Prevention and Treatment of Vivax Malaria

J. Kevin Baird, PhD, Eli Schwartz, MD, and Stephen L. Hoffman, MD

Corresponding author
J. Kevin Baird, PhD
ALERTAsia Foundation, c/o Eijkman Institute for Molecular Biology, Jalan Diponegoro No. 69, Menteng, Jakarta 10430, Indonesia.
E-mail: kbaird@alertasia.org

Current Infectious Disease Reports 2007, **9:**39–46
Current Medicine Group LLC ISSN 1523-3847

Plasmodium vivax is a significant public health threat throughout most of the tropics and to travelers to these regions. The infection causes a debilitating febrile syndrome that often recurs and in rare cases ends in death. The complex life cycle of the parasite compounds the difficulty of prevention and treatment, principally due to the phenomenon of relapse. Most commonly used drugs for preventing malaria fail to prevent late relapses by this parasite. Treatment requires dealing with both blood and liver stages. Since 1950, primaquine has been the only drug available for treatment of liver stages, and important clinical questions surround its appropriate use (ie, dosing, efficacy, safety, and tolerability). Likewise, chloroquine has been first-line therapy for vivax malaria since 1946, and the emergence of resistance to the drug further complicates therapeutic management decisions.

Introduction

Infection by *Plasmodium vivax* causes an acute, debilitating, and occasionally life-threatening febrile disease marked by cyclical spiking fevers with drenching sweats, and chills with shaking rigors. Headache, nausea, vomiting, myalgia, and profound malaise also routinely occur. An estimated 80 million people each year are infected [1], and many of these will experience two or more further episodes of disease with relapses. The number of fatalities caused by this parasite is unknown, but occasional well-documented case reports confirm that death is a possible, albeit uncommon, outcome. Recent studies bringing less ambiguous diagnostic technologies to bear suggest severe and fatal malaria with *P. vivax* may be more common than is now appreciated [2•].

Prevention and treatment of vivax malaria present challenges due to the unique biology of the parasite. Unlike *Plasmodium falciparum*, *P. vivax* has eluded determined attempts to maintain it in continuous culture in vitro, largely because it primarily invades and develops in reticulocytes, which make up only a small percentage of red blood cells, severely limiting laboratory studies of its biology, susceptibility to drugs, and mechanisms of immune attack. This difficulty is further compounded by the relatively greater complexity of its life cycle, principally the phenomenon of relapse (Fig. 1). Relapse, the key biologic distinction of this parasite from *P. falciparum*, impacts prevention and treatment. Relapse is a recurrent parasitemia originating from latent liver stages of the parasite known as hypnozoites [3], and it confounds the evaluation of the efficacy of drugs against the asexual blood stage of *P. vivax*.

Relapse also compounds the difficulty of practical prevention and treatment strategies. Most recommended regimens of chemoprophylaxis and recommended treatments for acute attacks of vivax malaria do not prevent relapse. Instead, a separate treatment is required. The only currently available drug for prevention of relapse is primaquine, an 8-aminoquinoline drug used for over 50 years and still surrounded by key unknowns about its mechanism of action, dosing and administration, efficacy, safety, and tolerability. Much of this review focuses on these issues, all of which engage the clinical problem of relapse.

Clinical Aspects

Incubation time

The life cycle of *P. vivax* explains its bimodal incubation time: one period for primary attack following exposure to infectious sporozoites and another for relapse following activation and maturation of the dormant liver stage hypnozoite (Fig. 1). The incubation time for the primary attack has been reported to be 14 ± 3 days after the mosquito bite [4]. The incubation time for *P. falciparum* is about 12 days [5]. However, delayed primary attacks for temperate strains have been reported 9 or more months after last exposure [6]. The risk and incubation time for relapse largely depends upon geographic origin of the infection. Compared to temperate strains, tropical *P. vivax* strains tend to have a higher probability of relapse (> 30%), a shorter period

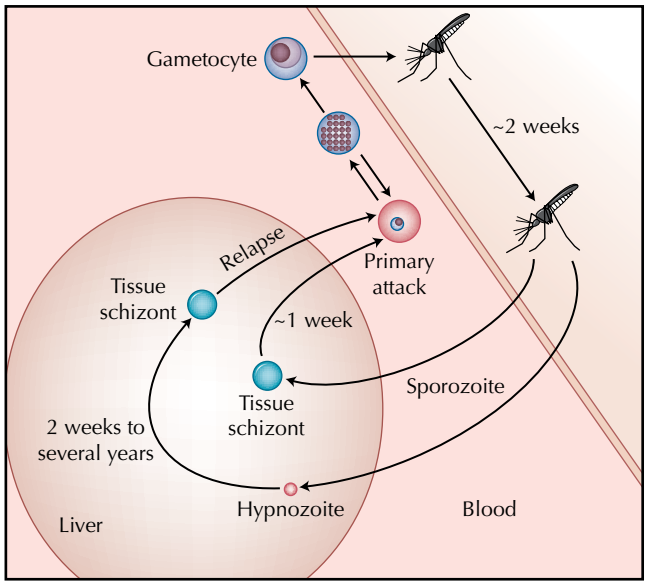

Figure 1. Life cycle of *Plasmodium vivax*.

