Am. J. Trop. Med. Hyg., 91(1), 2014, pp. 11–17
doi:10.4269/ajtmh.12-0610

Plasmodium vivax Hospitalizations in a Monoendemic Malaria Region: Severe Vivax Malaria?

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Abstract. Severe malaria caused by *Plasmodium vivax* is no longer considered rare. To describe its clinical features, we performed a retrospective case control study in the subregion of Luciano Castillo Colonna, Piura, Peru, an area with nearly exclusive vivax malaria transmission. Severe cases and the subset of critically ill cases were compared with a random set of uncomplicated malaria cases (1:4). Between 2008 and 2009, 6,502 malaria cases were reported, including 106 hospitalized cases, 81 of which fit the World Health Organization definition for severe malaria. Of these 81 individuals, 28 individuals were critically ill (0.4%, 95% confidence interval = 0.2–0.6%) with severe anemia (57%), shock (25%), lung injury (21%), acute renal failure (14%), or cerebral malaria (11%). Two potentially malaria-related deaths occurred. Compared with uncomplicated cases, individuals critically ill were older (38 versus 26 years old, $P < 0.001$), but similar in other regards. Severe vivax malaria monoinfection with critical illness is more common than previously thought.

INTRODUCTION

Malaria continues to exert a significant disease burden across the world.[1] Of five *Plasmodium* species that cause human disease, *P. falciparum* and *P. vivax* are responsible for most malaria cases worldwide. Research efforts have traditionally focused on *P. falciparum* because of the mortality that it causes in Africa.[2] However, *P. vivax* is the most widely distributed malaria species, and more than 2.8 billion people are at risk of acquiring *P. vivax*. In the Americas, *P. vivax* is responsible for 70% of the reported malaria cases.[3] Additionally, there is increasing concern regarding the global health impact of *P. vivax* infections because of our apparent underestimation of its potential disease burden and its extensive geographic distribution.[4,5] Finally, even as global malaria elimination efforts focus on reducing the blood-stage *P. falciparum* cases, the latent hypnozoite liver stage confers a unique survival advantage to *P. vivax*.

Recent reports of severe and fatal malaria have challenged the dogma that *P. vivax* is a benign disease.[6] A wide variety of severe complications have been described and associated with *P. vivax* monoinfection, ranging from single organ failure (brain, liver, lungs, kidneys, blood, spleen, etc.) to life-threatening multiple organ failure.[7–12] Also, strong evidence from prospective studies with well-established examination of comorbidities, including *P. falciparum*, has been recently published.[13,14] Based on this new evidence, more researchers now propose that severe malaria could be caused by *P. vivax* monoinfection,[15] especially when comorbidities, such as dengue, leptospirosis, viral hepatitis, bacterial sepsis, and *P. falciparum*, have been ruled out by highly sensitive methods, such as polymerase chain reaction (PCR). Nevertheless, because most of the evidence originates from *P. vivax/P. falciparum* coendemic areas, recurrent or previous exposure to *P. falciparum* may prevent us from fully accounting for the role of *P. vivax* alone as the cause of severe disease.

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In Peru, after the emergence of malaria in the 1990s,[16] the number of cases of *P. falciparum* started to wane, particularly in the north coast of Peru. Tumbes, which borders directly with Ecuador, is the only area in this region that continues to report local transmission of *P. falciparum*.[17] In the Luciano Castillo Colonna Health Region in the department of Piura, also located in the Peruvian north coast, *P. vivax* has been the single malaria species with autochthonous transmission for nearly 10 years. This finding provided a unique opportunity to retrospectively study the frequency, clinical presentation, and epidemiology of reported severe vivax malaria in a population with almost non-existent exposure to *P. falciparum* malaria.

MATERIALS AND METHODS

Study design. A retrospective case control study was conducted in the subregion of Luciano Castillo Colonna, province of Sullana (04°53′ S, 80°31′ W, population ~250,000), department of Piura, in the northern coast region of Peru. We reviewed the clinical charts of malaria patients hospitalized at the Sullana Hospital, the single regional referral center for malaria hospitalization in the subregion. All malaria cases hospitalized from January of 2008 to December of 2009 were evaluated, and all cases that fulfilled the severe malaria criteria were enrolled. In addition, a randomly selected group of outpatient uncomplicated vivax malaria cases treated at other health facilities in the subregion (non-severe controls) was enrolled (1:4 case:control ratio).

