Epidemiological risk factors for severe *Plasmodium vivax* malaria in Peru

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Introduction

Recent investigation has produced a significant shift in the paradigm of *Plasmodium vivax*. No longer characterized as a mild and clinically benign disease, *P. vivax* can produce severe and life-threatening symptoms similar to those of severe falciparum malaria. Many of the pernicious aspects of *P. falciparum* hold true for severe vivax; however, vivax-associated disease has been historically neglected and regarded as benign until recent years.[1] *P. vivax* comprises 84% of the malaria incidence in Peru, and thus is a considerable contribution to the disease burden in the Loreto department of Peru.[2,3]

In monoendemic areas of Peru, severe vivax malaria has been shown to be more widespread than previously thought[4] so its incidence may be similarly underestimated in areas where falciparum exists as well. While chloroquine resistance is on the rise, *P. vivax* is an ever increasing public health concern and area of active investigation. Most of the recent literature seeks to address the clinical manifestations associated with severe vivax infection,[5] but few studies report potentially linked epidemiological risk factors.[6]

We have chosen to examine epidemiological risk factors in the progression to severe disease. Factors we found to be associated with severe malaria from *P. vivax* monoinfection include sex, previous infection with malaria, and residence proximity to water. Sex, perhaps linked with occupation and corresponding magnitude of mosquito exposure, was not previously shown to be a significant risk factor for malaria infection;[7] yet discrepancies between men and women in their health risk behaviors and health perceptions[8] may influence predisposition to developing severe vivax illness in Peruvian Amazon communities. Previous infection also may reduce risk for severe disease by protective immunity as shown in populations living in highly endemic areas or for falciparum malaria.[9,10] Dependence on water sources outside the home increases risk of malaria infection[11] and may be linked to residence proximity to water as a risk factors for severe vivax for our study population.

Sex		
Women	95	44%
Men	120	56%
Total	215	100%
Enrollment Status		
Cases	125	58%
Controls	90	42%
Total	215	100%
Age		
0-10	13	6%
13-20	34	16%
21-30	54	25%
31-40	26	12%
41-50	27	13%
51-60	31	14%
61-70	17	8%
>71	13	6%
Total	215	100%

Table 1. Patient population of study included by sex, enrollment status, and age.

Methods and Results:

The original case-control study was conducted in the Peruvian Amazon Basin at the Regional Hospital of Loreto and the Support Hospital of Iquitos. Severe *P. vivax* patients were enrolled upon hospitalization and 3 controls were enrolled per case. Patients were classified as severe based on several criteria outlined by the WHO for *P. falciparum.*

For this poster, we obtained the original data from the 2012-2015 case-control study in order to conduct a secondary statistical analysis to elucidate any potential epidemiological risk factors associated with severe *P. vivax* malaria. To begin the analysis, we surveyed the data, and after much debate regarding the updated WHO severe malaria guidelines, we decided to reassess the assignment of "case" and "control" in our patient population. Using the WHO Third Edition Practical Handbook, *Management of Severe Malaria,* as a guide, we determined the new criteria to be as follows:

Clinical Features:
- Impaired consciousness (including unrousable coma)
- Prostration, i.e. generalized weakness so the patient is unable to sit, stand, or walk without assistance
- Multiple Convulsions: more than 2 episodes within 24h
- Deep breathing and respiratory distress (acidotic breathing)
- Acute Pulmonary edema and acute respiratory distress syndrome
- Circulatory collapse or shock, systolic blood pressure <80 mmHg in adults and <50 mmHg in children
- Acute kidney injury
- Clinical jaundice plus evidence of other vital organ dysfunction
- Abnormal Bleeding

Laboratory and other findings:
- Hypoglycemia <40mg/dl
- Metabolic Acidosis (plasma bicarbonate <15 mmol/L)
- Severe Normocytic Anemia (Hb <5g/dl, hematocrit <15 in children, <20 in adults)
- Hemoglobinuria
- Renal impairment (Serum creatinine >265micromol/l)

World Health Organization

After reassessing the data, the study population included 125 cases and 90 controls for a total of 215 patients (Table 1).

Next, In order to determine any potential associations within the newly stratified epidemiological data, we performed chi-squared and logistic regression analyses on each variable. For statistical significance, we obtained odds ratios, p-values, and 95% confidence intervals using STATA software. The data was then subsequently analyzed using SAS statistical software, yielding the same result.

Factors we found to be associated with severe malaria from *P. vivax* include sex, previous infection with malaria, and residence proximity to water (Table 2).

Severe malaria impacted women (54 cases of 95 women) more than men (36 cases of 120 men) in the study ($p<0.001$). In other words, women were three times more likely to present with severe *vivax* malaria.

Our analyses also show that patients who reported no previous malarial infection may be more likely to present with severe malaria regardless of the number of prior infections. Patients with previous infection(s) with malaria of any species were less likely to develop severe malaria ($p<0.001$, OR of 4.16), suggesting that prior infection may be protective.

Finally, we observed that study participants who lived near a source of water are 2.9 times more likely to present with severe infection ($p<0.001$), indicating that repeated exposure to infected vectors may constitute increased risk for severe disease.

Variable	**Odds ratio**	**95% Confidence interval**	**P > |Z|**
Sex	3.07	1.75, 5.40	0.001
Previous infection	4.16	2.05, 8.44	0.001
Residence near water	2.95	1.62, 5.34	0.001

Table 2. Single-variate analysis of by sex, previous malaria infection, and residence near water.

Conclusion

Further analyses should investigate the impacts that co-morbities and co-infections have on development of severe vivax disease.[4] Additionally, the three potentially malaria-related deaths that occurred in the study should be investigated in order to better understand the course of severe complications that led to the fatalities. These case studies could broaden our understanding of the development of severe malaria in young, seemingly healthy individuals that have no prior clinical complications.

Future studies should focus on identifying the relative contributions of innate host factor (immunotolerance and genetics) with differences associated with pathogen exposure (parasite load strain).[9,10] Since the Amazon Basin is a sub-endemic region for vivax malaria, the decreased exposure to *P. vivax* surface proteins may limit naturally acquired immune responses in the inhabitants of this area.

Importantly, future studies on the epidemiology of severe vivax malaria should help to describe prevalence as well as to dissociate causative factors from factors associated with development of severe disease.[6,7] As we begin to see that severe vivax malaria is, in fact, a threat to the health of those living in regions around the world where *P. vivax* occurs, we are paying more attention to the changing paradigm of this disease that was previously thought to be more mild and benign than severe *P. falciparum*.

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