Epidemiology, Drug Resistance, and Pathophysiology of Plasmodium vivax Malaria

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Abstract

Plasmodium vivax, a major human malaria parasite, is highly prevalent in Southeast Asia and South America. Although P. vivax infections have long been considered to be benign, in recent years, the infections have been shown to cause life threatening severe diseases, including acute respiratory distress syndrome, cerebral malaria, multi organ failure, dyserythropoiesis, anemia and other hematological complications. Despite exhibiting low parasite biomass due to parasite’s specificity to infect reticulocytes but not matured red blood cells, P. vivax infection triggers greater inflammatory responses and clinical symptoms such as fever and chills as compared to the more virulent P. falciparum. Another characteristic feature of P. vivax infections compared to P. falciparum infection is parasite remaining as dormant liver-stage hypnozoites, causing recurrent episodes of malaria. In this review article, we summarize the published information on P. vivax epidemiology, drug resistance and pathophysiology.

Keywords

Plasmodium vivax; Epidemiology; Pathogenesis; Severe malaria; Clinical manifestations; Drug resistance

Introduction

P. vivax is the most widespread human malaria parasite found in many parts of the tropical and subtropical regions except sub Saharan Africa. Globally, approximately 3.2 billion people are at risk of P. vivax infection and more than 200 million clinical cases occur annually1,2. The highest burden of P. vivax infection is seen throughout Southeast Asia, South America and sub Saharan Africa3. P. vivax infection is absent or rarely prevalent in...
most parts of Africa because of the inherited lack of Duffy glycoprotein receptor expression on the surface of red blood cells in the majority of people. However, recently there are few reports suggesting submicroscopic P. vivax infection prevalence in certain parts of Africa suggesting that either the parasite is evolving to use alternative receptors for erythrocyte invasion or population in those regions express Duffy receptors. The geographical distribution of P. vivax malaria often overlaps with that of falciparum malaria, except in certain regions of Southeast Asia, such as South Korea, where P. vivax is almost exclusively prevalent.

In infected individuals, while P. falciparum infection tends to show higher mean parasitemia index, P. vivax infection generally exhibit low parasitemia index due to its preference to invade reticulocytes rather than erythrocytes. Therefore, determining the extent of P. vivax parasitemia burden requires a more sensitive diagnostic tool as it is difficult to detect P. vivax in infected asymptomatic individuals and in mixed species infections by conventional light microscopy. The current rapid diagnostic tests that relies on detecting lactate dehydrogenase or aldolase are also not sufficiently sensitive in detecting P. vivax, and the techniques unable to determine if parasitemia is lower than 200 parasites per 1 μl blood. The PCR-based detection methods are more sensitive, but they are not practicable in routine diagnostic procedures especially in rural settings. Therefore, a more sensitive and simple P. vivax specific diagnostic assays are needed for routine clinical diagnosis. Immunological assays may be attractive alternatives since they can be used to diagnose asymptomatic carriers and individuals recently exposed to P. vivax.

Population studies from many parts of the world have shown that individuals exposed to multiple infections and experienced clinical episodes of P. vivax or P. falciparum acquires clinical immunity to P. vivax more rapidly than to P. falciparum, irrespective of overall transmission intensity. The mechanisms that underlie the more rapid acquisition of immunity to P. vivax remain poorly understood. In most high endemic areas, morbidity associated with P. vivax infection peaks at a much younger age than P. falciparum infection. Thus, in these regions, older children and adults with P. vivax infection are more likely to be asymptomatic than their P. falciparum-infected counterparts. In P. vivax low-transmission settings, all age groups often are at risk of severe disease, and most infections appear to be sub microscopic and asymptomatic.

A distinctive characteristic feature of P. vivax compared to other human malaria parasites is the persistent presence of dormant parasites (liver-stage hypnozoites), which cause several malaria episodes. The hypnozoites can remain dormant up to 2 years after an initial inoculation of sporozoites by a mosquito bite and they are activated to initiate blood-stage infections. Usually parasite strains from temperate and subtropical regions exhibit longer dormant period between the primary infection and relapse (around 8–10 months or longer), whereas those in tropical regions generally exhibit shorter relapse intervals (around 3–6 weeks). Thus, relapse pattern varies from region to region and the exact mechanism of how hypnozoite relapses are triggered, and the source of this phenotypic variation, remains unknown. Frequent relapses that occur at 2–3 weeks intervals induce early disease tolerance, characterized by high threshold for fever, and sometimes asymptomatic infections. However, frequent recurrent episodes result in inadequate time for patients to
recover from hematological damages, leading to severe anemia\(^{19}\). Currently, primaquine, an 8-aminquinoline antimalarial agent, is the drug of choice to kill liver hypnozoites and prevent relapse. However, the drug is highly toxic to people having glucose-6-phosphate dehydrogenase (G6PD) deficiency as it causes fatal hemolysis\(^{20}\).