From 2001 to 2010, Sullana has experienced exclusive transmission of *P. vivax*, with only eight possible *P. falciparum* malaria cases identified in 2005, 2006, and 2008, of which only four cases were officially reported.[18,19] All these falciparum cases were investigated by E.P. and associated with a history of recent travel to the Amazon Basin, where *P. falciparum* is endemic. During the same period, over 10,000 cases of vivax malaria were reported, with a range of 588–4,037 cases per year. The highest incidence was reported during the years 2008 and 2009, with over 6,000 cases in total, representing 63% of total cases throughout the decade.[19]

Study population. The Sullana Hospital is the only Ministry of Health hospital in the Luciano Castillo Colonna subregion

and the only referral site to manage severe malaria cases. According to national guidelines, all malaria cases presenting with severe malaria complications must be hospitalized. In consequence, reviewing records of malaria hospitalizations in the Sullana Hospital was considered the best approach to identify cases of severe malaria, because the study area is urban with relatively good access to healthcare. Local regulations mandate that infectious diseases physicians in public hospitals evaluate all patients with suspicion of severe malaria using a standardized protocol, request additional tests to decide whether the patient fits the criteria for severe malaria, and prescribe the proper malaria treatment following World Health Organization (WHO) recommendations. From January of 2008 to December of 2009, in total, 16,874 patients were hospitalized at the Sullana Hospital for any cause, and those patients with blood smears positive for *P. vivax* were considered as potential cases. Uncomplicated vivax malaria control cases were selected by permuted block random sampling among outpatient cases registered in the subregion's system of febrile surveillance during the study period. Only the primary care health facilities that referred most of the hospitalized malaria cases during the study period were included in the selection of controls: Bellavista (40%), Sullana (16%), Santa Teresita (12%), and Querocotillo (12%).

Selection criteria for cases. We included as potential cases all subjects hospitalized at the Sullana Hospital from 2008 to 2009 with a positive malaria thick smear for *P. vivax*. Among them, severe malaria was diagnosed if the medical chart of the patient had records of at least one of the criteria of the WHO for severe malaria.[20] Severe hospitalized malaria cases were considered to be critically ill if they had any of the following malaria complications: (1) very severe anemia (hemoglobin < 5 g/dL), (2) lung injury, (3) shock (hypotension [systolic blood pressure < 80 mmHg] resistant to fluid), (4) renal failure, or (5) cerebral malaria. This subgroup of severe cases with life-threatening clinical features that demand intensive and immediate clinical care is important given the absence of a specific definition of severe vivax. Studying critically ill cases may help to elucidate the pathophysiology of severe vivax instead of evaluating clinical conditions that are life-threatening mostly when associated with *P. falciparum* rather than when associated with *P. vivax*. Multiorgan dysfunction was defined by the report of two or more of five malaria complications.[14] Individuals who had a specific discharge diagnosis of coinfection or concurrent illness, such as typhoid fever, hepatitis B or C, leptospirosis, dengue, or human immunodeficiency virus (HIV), were excluded from the study. Therefore, morbidity in the study sample has a higher likelihood to be caused by vivax malaria.

Selection criteria for uncomplicated vivax controls. We randomly selected four uncomplicated malaria controls for each case using the simple random sample with replacement methodology and the malaria registry program as the sample frame. The inclusion criteria for controls were (1) outpatient malaria cases were smear-positive for *P. vivax* monoinfection, (2) cases were registered in the subregion's system of febrile surveillance during years 2008–2009, (3) cases were fully treated by standard directly observed therapy at one of four aforementioned primary care health facilities, and (4) cases had a negative blood smear on the seventh day of treatment. Controls were selected using the proportional distribution of hospitalized patients per facility and the chronological order of the malaria registries. Controls who did not meet the inclusion criteria were systematically replaced during the selection process.