between primary attack and relapse (17–45 days), and a higher incidence of multiple relapses (> 2). Clinicians should be alert to the possibility of vivax malaria several months or even a year or more following travel to an endemic area [7], especially in strains acquired in temperate zones such as Korea [6].

Clinical presentation

Headache, nausea, and vomiting accompanied by a low-grade fever mark onset of vivax malaria. Within a few hours of onset of symptoms, a high fever and profuse sweating often occur and resolve within a few more hours, but are followed by severe shaking chills. The cycles of drenching sweats, fever, and "bed-shaking" chills called paroxysms tend to be more severe with vivax compared to falciparum malaria. Relatively higher levels of inflammatory cytokines may account for this difference [8]. When all parasites are at the same stage of development, they are called synchronous. In a synchronous infection, both *P. vivax* and *P. falciparum* have an approximately 48-hour life cycle in the erythrocyte, and the paroxysms occur every 48 hours or every third day. Thus, they were formerly referred to as "tertian" malarias.

Because synchronous infections are especially uncommon in falciparum malaria, one rarely sees these regular paroxysms clinically, but rather sees patients with continuous or almost continuous fevers. Vivax malaria was referred to as benign tertian malaria and falciparum malaria as malignant tertian, because falciparum malaria was associated with significant risk of more severe disease and death. Laboratory findings may reveal low to normal white blood cell counts and low platelet counts. Anemia is rarely seen among travelers. A mild elevation of liver enzymes may be seen [9].

Complicated vivax malaria

Severe and complicated vivax malaria without coinfection with *P. falciparum* has been documented. Its presentation may be remarkably similar to severe and complicated falciparum malaria and can include hyperparasitemia (density of infection can reach 10%–20%), severe anemia, thrombocytopenia, cerebral malaria, acute respiratory distress syndrome, and renal failure [2•,10–14]. Vivax malaria causes splenic rupture, hematoma, and torsion more commonly than does falciparum malaria. In the few studies evaluating severe and complicated vivax malaria, the falciparum-like complications appeared more commonly than injury to the spleen [2•,15,16]. The risk of death with complicated vivax malaria was 18% in one study of 11 patients in India proven to have *P. vivax* as a single infection [2•]. In another study in Indonesia, risk of death with severe malaria was similar (25% vs 24%) among 36 severely ill patients with *P. vivax* and 277 patients with falciparum malaria (Baird, unpublished data). The pathogenesis of severe vivax malaria is presumably due to host inflammatory response, as microcirculatory obstruction due to cytoadherence of infected erythrocytes to endothelium of post-capillary venules (as seen in *P. falciparum*), has not been described in *P. vivax*.

Prevention

Control

A thorough discussion of control strategies is beyond the scope of this paper, but effective control of vivax malaria involves measures directed against mosquitoes. Unfortunately, the last few decades have seen the broad collapse of vector control programs throughout the tropics [17].

Personal protection

Even in areas highly endemic for vivax malaria such as the island of New Guinea, the risk of infection is much lower than for falciparum malaria in the heavily endemic zones of sub-Saharan Africa (~1 infection/person-year vs 5–8 infections/person-year, respectively). Where risk is relatively low (eg, << 1 infection/person-year), travelers may opt for measures of personal protection instead of chemoprophylaxis. These measures include avoiding peak malaria seasons, remaining out of the countryside at night, sleeping in an air-conditioned room, and using insecticide-impregnated clothing and mosquito nets. Wearing clothing that covers as much bare skin as possible after nightfall and mosquito repellents on exposed skin (ie, 35% DEET formulations) provide good protection. Strict adherence to these measures significantly reduces the chances of acquiring malaria but cannot be relied upon to prevent malaria where anopheline mosquitoes and infected people both occur in abundance.

