggest that despite extreme sequence variation, diversity of PfHRP2 does not appear to be a major cause of RDT sensitivity variation.
Ti - A large proportion of P. falciparum isolates in the Amazon region of Peru lack pfhrp2 and pfhrp3: implications for malaria rapid diagnostic tests.

AB - BACKGROUND: Malaria rapid diagnostic tests (RDTs) offer significant potential to improve the diagnosis of malaria, and are playing an increasing role in malaria case management, control and elimination. Peru, along with other South American countries, is moving to introduce malaria RDTs as components of malaria control programmes supported by the Global Fund for AIDS, TB and malaria. The selection of the most suitable malaria RDTs is critical to the success of the programmes. METHODS: Eight of nine microscopy positive P. falciparum samples collected in Iquitos, Peru tested negative or weak positive using HRP2-detecting RDTs. These samples were tested for the presence of pfhrp2 and pfhrp3 and
their flanking genes by PCR, as well as the presence of HRP proteins by ELISA. To investigate for geographic extent of HRP-deleted parasites and their temporal occurrence a retrospective study was undertaken on 148 microscopy positive P. falciparum samples collected in different areas of the Amazon region of Peru. FINDINGS: Eight of the nine isolates lacked the pfhrp2 and/or pfhrp3 genes and one or both flanking genes, and the absence of HRP was confirmed by ELISA. The retrospective study showed that 61 (41%) and 103 (70%) of the 148 samples lacked the pfhrp2 or pfhrp3 genes respectively, with 32 (21.6%) samples lacking both hrp genes. CONCLUSIONS: This is the first documentation of P. falciparum field isolates lacking pfhrp2 and/or pfhrp3. The high frequency and wide distribution of different parasites lacking pfhrp2 and/or pfhrp3 in widely dispersed areas in the Peruvian Amazon implies that malaria RDTs targeting HRP2 will fail to detect a high proportion of P. falciparum in malaria-endemic areas of Peru and should not be used. RDTs detecting parasite LDH or aldolase and quality microscopy should be used for malaria diagnosis in this region. There is an urgent need for investigation of the abundance and geographic distribution of these parasites in Peru and neighbouring countries.

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AIM OF THE STUDY: Ninety-four ethanolic extracts of plants used medicinally by the Yanesha, an Amazonian Peruvian ethnic group, for affections related to leishmaniasis and malaria were screened in vitro against Leishmania amazonensis amastigotes and against a Plasmodium falciparum chloroquine resistant strain. MATERIALS AND METHODS: The viability of Leishmania amazonensis amastigote stages was assessed by the reduction of tetrazolium salt (MTT) while the impact on Plasmodium falciparum was determined by measuring the incorporation of radio-labelled hypoxanthine. RESULTS AND CONCLUSIONS: Six plant species displayed good activity against Plasmodium falciparum chloroquine resistant strain (IC(50) < 10 microg/ml): a Monimiaceae, Siparuna aspera (Ruiz & Pavon), A. DC., two Zingiberaceae, Renealmia thyrsoida (Ruiz & Pavon) Poepp. & Endl. and Renealmia alpinia (Rottb.), two Piperaceae (Piper aduncum L. and Piper sp.) and the leaves of Jacaranda copaia (Aubl.) D. Don (Bignoniaceae). Eight species displayed interesting leishmanicidal activities (IC50 < 10 microg/ml): Carica papaya L. (Caricaceae), Piper dennisii Trel (Piperaceae), Hedychium coronarium J. König (Zingiberaceae), Cestrum racemosum Ruiz & Pav. (Solanaceae), Renealmia alpinia (Rottb.) Zingiberaceae, Lantana sp. (Verbenaceae), Hyptis lacustris A. St.-Hil. ex Benth. (Lamiaceae) and Calea montana Klat. (Asteraceae). Most of them are used against skin affections by Yanesha people. Results are discussed herein, according to the traditional use of the plants and compared with data obtained from the literature.

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Antibody response dynamics to the Plasmodium falciparum conserved vaccine candidate antigen, merozoite surface protein-1 C-terminal 19kD (MSP1-19kD), in Peruvians exposed to hypoendemic malaria transmission.