Treatment of vivax malaria. All patients received treatment uniformly for free according to the Peruvian malaria treatment guidelines.[21] The treatment of choice for uncomplicated vivax malaria cases in adults and children is chloroquine (25 mg/kg, total dose) over 72 hours plus primaquine (0.5 mg/kg) taken orally daily for 7 days. Pregnant women receive chloroquine (25 mg/kg, total dose) over 72 hours and then a weekly dose of 5 mg/kg until delivery, after which time they receive primaquine phosphate (0.5 mg/kg) daily for 7 days. Infants under 6 months of age receive chloroquine only. Unconscious patients are treated with clindamycin (20 mg base/kg per day) and quinine sulfate (10 mg salt/kg per day) intravenously three times daily until they can start standard oral treatment.

Data collection. We retrospectively reviewed the medical charts and registries at the Sullana Hospital corresponding to the study period and systematically recorded signs, symptoms, pre-conditions, comorbidities, and laboratory results of the first 72 hours using a structured form. The primary data source for hospitalized patients was the data recorded by the infectious diseases physician in the standardized admission sheet, which was complemented by available data from other sources. Baseline laboratory results and parasitemia were transcribed from clinical charts for cases and outpatient treatment registries for controls. In most severe malaria cases, we only had access to the laboratory results requested to support the patients' diagnoses and not the tests needed to rule out all of the malaria complications that might have affected them. To identify potential fatalities related to malaria, we cross-referenced the list of reported fatal malaria cases from the Epidemiology Directorate of the subregion and the list of all fatalities registered in the hospitalization database of the Sullana Hospital. Any patient who started malaria treatment within 1 week before hospital admission and died during hospitalization was considered a potential malaria-related fatality.

Data analysis. Three main comparisons among malaria cases were conducted: (1) severe hospitalized versus uncomplicated hospitalized cases, (2) critically ill severe hospitalized versus non-critically ill severe hospitalized cases, and (3) critically ill severe hospitalized versus uncomplicated outpatient controls. Differences were tested using only available comparable data, which for comparison 3, included only age, sex, and parasitemia. Parasitemia was measured using the parasite counts as a surrogate (total number of asexual parasites detected on thick blood smears per 100 oil immersion fields [o.i.f.]) following the equivalencies and procedures used by the Ministry of Health.[22] Parasite counts and sex were compared using the χ^2 test, and age was compared using the Student's t test. All analyses were conducted with Stata 12.0 (Stata Corporation, College Station, TX) using a significance level of $P < 0.05$.

Ethical considerations. The Institutional Review Board of the US Naval Medical Research Unit No. 6 (NAMRU-6) in Lima, Peru reviewed and approved the protocol of this study. Personal identifiers were coded immediately after collection to protect the confidentiality of the participants.

RESULTS

Severe and non-severe malaria hospitalized cases. The subregion reported 6,502 cases of malaria between 2008 and 2009,

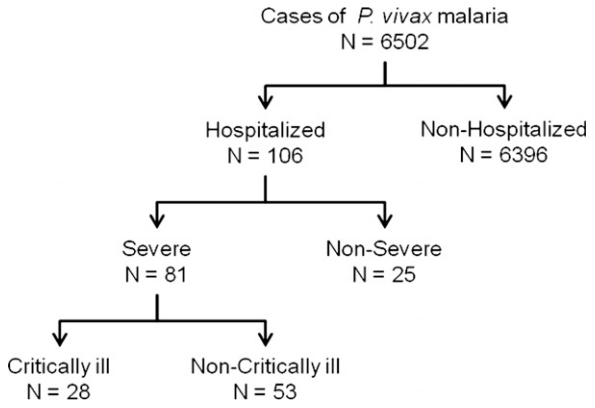

FIGURE 1. Flow diagram of patients' enrollment and inclusion criteria.