**Drug Resistance**

In recent years, anti-malarial resistance has been a major concern in treating malaria. For many years, chloroquine (CQ) was the drug of choice in treating both *P. vivax* and *P. falciparum* infections since the drug is cheap and effective. However, currently in most endemic areas, parasites have developed resistance to this drug\(^{21}\). Resistance to CQ in *P. vivax* was first reported in Papua New Guinea in 1989 and subsequently resistance was also seen in most endemic places in Southeast Asia. Highest prevalence of CQ-resistant to *P. vivax* was reported in Northeastern coast of Indonesian Papua\(^{22}\). CQ treatment failure and resistance with failures of primaquine as anti-relapse therapy for *P. vivax* malaria have also been reported in some parts of Southwestern and Northeastern regions of India\(^{23}, 24\). Since *P. vivax* infections after drug treatment could be due to either recrudescence of CQ-resistant strains or due to reinfection, it is difficult to confirm primaquine resistance in many of these cases. In India, molecular epidemiologic information on *P. vivax* resistance to CQ and primaquine is low. In many regions of the world where CQ resistance to *P. vivax* is seen, artemisinin combination therapy along with primaquine is used as an alternative treatment strategy\(^{25}\). Effective artemisinin combination therapies such as dihydroartemisinin-piperaquine and artesunate-mefloquine provide greater post-exposure prophylaxis against early recurrence of infection in *P. vivax*\(^{26}\).

Compared to *P. falciparum*, the molecular basis of anti-malarial drug resistance in *P. vivax* has not been studied extensively, mainly because of difficulty in establishing *in vitro* culture. But in recent years, many laboratories around the world have reported methods for conducting *in vitro* *P. vivax* drug susceptibility studies\(^{27}, 28\). Anti-malarial drug resistance appears to be mainly due to mutations in genes encoding essential enzymes or transporters. The *P. vivax* multidrug resistance (*Pvmdr*) and putative transporter protein (*Pvcrt-o*), which are orthologous to *Pfmdr1* and *Pfcrtr* genes, have been identified as chloroquine resistance markers in *P. vivax*. The mutant alleles of both genes were suggested to be associated with chloroquine resistance in *P. vivax* in Southeast Asia by both *in vivo* and *in vitro* studies\(^{29}, 30\). There are reports suggesting that genotypic variations in *P. vivax* dihydrofolate reductase gene (*pvdhfr*) and dihyropteroate synthetase (*pvdhps*) have also been associated in drug resistance\(^{16}, 31\). The Y976F and F1076L mutations in *Pvmdr1* gene have been reported to be associated with chloroquine resistance\(^{29}\), and point mutations at F57L/I, S58R, T61M, and S117T/N codons of *Pvdhfr* gene have been linked to pyrimethamine resistance and treatment failure in *P. vivax*. Whole sequence analysis of *Pvmdr1* and *Pvcrt-o* in *P. vivax* field isolates has revealed that *Pvmdr1* gene contained 24 single nucleotide polymorphisms (SNPs), whereas *Pvcrt-o* gene contained 5 SNPs and lysine insertion at the amino acid position 10\(^{32}\). Recently, mutations in the *PF3D7_1343700* kelch propeller domain (K13-propeller) of *Pfk13* gene have been shown to be associated with artemisinin resistance in *P. falciparum*, which is demonstrated as delayed parasite clearance post artemisinin treatment\(^{33}, 34\). Similar
mutations mediating artemisinin resistance in the \textit{Pfk13} orthologue of \textit{P. vivax} Pvk12 (mutation V552I) was identified in Cambodia at a very low frequency\textsuperscript{35}.