BACKGROUND: In high-transmission areas, developing immunity to symptomatic Plasmodium falciparum infections requires 2–10 years of uninterrupted exposure. Delayed malaria-immunity has been attributed to difficult-to-develop and then short-lived antibody responses.

METHODS: In a study area with <0.5 P. falciparum infections/person/year, antibody responses to the MSP1-19kD antigen were evaluated and associations with P. falciparum infections in children and adults. In months surrounding and during the malaria seasons of 2003–2004, 1,772 participants received > or =6 active visits in one study-year. Community-wide surveys were conducted at the beginning and end of each malaria season, and weekly active visits were completed for randomly-selected individuals each month. There were 79 P. falciparum infections with serum samples collected during and approximately one month before and after infection. Anti-MSP1-19kD IgG levels were measured by ELISA. RESULTS: The infection prevalence during February–July was similar in children (0.02–0.12 infections/person/month) and adults (0.03–0.14 infections/person/month) and was negligible in the four-month dry season. In children and adults,
the seroprevalence was maintained in the beginning (children = 28.9%, adults = 61.8%) versus ending malaria-season community survey (children = 26.7%, adults = 64.6%). Despite the four-month non-transmission season, the IgG levels in Plasmodium-negative adults were similar to P. falciparum-positive adults. Although children frequently responded upon infection, the transition from a negative/low level before infection to a high level during/after infection was slower in children. Adults and children IgG-positive before infection had reduced symptoms and parasite density. CONCLUSION: Individuals in low transmission areas can rapidly develop and maintain alphaMSP1–19kD IgG responses for >4 months, unlike responses reported in high transmission study areas. A greater immune capacity might contribute to the frequent asymptomatic P. falciparum infections in this Peruvian population.

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PT - Journal Article
PT - Research Support, N.I.H., Extramural
PT - Research Support, Non-U.S. Gov't
DEP - 20080909
PL - England
TA - Malar J
JT - Malaria journal
JID - 101139802
RN - 0 (Antibodies, Protozoan)
RN - 0 (Immunoglobulin G)
RN - 0 (Malaria Vaccines)
RN - 0 (Merozoite Surface Protein 1)
Evaluation of an in vitro and in vivo model for experimental infection with Leishmania (Viannia) braziliensis and L. (V.) peruviana.
humans despite a high genetic similarity. We hypothesized previously that L. (V.) peruviana would descend from L. (V.) braziliensis and would have acquired its 'peruviana' character during the southward colonization and adaptation of the transmission cycle in the Peruvian Andes. In order to have a first appreciation of the differences in virulence between both species, we evaluated an in vitro and in vivo model for experimental infection. A procedure was adapted to enrich culture forms in infective stages and the purified metacyclics were used to infect macrophage cell lines and golden hamsters. The models were tested with 2 representative strains of L. (V.) braziliensis from cutaneous and mucosal origin respectively and 2 representative strains of L. (V.) peruviana from Northern and Southern Peru respectively. Our models were reproducible and sensitive enough to detect phenotypic differences among strains. We showed in vitro as well as in vivo that the L. (V.) braziliensis was more infective than L. (V.) peruviana. Furthermore, we found that in vitro infectivity patterns of the 4 strains analysed, were in agreement with the geographical structuring of parasite populations demonstrated in our previous studies. Further work is needed to confirm our results with more strains of different geographical origin and their specific clinical outcome. However, our data open new perspectives for understanding the process of speciation in Leishmania and its implications in terms of pathogenicity.
Putative markers of infective life stages in Leishmania (Viannia) braziliensis.

Gene expression is known to vary significantly during the Leishmania life-cycle. Its monitoring might allow identification of molecular changes associated with the infective stages (metacyclics and amastigotes) and contribute to the understanding of the complex host-parasite relationships. So far, very few studies have been done on Leishmania (Viannia) braziliensis, one of the most pathogenic species. Such studies require, first of all, reference molecular markers. In the present work, we applied differential display analysis (DD analysis) in order to identify transcripts that might be (i) candidate markers of metacyclics and intracellular amastigotes of L. (V.) braziliensis or (ii) potential controls, i.e. constitutively expressed. In total, 48 DNA fragments gave reliable sequencing data, 29 of them being potential markers of infective stages and 12 potential controls. Eight sequences could be identified with reported genes. Validation of the results of DD analysis was done for 4 genes (2 differentially expressed and 2 controls) by quantitative real-time PCR. The infective insect stage-specific protein (meta 1) was more expressed in metacyclic-enriched preparations. The oligopeptidase b showed a higher expression in amastigotes. Two genes, glucose-6-phosphate dehydrogenase and a serine/threonine protein kinase, were found to be similarly expressed in the different biological samples.