of which 106 cases (1.6%) were hospitalized at the Sullana Hospital. These cases included two hospitalized individuals who were identified as malaria cases only after matching the hospital mortality registries and the malaria records of the referral centers. An additional 10 hospitalized cases that had underlying or acute comorbidities (dengue = 6, HIV = 2, hepatitis B = 1, and hepatitis C = 1) were excluded from analysis. All clinical charts of 106 hospitalized patients who had malaria were found and reviewed, and 81 of these cases matched the WHO criteria for severe malaria (Figure 1). Twenty-five malaria cases that were hospitalized but did not fit the criteria for severe malaria had the following diagnoses other than malaria: hemoglobin between 7 and 9 g/dL ($N = 8$), jaundice ($N = 6$), dengue ($N = 4$), urinary tract infection ($N = 2$), decompensated diabetes ($N = 2$), hypoglycemia ($N = 2$), and decompensated hypertension ($N = 1$). Compared with severe cases, these 25 non-severe hospitalized malaria cases were slightly more often pregnant women (7/25 = 28% versus 10/81 = 12%, $P = 0.062$), but there were no differences in their age or sex.

Critically ill and non-critically ill severe malaria hospitalized cases. Twenty-eight (35%) of eight-one severe malaria hospitalized cases were identified as critically ill (Table 1). Therefore, we estimated that the proportion of critical illness among all 6,502 malaria patients was 0.43% (95% confidence interval [95% CI] = 0.28–0.62%). Of five malaria complications used to define critical illness, the most frequent was very severe anemia (57%). The remaining four complications were less common: shock (25%), lung injury (21%), acute renal failure (14%), and cerebral malaria (11%). The mean number of complications per patient was 1.3 ± 0.7 (range = 1–3, mode = 1). Multiorgan dysfunction (two or more malaria complications) was observed in 5 (18%) of 28 critically ill subjects. Compared with 53 non-critically ill cases, critically ill cases had hypoglycemia slightly less frequently (0% versus 11%, $P = 0.064$), but we failed to observe differences in the remaining malaria complications (i.e., thrombocytopenia and jaundice), which were possibly limited by the small sample size. There were no pregnant women among the critically ill compared with 10 (19%) of 53 pregnant women in the non-critically ill group ($P = 0.010$). Five of the pregnant women had miscarriages, and two pregnant women had threat of miscarriage without other severe complications. Four of five viable pregnancies had low birth weight neonates (one neonate was born pre-term), whereas the fifth neonate was

TABLE 1
Clinical presentation of critically ill *P. vivax* severe malaria cases

Number	Age (years)/sex	Parasites/100 o.i.f.	Critical illness criteria	Severe but not critical illness criteria	Critical care*
1	2M	1	Hb < 5 g/dL, lung injury and shock		ICU/transfusion
2	4M	2–20	Hb < 5 g/dL		Transfusion
3	5M	1	Hb < 5 g/dL		Transfusion
4	7M	1	Hb < 5 g/dL	Jaundice	Transfusion
5	20F	1	Cerebral malaria		ICU
6	20M	1	Hb < 5 g/dL	Jaundice	Transfusion
7	22M	2–20	Hb < 5 g/dL	Jaundice	Transfusion
8	23M	1	Renal failure		ICU
9	25M	1	Hb < 5 g/dL		ICU/transfusion
10	26M	1	Hb < 5 g/dL	Jaundice	Transfusion
11	28F	< 1	Lung injury and shock	Hb < 7 g/dL	Fatal case
12	28F	< 1	Hb < 5 g/dL	Jaundice	–
13	33F	< 1	Shock		ICU
14	34F	1	Hb < 5 g/dL		Transfusion
15	37M	1	Lung injury		ICU
16	37F	1	Hb < 5 g/dL	Jaundice	ICU/transfusion
17	46M	1	Cerebral malaria		ICU
18	47M	2–20	Cerebral malaria		ICU
19	50F	1	Renal failure	Hb < 7 g/dL	ICU
20	53M	1	Hb < 5 mg/dL		Transfusion
21	54M	21–200	Lung injury, shock, and renal failure	Hb < 7 g/dL	ICU/transfusion
22	54F	21–200	Lung injury	Jaundice	ICU
23	56F	1	Hb < 5 g/dL		–
24	57F	1	Hb < 5 g/dL		Transfusion
25	65F	1	Shock		ICU
26	68F	2–20	Shock and lung injury	Hb < 7 g/dL	ICU/transfusion (fatal case)
27	78M	1	Hb < 5 g/dL (shock)		ICU/transfusion
28	87F	1	Renal failure		ICU

F = female; Hb = hemoglobin; M = male.
*Transfusion implies red blood cell transfusion.