\section*{Pathophysiology}

Malaria illnesses are generally associated with periodic fever, chills, shivering, headache, nausea, vomiting, and may other clinical conditions. However, in the case of \textit{P. falciparum}, severe diseases such as severe anemia, respiratory distress, cerebral malaria and other organ dysfunction are also common\textsuperscript{10}. It has long been believed that \textit{P. vivax} infections are relatively benign and cause mild clinical symptoms, and parasites do not sequester in the deep capillaries of organs\textsuperscript{36}. However, recent studies have suggested the possibility of parasite sequestration in organs as evidenced by the \textit{P. vivax} infection-associated severe illnesses and deaths\textsuperscript{37}.

Clinical symptoms of malarial infections are initiated soon after the initial liver stage infection transferred to the blood infection, in which merozoite forms of parasite invade red blood cells (RBCs)\textsuperscript{38}. Unlike \textit{P. falciparum}, which invades erythrocytes and parasitemia can exceed 20–30\%, \textit{P. vivax} exhibits exclusive specificity to invade reticulocytes\textsuperscript{39}. This distinctive property of \textit{P. vivax} results in lower parasite biomass, rarely exceeding 2–3\% parasitemia, even in the face of infections causing severe diseases. In spite of having lower pyrogenic threshold than \textit{P. falciparum}, cytokine production, endothelial activation, and pulmonary inflammatory responses are higher in \textit{P. vivax} infection compared to \textit{P. falciparum} infection\textsuperscript{40,41}. The main reason for this phenomenon appears to be due to \textit{P. vivax} genome having higher GC content, approximately two times higher than that of \textit{P. falciparum}, and thus higher contents of Toll-like receptor 9-stimulating CpG motifs\textsuperscript{42–45}. Lipids found in the cholesterol/triglyceride fractions of plasma at the time of paroxysmal fever have also been proposed as a putative malaria toxin unique to \textit{P. vivax}, and they may also contribute to the pyrogenicity of \textit{P. vivax}\textsuperscript{46}. It has been suggested that the cholesterol/triglyceride fractions of \textit{P. vivax} exhibit greater inflammatory response-inducing activity than glycosylphosphatidylinositol anchors\textsuperscript{46,47}. Several clinical conditions seen in \textit{P. vivax} malaria are due to imbalance in pro- and anti-inflammatory cytokine production, resulting in greater concentrations of both pro- and anti-inflammatory cytokines than \textit{P. falciparum}\textsuperscript{48}. Plasma concentrations of the pro-inflammatory cytokines TNF-\(\alpha\) and IFN-\(\gamma\) was shown to directly related to disease severity, whereas plasma concentrations of IL-10 was shown inversely related to disease severity\textsuperscript{49}. Also, plasma concentration of superoxide dismutase, an enzyme produced during oxidative stress, has also been associated with \textit{P. vivax} disease severity\textsuperscript{50}.