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BACKGROUND: Multi-drug resistant falciparum malaria is an important health problem in the Peruvian Amazon region. We carried out a randomised open label clinical trial comparing mefloquine-artesunate, the current first line treatment in this region, with dihydroartemisinin-piperaquine.

METHODS AND FINDINGS: Between July 2003 and July 2005, 522 patients with P. falciparum uncomplicated malaria were recruited, randomized (260 with mefloquine-artesunate and 262 with dihydroartemisinin-piperaquine), treated and followed up for 63 days. PCR-adjusted adequate clinical and parasitological response, estimated by Kaplan Meier survival and Per Protocol analysis, was extremely high for both drugs (99.6% for mefloquine-artesunate and 98.4% and for dihydroartemisinin-piperaquine) (RR: 0.99, 95%CI [0.97-1.01], Fisher Exact p = 0.21). All recrudescences were late parasitological failures. Overall, gametocytes were cleared faster in the mefloquine-artesunate group (28 vs 35 days) and new gametocytes tended to appear more frequently in patients treated with dihydroartemisinin-piperaquine (day 7: 8 (3.6%) vs 2 (0.9%), RR: 3.84, 95%CI [0.82-17.87]). Adverse events such as anxiety and insomnia were significantly more frequent in the mefloquine-artesunate group, both in adults and children. CONCLUSION: Dihydroartemisinin-piperaquine is as effective as mefloquine-artesunate in treating uncomplicated P. falciparum malaria but it is better tolerated and more affordable than mefloquine-artesunate (US$1.0 versus US$18.65 on the local market). Therefore, it should be considered as a potential candidate
for the first line treatment of P. falciparum malaria in Peru. TRIAL REGISTRATION: ClinicalTrials.gov NCT00373607.

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SI - ClinicalTrials.gov/NCT00373607
PT - Journal Article
PT - Randomized Controlled Trial
PT - Research Support, Non-U.S. Gov't
DEP - 20071031
PL - United States
TA - PLoS One
JT - PloS one
JID - 101285081
RN - 0 (Antimalarials)
RN - 0 (Artemisinins)
RN - 0 (Quinolines)
RN - 0 (Sesquiterpenes)
RN - 60W3249T9M (Artesunate)
RN - 6A9050735X (artenimol)
RN - A0HV2Q956Y (piperaquine)
RN - TML814419R (Mefloquine)
SB - IM
MH - Adolescent
MH - Adult
MH - Antimalarials/*pharmacology
MH - Artemisinins/*administration & dosage
MH - Artesunate
MH - Child
MH - Child, Preschool
MH - Female
Isolation and molecular identification of Leishmania (Viannia) peruviana from naturally infected Lutzomyia peruensis (Diptera: Psychodidae) in the Peruvian Andes.

Leishmania (Viannia) peruviana was isolated from 1/75 Lutzomyia peruensis captured during May 2006 in an endemic cutaneous leishmaniasis region of the Peruvian Andes (Chaute, Huarochiri, Lima, Peru). Sand fly gut with promastigotes was inoculated into a hamster and the remaining body was fixed in ethanol. L. (Viannia) sp. was determined by polymerase chain reaction (PCR), and Leishmania species through molecular genotyping by PCR-restriction fragment length polymorphism analyses targeting the genes cpb and hsp70, resulting L. (V.) peruviana. The infected sand fly
appeared 15 days after the rains finished, time expected and useful real-time data for interventions when transmission is occurring.