TABLE 2

Critical illness among severe cases of *P. vivax* malaria monoinfection

Characteristics	Critically ill ($N = 28$)	Non-critically ill ($N = 53$)	P value
Age (years)	38 ± 22	33 ± 20	0.313
< 18	4 (14%)	8 (15%)	0.928
18–64	20 (72%)	39 (74%)	
≥ 65	4 (14%)	6 (11%)	
Female sex	13 (46%)	29 (55%)	0.478
Pregnant	0 (0%)	10 (19%)	0.014
Parasite counts*			
< 1	3 (11%)	4 (8%)	0.946
1	19 (68%)	37 (70%)	
2–20	4 (14%)	9 (17%)	
21–200	2 (7%)	3 (6%)	
Number of symptoms/patient	6.8 ± 2.3	5.1 ± 2.6	0.006
Fever at hospitalization	26 (93%)	45 (85%)	0.301
Malaise	18 (64%)	23 (43%)	0.074
Headache	18 (64%)	27 (51%)	0.250
Myalgia	17 (61%)	15 (28%)	0.005
Chills	14 (50%)	27 (51%)	0.936
Appetite loss	14 (50%)	23 (43%)	0.570
Joint pain	11 (39%)	12 (23%)	0.114
Ocular pain	10 (36%)	8 (15%)	0.034
Nausea	10 (36%)	19 (36%)	0.990
Vomiting	9 (32%)	22 (42%)	0.409
Abdominal pain	9 (32%)	16 (30%)	0.856
Bone pain	8 (29%)	6 (11%)	0.051
Lumbar pain	6 (21%)	5 (8%)	0.071
Cough	2 (7%)	3 (6%)	0.792

*Total number of asexual parasites detected on thick blood smears per 100 o.i.f.

normal. All other epidemiological characteristics of the critically ill and non-critically ill severe malaria hospitalized cases were similar (Table 2).

Clinically, critically ill patients reported more symptoms, on average, than non-critically ill severe malaria patients (6.8 ± 2.3 versus 5.1 ± 2.6, $P = 0.006$) and also, more myalgia (61% versus 28%, $P = 0.005$) and ocular pain (36% versus 15%, $P = 0.034$). Additionally, marginal differences were found in bone pain (29% versus 11%, $P = 0.051$), lumbar pain (21% versus 8%, $P = 0.071$), and malaise (64% versus 43%, $P = 0.074$). The most frequent symptoms reported by the critically ill severe malaria cases were fever at hospitalization (93%), malaise (64%), headache (64%), myalgia (61%), chills (50%), and appetite loss (50%). In addition, both critically ill and non-critically ill severe malaria cases presented with relatively low parasite densities; the most frequent parasite density detected was 1 parasite/100 o.i.f. (68% and 70%, respectively).