\section*{Parasite sequestration and severe malaria}

Severe \textit{P. falciparum} pathology is associated with the sequestration of parasites in microvascular endothelia through the binding of parasite-infected RBCs to endothelial cell receptors, such as CD36, ICAM-1, and VCAM-1 in organs, causing microvascular obstruction, hypoxia, and inflammation\textsuperscript{51–52}. High levels of inflammatory responses locally may lead to tissue disruption and single- or multi-organ dysfunction and mortality. Sequestration of parasites does not usually occur to a substantial degree in \textit{vivax} malaria and
therefore, organ dysfunction and mortality is not frequent compared to *P. falciparum*. Autopsy studies of *P. vivax* infected severe malaria cases showed little evidence for microvascular accumulation of infected *P. vivax* RBCs. However, other studies have shown that *P. vivax*-infected RBCs bind to endothelial cells via receptors, such as ICAM-1, with a similar strength but a 10-fold lower frequency than *P. falciparum*-infected RBCs. Further, it has also been reported that *P. vivax*-infected RBCs bind to glycosaminoglycans, such as chondroitin sulfate A and hyaluronic acid. Indirect physiological studies, partitioning pulmonary gas transfer in adults with *P. vivax* malaria, showed impairment of the pulmonary capillary vascular component, suggesting invasion and sequestration by parasitized red cells in the lung. Autopsy of Brazilian *P. vivax*-infected people who had acute respiratory distress syndrome (ARDS) showed parasitized RBCs, despite at low levels, in alveolar capillaries even after clearance of parasites from peripheral blood by antimalarial drug treatment. Thus, it seems that in some circumstances, limited cytoadherence to endothelial cells occur, contributing to inflammatory responses in affected organs, such as the lung. Rosetting/autoagglutination, i.e. adherence of non-infected RBCs to infected RBCs and thus cell clumping together is an important phenomenon of cytoadherence and pathophysiology in *P. falciparum* malaria is initiated by binding of infected RBCs to CD36 and P-selectin on platelets. However, this mechanism is not seen in *P. vivax* malaria. In *P. falciparum* infection, impaired nitric oxide bioavailability, and endothelial activation and dysfunction are significant contributors to impaired microvascular perfusions and complications. The levels of endothelial activation markers, ICAM-1, E-selectin and angiopoietin-2, are as high in uncomplicated vivax malaria as they are in falciparum malaria. However, their significance in severe vivax malaria is not known. Autopsies of brain and lung sections in severe cases of *P. vivax* have demonstrated endothelial stimulation and activation. Since *P. vivax* show limited ability to cytoadhere, pathogenic consequences of endothelial activation and sequestration of parasitized RBCs are likely much less in vivax malaria than in falciparum malaria. However, other consequences of endothelial activation and altered thrombostasis in *P. vivax* infection are imperative. *P. vivax* infection is associated with elevated thrombomodulin, von Willebrand factor, procoagulant activity, thrombotic microangiopathy and reduced a disintegrain and metalloprotease with thrombospondin type 1 motif 13 termed ADAMTS-13. These altered hemostatic pathways could result in intravascular coagulation and endothelial inflammation through increased formation of large von Willebrand factor and platelet aggregates. In general, malaria parasite-infected RBCs exhibit greater rigidity and lower deformability than normal RBCs. Compared to *P. falciparum*-infected RBCs, *P. vivax*-infected RBCs show lower levels of deformability. This enable *P. vivax* to pass through the narrow inter-endothelial slits of the splenic sinusoids resulting in inefficient trapping of *P. vivax*-infected RBCs and splenic clearance. However, low deformability may contribute to increased fragility of *P. vivax*-infected RBCs.

**Severe malarial anemia (SMA)**

Severe malarial anemia is defined as a hemoglobin concentration of < 50 g/L (5 g/dL) and the presence of high parasitemia (>10,000 parasites/μL). Anemia is the most common clinical condition of *P. vivax* infection in both adults and children in endemic areas, where
transmission is intense and relapses are frequent.\textsuperscript{73, 74} \textit{P. vivax}-associated anemia is complex and confounded by coinfection of \textit{P. falciparum}. The likely mechanisms involved in severe malaria anemia is a cumulative of loss of RBCs due to mixed infection, lysis of uninfected RBCs in the circulation and impaired RBC production.\textsuperscript{42, 75} In \textit{P. vivax} infections, ~34 uninfected red cells are removed for every infected uninfected RBC in the circulation, whereas in \textit{P. falciparum} infections, about 8 uninfected RBCs for lysed every infected RBC.\textsuperscript{77, 78} Thus, compared to \textit{P. falciparum} infections, lysis of uninfected RBCs is higher in \textit{P. vivax} infections, resulting in greater loss of RBCs and severe anemia. However, mechanisms that underlie in the higher loss of RBCs in \textit{P. vivax} infections despite lower parasitemia index compared to \textit{P. falciparum} infections are not well understood. Higher inflammatory responses even to lower \textit{P. vivax} parasitemias in the spleen, where the majority of extravascular hemolysis occurs, seems to be an important factor.\textsuperscript{41, 75} Consistent with this prediction, higher inflammatory responses in \textit{P. vivax} infections have been shown to be associated with greater oxidative stress in RBCs.\textsuperscript{75, 79} Although malaria-related clearance of uninfected RBCs has been shown to persist for at least 5 weeks after antimalarial treatment,\textsuperscript{80} over 80% of \textit{P. vivax} infections results in relapse at 3–4 week intervals and recurrent episodes leads to anemia progressively due to hemolysis and dyserythropoiesis before hematological recovery from the preceding infection occurs.\textsuperscript{81, 82} Inflammatory cytokine contributing to dyserythropoiesis likely due to direct toxicity of \textit{P. vivax} on erythroblasts or enhanced bone marrow phagocyte activity has been demonstrated in vivax malaria.\textsuperscript{83, 84}