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PT - Journal Article
PL - Brazil
TA - Mem Inst Oswaldo Cruz
JT - Memorias do Instituto Oswaldo Cruz
JID - 7502619
RN - 0 (DNA, Protozoan)
SB - IM
MH - Animals
MH - Cricetinae
MH - DNA, Protozoan/*analysis
MH - Female
MH - Genotype
MH - Leishmania braziliensis/genetics/*isolation & purification
MH - Male
MH - Peru
MH - Polymerase Chain Reaction
MH - Polymorphism, Restriction Fragment Length
MH - Psychodidae/*parasitology
EDAT- 2007/08/22 09:00
MHDA- 2008/04/18 09:00
CRDT- 2007/08/22 09:00
PHST- 2007/02/13 00:00 [received]
PHST- 2007/07/02 00:00 [accepted]
PHST- 2007/08/22 09:00 [pubmed]
PHST- 2008/04/18 09:00 [medline]
PHST- 2007/08/22 09:00 [entrez]
AID - S0074-02762007000500020 [pii]
AID - 10.1590/s0074-02762007005000077 [doi]
PST - ppublish
Clustered local transmission and asymptomatic Plasmodium falciparum and Plasmodium vivax malaria infections in a recently emerged, hypoendemic Peruvian Amazon community.

BACKGROUND: There is a low incidence of malaria in Iquitos, Peru, suburbs detected by passive case-detection. This low incidence might be attributable to infections clustered in some households/regions and/or undetected asymptomatic infections. METHODS: Passive case-detection (PCD) during the malaria season (February-July) and an active case-detection (ACD) community-wide survey (March) surveyed 1,907 persons. Each month, April-July, 100-metre at-risk zones were defined by location of Plasmodium falciparum infections in the previous month. Longitudinal ACD and PCD (ACP+PCD) occurred within at-risk zones, where 137 houses (573 persons) were randomly selected as sentinels, each with one month of weekly active sampling. Entomological captures were conducted in the sentinel houses. RESULTS: The PCD incidence was 0.03 P. falciparum and 0.22 Plasmodium vivax infections/person/malaria-season. However, the ACD+PCD prevalence was 0.13 and 0.39, respectively. One explanation for this 4.33 and 1.77-fold increase, respectively, was infection clustering within at-risk zones and contiguous households. Clustering makes PCD, generalized to the entire population, artificially low. Another attributable-factor was that only 41% and 24% of the P. falciparum and P. vivax infections were associated with fever and 80% of the asymptomatic
infections had low-density or absent parasitaemias the following week. After accounting for asymptomatic infections, a 2.6-fold increase in ACD+PCD versus PCD was attributable to clustered transmission in at-risk zones. CONCLUSION: Even in low transmission, there are frequent highly-clustered asymptomatic infections, making PCD an inadequate measure of incidence. These findings support a strategy of concentrating ACD and insecticide campaigns in houses adjacent to houses were malaria was detected one month prior.

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GR - R01 AI064831/AI/NIAID NIH HHS/United States
GR - R03 TW008064/TW/FIC NIH HHS/United States
PT - Journal Article
PT - Research Support, N.I.H., Extramural
PT - Research Support, U.S. Gov't, P.H.S.
DEP - 20050623
PL - England
TA - Malar J
JT - Malaria journal
JID - 101139802
RN - 0 (Antimalarials)
SB - IM
MH - Adolescent
MH - Adult
MH - Aged
Genomic rearrangements in trypanosomatids: an alternative to the "one gene" evolutionary hypotheses?

Most molecular trees of trypanosomatids are based on point mutations within DNA sequences. In contrast, there are very few evolutionary
studies considering DNA (re) arrangement as genetic characters. Waiting
for the completion of the various parasite genome projects, first
information may already be obtained from chromosome size-
polymorphism,
using the appropriate algorithms for data processing. Three
illustrative
models are presented here. First, the case of Leishmania
(Viannia)
braziliensis/L. (V.) peruviana is described. Thanks to a fast evolution
rate (due essentially to amplification/deletion of tandemly repeated
genes), molecular karyotyping seems particularly appropriate
for studying
recent evolutionary divergence, including eco-geographical diversification. Secondly, karyotype evolution is considered
at the level
of whole genus Leishmania. Despite the fast chromosome
evolution rate,
there is qualitative congruence with MLEE- and RAPD-based evolutionary
hypotheses. Significant differences may be observed between major
lineages, likely corresponding to major and less frequent rearrangements
(fusion/fission, translocation). Thirdly, comparison is made with
Trypanosoma cruzi. Again congruence is observed with other hypotheses and major lineages are delineated by significant chromosome rearrangements.
The level of karyotype polymorphism within that "species" is similar to the one observed in "genus" Leishmania. The relativity of the species concept among these two groups of parasites is discussed.

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