Clinical outcomes of critically ill malaria cases. During 2008 and 2009, no fatal malaria cases were reported in the subregion, but two individuals registered in the hospital mortality records had been diagnosed with malaria at one of the referral centers in the previous 7 days. Therefore, they were included in our study among 28 critically ill severe malaria hospitalized cases and considered critically ill severe malaria cases. These two individuals died during hospitalization without a malaria diagnosis made at the hospital and as such, had not been officially recorded as deaths secondary to *P. vivax* infection. The first patient, a 28-year-old non-pregnant female, was diagnosed at a health center with a parasite density of 1 parasite/100 o.i.f. and began receiving antimalarial treatment as an outpatient 1 day before hospitalization. She was admitted to the Sullana Hospital with a diagnosis of acute respiratory distress syndrome (ARDS) and died 2 days later. The second possible malaria death, the death of a 68-year-old male, was also diagnosed with *P. vivax* malaria at a health center. He presented with a parasite density of 2–20 parasites/100 o.i.f. and began antimalarial treatment as an outpatient 2 days before admission to the Sullana Hospital. This patient died 2 days after hospital admission and 1 day after being admitted to the intensive care unit (ICU) with a diagnosis of septic shock and severe anemia. Based on the clinical presentation of these two cases, we highly suspect that they died because of the severity of their malaria infection. However, we cannot be entirely sure that other underlying medical conditions may better explain their deaths. No autopsy findings or materials were available. The remaining 26 critically ill malaria hospitalized cases (93%) showed signs of favorable response to treatment with chloroquine and primaquine. Before the fourth day of treatment, ICU patients were transferred to the regular hospitalization ward, and non-ICU patients were medically discharged.

TABLE 3

Critically ill hospitalized versus uncomplicated outpatient malaria cases caused by *P. vivax* monoinfection

Characteristics	Critically ill hospitalized malaria cases ($N = 28$)	Uncomplicated outpatient malaria cases ($N = 112$)	P value
Female sex	13 (46%)	38 (34%)	0.219
Age (years)	38 ± 22	26 ± 15	< 0.001
Parasite counts*			
< 1	3 (11%)	38 (34%)	0.004
1	19 (68%)	35 (31%)	
2–20	4 (14%)	30 (27%)	
21–200	2 (7%)	9 (8%)	

*Total number of asexual parasites detected on thick blood smears per 100 o.i.f.

Case control analysis. Compared with uncomplicated outpatient vivax cases, critically ill severe hospitalized cases were older (38 versus 26 years old, $P = 0.001$) and showed a different distribution of parasite densities, with 1 parasite/100 o.i.f. being the most common (68% versus 31%, $P = 0.004$) (Table 3). Missing data did not allow other categories to be strictly compared. Four pregnant women were randomly sampled in the outpatient non-severe malaria controls.

DISCUSSION

We conducted a comprehensive characterization of severe vivax malaria in an endemic area with an extended absence of *P. falciparum* and found that approximately 0.4% of all vivax cases presented with critical clinical conditions, including two potentially malaria-related fatalities. Over one-half of these cases had severe anemia, and nearly 20% presented multiorgan dysfunction. These estimates correspond to a coastal urban area with lower malaria endemicity, greater access to healthcare, and better overall health status than the Amazon region,[23] where 85% of malaria cases reported in Peru occur. Additionally, tests assessing malaria severity were only conducted in subjects with clinical suspicion, and it is possible that our results underestimate the incidence of this poorly understood facet of vivax malaria in other regions. However, the retrospective assessment of coinfections and comorbidities may have prevented assessment of all causes of severe disease, potentially overestimating the true burden of severe vivax malaria. In general, this study highlights our limited knowledge regarding the morbidity and mortality of vivax malaria, particularly regarding the frequency and etiology of its severe and critical presentations.

Our results concur with the growing evidence supporting the hypotheses that vivax malaria patients can experience severe and life-threatening illness and that *P. vivax* is associated with severe illness similar to *P. falciparum*.[7–9,13,24–34] Furthermore, our study in a vivax monoendemic setting adds to the only two case series that strictly ruled out *P. falciparum* coinfection by highly specific techniques (i.e., PCR) and shows that *P. vivax* alone may, indeed, present with severe manifestations.[13,14] In agreement with these two studies conducted in Brazil and India, respectively, we found that four criteria (severe anemia, shock, lung injury, and acute renal failure) (Table 4) are commonly present in critical illness with *P. vivax*, despite our use of few criteria to identify critically ill severe vivax cases. However, our fifth criterion for critical illness, cerebral malaria, was infrequent in both Peru and India and not observed in Brazil, supporting the hypothesis that cerebral malaria caused by *P. vivax* is probably a rare event. Also, Kochar and others[14] observed that acute renal failure was very common, possibly a unique feature of severe vivax malaria in India. Severe anemia (hemoglobin < 5 g/dL) was consistently the most frequent finding in all three studies, consistent with observation that anemia is a frequent and often severe result of vivax malaria.[12,35–38] However, the anemia of *P. vivax* is a very complex phenomenon, and important questions remain unanswered, such as the roles of acute, chronic, and relapsing infections and the interaction of vivax-related anemia with iron deficiency resulting from helminthiasis and malnutrition.[39] Proper understanding of vivax pathogenesis and identification of clinical manifestations that are directly life-threatening and demand critical care are needed. Additional prospective studies may lead to the establishment of a much-needed globally accepted definition of severe vivax malaria.