**Acute respiratory distress syndrome**

Acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) has been reported in complicated malarial cases worldwide. This condition is associated with deep breathing, respiratory distress, pulmonary edema, airway obstruction, impaired alveoli, decreased gas exchange, and an increase in pulmonary activity.\textsuperscript{85} In both \textit{falciparum} and \textit{vivax} malaria, the majority of ARDS occurs in young children.\textsuperscript{19, 86} An autopsy study in ARDS cases from \textit{P. vivax} prior to antimalarial treatment has showed heavy infiltrates of intravascular mononuclear cells, diffused endothelial and alveolar damages, and absence of parasite sequestration in the pulmonary vasculature.\textsuperscript{64} Another autopsy study from Brazil has reported infiltration of neutrophils in alveolar capillaries even after parasites were from peripheral blood with antimalarial drug treatment.\textsuperscript{53} Thus, it seems that ARDS in \textit{P. vivax} infections are caused by inflammatory mediators.\textsuperscript{87, 88}

**Pregnancy-associated malaria**

Pregnancy-associated malaria (PAM) is associated with high morbidity and mortality causing about 75,000–200 000 infant deaths globally each year.\textsuperscript{89} Pregnant women are more susceptible to malaria infections because of their somewhat compromised immune status, especially in first and second trimester of pregnancy.\textsuperscript{90, 91} PAM-associated severe pathological conditions are mainly attributed to \textit{P. falciparum} infections because of parasite’s ability to massively sequester in the placenta.\textsuperscript{92} PAM presents a wide-spectrum of clinical conditions, including severe anemia, intrauterine growth retardation, low birth weight, preterm delivery, miscarriage; in addition perinatal mortality and death in the mother
are also associated\(^93, 94\). The sequestration of parasite-infected RBCs in the intervillous space of placenta is the contributor to PAM pathogenesis\(^91\). The sequestration is mediated by the binding of VAR2CSA, a variant \textit{P. falciparum} erythrocyte membrane protein 1 (PfEMP1) expressed on the surface of infected RBCs to chondroitin sulfate A (CSA) expressed in the placenta\(^95-97\). Accumulation of parasite in the placenta results in the deposition of hemozoin and fibrin as well as leukocyte infiltration. These result in alteration of intervillous and perivillous spaces, trophoblasts membrane dysfunction and compromised nutrient and oxygen transport to the developing fetus\(^98\). Production of cytokines such as IL-1, IFN-\(\gamma\), TNF-\(\alpha\), IL-2 leads to inflammation in the placenta\(^99, 100\). Additionally, complement activation plays a pathogenetic role during PAM\(^101\).

In \textit{P. vivax} infections, however, there have been only few studies on clinical outcomes of PAM. Of these studies, the majority has been conducted in the Asia-Pacific region\(^102-104\). Compared to PAM caused by \textit{P. falciparum}, \textit{P. vivax} associated PAM appears to be less severe. An histopathological study of \textit{P. vivax} infected placenta showed the accumulation of parasitized RBCs and malarial pigment deposits in intervillous spaces, but there were no other significant tissue changes\(^105\). An epidemiological study from Brazil showed \textit{P. vivax} infection contributing to low birth weight, abortion, and premature delivery; maternal anemia seems to have contributed to low birth weights\(^91\). An observational case control study from Brazil has reported that women with \textit{P. vivax} infections during pregnancy harbored parasites and infiltrated immune cells in the placenta\(^106\). Thus, systemic and placental inflammatory responses and microvascular dysfunction from \textit{vivax} malaria may cause deleterious utero-placental hemodynamic effects and fetal growth restriction\(^91, 105, 107\).

\section*{Conclusion}

Although, in the past, \textit{P. vivax} infections were thought to mostly benign and rarely life threatening, parasites are becoming increasingly virulent and cause fetal illnesses. The molecular mechanisms for this shift in pathophysiology of \textit{P. vivax} infection still remain poorly understood. It is possible that drug resistance and evolving alterations in parasite’s genomic make up, and changes in host responses due to altered microbiomes may result in dysregulated immune responses, contributing to severity of infections. In any event, there is a critical gap in the current knowledge on \textit{P. vivax} biology, pathophysiology and immunity. Coordinated multidisciplinary efforts are essential to bridge this knowledge gap.

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