In our retrospective study, we could not conclusively rule out the role of other coinfections, such as dengue, leptospirosis, bacterial sepsis, and other conditions, that also might explain the severe illness observed because of lack of laboratory data. However, one important selection criterion in our study is that we only included those subjects who received the standard directly observed treatment of non-complicated vivax malaria and except for the two deaths, had a negative blood smear on the seventh day of treatment and an otherwise favorable outcome. Indeed, before it disappeared, *P. falciparum* in this area was largely resistant to chloroquine,[16] arguing against successful outcomes if, indeed, *P. falciparum* alone or in a mixed infection was the culprit. Additionally, all cases had a relatively short hospital course after starting treatment (3–5 days). Nevertheless, the possibility that the critical illness observed in these cases could be caused by comorbidities cannot be completely rejected, and the role of coinfections should be evaluated in future studies.

Critically ill cases were primarily adults, with equal sex distribution. The older age of critical compared with outpatient cases may be related to their higher rates of comorbidities and greater resulting chances of hospitalization and decompensation, which was observed by Lacerda and others.[40] Additionally, critically ill patients commonly showed low parasite counts, even lower than the parasitemia of uncomplicated outpatient cases. Relatively low parasitemia of severe vivax infections was observed by Kochar and others[14] (19,665 ± 9,876 parasites/μL) and Alexandre and others[13] (8,077 ± 8,685 parasites/μL). Nearly all the severe *P. vivax* malaria cases had parasite densities below 30,000 parasites/μL, consistent with the notion that high parasitemia is not a typical feature of severe vivax.[41] *P. vivax* can cause fever at a lower parasitemia compared with *P. falciparum*, and it is also associated with increased cytokine production at similar parasitemias.[41] However, the mechanisms leading to that increased inflammatory response at similar parasitemia have not been elucidated.

Another important finding of our study was the observation that vivax malaria may lead to severe complications during pregnancy. These complications, largely described as almost exclusive complications of *P. falciparum* infection, also have been reported as *P. vivax* complications.[42] We know that, in Africa, falciparum malaria infections have been associated with severe maternal anemia, low birth weight, and perinatal mortality, whereas outside Africa, vivax malaria has been associated with severe malaria, pre-term births, and fetal loss.[42] These findings are particularly true in Latin America, where the main pregnancy complications of *P. vivax* are pre-term births and miscarriages[43] regardless of whether associated with critical illness. The burden of vivax malaria on pregnancy fetal outcomes still needs to be better estimated using controlled studies.

Our data add to the evidence that indicates that vivax malaria can be a debilitating disease. Critically ill vivax malaria cases had significantly more symptoms than non-critically ill severe malaria cases; additionally, critically ill vivax malaria patients reported more pain-related symptoms than non-critically ill severe malaria patients. Malaise was also common, although symptoms should not be equated to severity and the limitations of retrospective data should be considered when interpreting these data. Considering the overall frequency of *P. vivax* worldwide, it can be a meaningful figure when translated into quality of life and disease burden. Chloroquine resistance could add to the severity of vivax malaria but probably

TABLE 4
Clinical presentation of critically ill severe vivax malaria cases

Severe malaria criteria	Brazil[13] (*N* = 17) WHO criteria (severe)	India[14] (*N* = 40) WHO criteria (severe)	Peru* (*N* = 28) modified WHO criteria (critically ill)
Critical illness criteria			
Severe anemia (Hb < 5 g/dL)	5 (29%)	13 (33%)	16 (57%)
Shock (systolic blood pressure < 80 mmHg) resistant to fluid	1 (6%)	3 (8%)	7 (25%)
Lung injury (ARDS or pulmonary edema)	2 (12%)	4 (10%)	6 (21%)
Acute renal failure (creatinine > 3 mg/dL)	2 (12%)	18 (45%)	4 (14%)
Cerebral malaria (Glasgow < 9/14)	0 (0%)	5 (13%)	3 (11%)
Non-critical illness criteria			
Jaundice (bilirubin > 3 mg/dL)	10 (59%)	23 (58%)	7 (25%)
Hypoglycemia (glucose < 40 mg/dL)	0 (0%)	1 (3%)	0 (0%)

*More strict criteria to identify critical hospitalized cases of severe vivax malaria, including only five WHO criteria, with a more demanding cutoff to select only life-threatening disease.

not in our study, given that only two cases have been reported in Peru.[44,45] Also, none of them occurred in the north coast where our study took place.

We observed two likely but unconfirmed fatal cases of severe vivax malaria (2.4% of all severe malaria cases and 7.1% of all critically ill cases). Similar rates were reported by Kochar and others[14] (5%) and Alexandre and others[13] (5.6%), showing that the case fatality rate among severe vivax malaria is not negligible. All deaths in the three studies had ARDS or lung injury, identical to many deaths in the literature. Severe anemia alone could have triggered respiratory decompensation, because all lung injury cases were anemic (two patients with hemoglobin < 5 g/dL and two patients with hemoglobin < 7 g/dL. This finding suggests that prompt treatment of subjects with two or three of these conditions is crucial, and because it has been shown in a recent post-mortem study, it is particularly true among cases with ARDS or pulmonary edema.[40] Additionally, although only one of our six lung-injured critically ill patients was an infant, lung ARDS is a relatively frequent event and particularly threatening, especially among children.[46] Therefore, we feel that the survival rate of patients, particular those patients presenting vivax-related lung injury, requires additional study as well.

It is important to further elucidate the mechanisms by which *P. vivax* can cause severe illness, and an appropriate definition for severe malaria related to *P. vivax* monoinfection will be vital to this effort. We propose that the five common life-threatening malaria complications that we used (very severe anemia, shock, lung injury, acute renal failure, and cerebral malaria) could be specific enough to guide future studies while still being reasonably sensitive. The value of other criteria, such as thrombocytopenia, is not necessarily practical,[47] particularly in the absence of coagulation complications. Along the same lines, hypoglycemia and jaundice do not seem to influence the outcome or appearance of severe or critical illness, because these complications have been more collateral than life-threatening in most cases in Peru. Jaundice, hypoglycemia, and thrombocytopenia most likely are not fatal unless occurring simultaneously with another organ failure. In general, we strongly support the hypothesis that *P. vivax* may present with life-threatening features requiring ICU support or a blood transfusion. Additional studies should help to delineate the proper criteria to identify such critically ill cases, which we try to propose from our results.

In summary, we observed that cases of vivax malaria monoinfection could become clinically severe, which is in agreement with observations made in other regions. Despite the recent literature on the subject, there is need for a consensus definition for severe vivax malaria as well as a clear understanding of the mechanism and global burden of this condition. A great need remains for increased surveillance and prospective, comprehensive research to better understand this understudied condition.

Received October 1, 2012. Accepted for publication February 19, 2014.

Published online April 21, 2014.

Acknowledgments: The authors thank Drs. Pilar Campos, Lourdes Jimenez, and Ana M. Palacios for their valuable support to study activities and Ms. Elena Sarango for her devoted work in the malaria program of Bellavista Health Center.

Financial support: Funding for this study was received through Grants CO348_10_L1 and CO466_11_L1 from the Armed Forces Health Surveillance Center/Global Emerging Infections Surveillance and Response System of the US Department of Defense. Additionally, this work was supported by Training Grant 2D43 TW007393 awarded to the US Naval Medical Research Unit No. 6 by the National Institutes of Health/Fogarty International Center.

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