Chemoprophylaxis

Primary attacks of vivax malaria may be effectively prevented using one or two types of drugs distinguished by

Table 1. Chemoprophylaxis against *Plasmodium vivax*

	Suppressive	Causal
Synonyms	Blood-stage prophylaxis	Liver-stage prophylaxis
Drug options	Mefloquine, doxycycline, Malarone® *	Primaquine
Use	Prevent primary attack	Prevent primary attack and relapse
Pre-exposure dosing required?	Yes	No
Terminal prophylaxis required?	Yes	No

*Causal agent against falciparum malaria (GlaxoSmithKline, London, UK).

the stage of the life cycle at which they act—liver-stage (causal) or blood-stage (suppressive) prophylactics. Liver-stage drugs (tissue schizonticides) prevent infection by their activity against parasite liver stages. Blood-stage drugs (blood schizonticides) attack erythrocytic-stage parasites. The distinction carries important clinical implications, primarily regarding relapse risk (Table 1) (Fig. 1).

Blood-stage (suppressive) prophylaxis

Blood-stage prophylaxis is the most common type of prophylaxis in use. Chloroquine, the first drug in this group to be used extensively, was introduced in 1946 for the prevention of both falciparum and vivax malaria. Chloroquine-resistant *P. falciparum* appeared in Thailand and Colombia in the late 1950s and spread across Africa by the late 1980s. In contrast, chloroquine-resistant *P. vivax* was first identified 30 years later in the late 1980s on the island of New Guinea. It is a major problem on that island and in eastern Indonesia, where more than half of infections with *P. vivax* appear resistant. Though resistance has been reported elsewhere in Southeast Asia, South Asia, and in South America, its prevalence remains quite low in these areas [18].

Mefloquine, doxycycline, and atovaquone/proguanil are highly effective against *P. falciparum*. Mefloquine is also highly effective against *P. vivax* (> 90% efficacy), but atovaquone/proguanil has had lower efficacy against it (84%) [19]. However, a recent study from Colombia reported 100% efficacy for atovaquone/proguanil against blood-stage vivax malaria [20•]. During the 1990s, well-controlled trials of all these drugs were conducted in northeastern Indonesian New Guinea, where vivax malaria is heavily endemic and highly resistant to chloroquine. Mefloquine and doxycycline each had greater than 95% protective efficacy [21,22]. These studies evaluated efficacy against primary attacks. Efficacy against relapse was anticipated to be null.

One disadvantage of the suppressive prophylactics is that they must be present in the bloodstream at effective concentrations when the parasites emerge from the liver. This requires dosing before travel, either by at least 2 weeks of standard dosing or a single loading regimen [23]. This also requires that they be continued for 4 weeks following travel to eliminate primary infections emerging from the liver. Another disadvantage of these drugs is that they do not prevent development of hypnozoites, and therefore do not prevent relapses. In fact in recent years, with increased travel to the tropics, it has become quite clear that using recommended blood-stage prophylaxis just postpones the first clinical attack to several months after return from the tropics. In a recent study, 80% of Israeli travelers diagnosed with vivax malaria had taken suppressive prophylaxis [7]. Thus, chloroquine and other drugs used for blood-stage prophylaxis given alone are inadequate for prevention of *P. vivax* malaria in travelers at significant risk of infection. There are two approaches to improving prevention.

One approach involves treating all individuals with 14 days of primaquine when they leave an endemic area. This approach is called terminal prophylaxis. It is intended to kill latent liver stages of *P. vivax* and thus prevent relapse. The term presumptive antirelapse therapy (PART) has been proposed to better describe this treatment strategy [24•]. The dose of primaquine for this purpose is under evaluation. Since the 1950s, 15 mg of primaquine base daily for 14 days has been used. However, most experts believe that this dose is inadequate and that the same dosage of primaquine used for radical cure of patients with *P. vivax* malaria, 30 mg of primaquine base daily for 14 days, should be used [24•,25•].

Liver-stage (causal) prophylaxis

A more elegant approach is by using liver-stage (causal) prophylaxis. This approach has the advantage of eliminating both primary attacks and relapses, and can be effective for both vivax and falciparum malaria [26–31]. Primaquine is the only commercially available drug known to have causal prophylactic activity against *P. vivax* malaria. Atovaquone/proguanil has causal protective activity against *P. falciparum* [32], but its activity against vivax malaria is unknown. In fact, recently acquired data from travelers to Papua New Guinea and Ethiopia indicate that atovaquone/proguanil prophylaxis does not prevent relapse (Schwartz, unpublished data).

Early clinical trials of primaquine demonstrated causal activity against *P. vivax* [33–35] and falciparum malaria [36]. Studies during the last 15 years have demonstrated protection against primary attacks of *P. vivax* and *P. falciparum* in children, nonimmune soldiers, and migrants [26–31]. In travelers, long-term follow-up shows

its efficacy also in preventing relapse [31]. Thus, a single 30-mg dose of primaquine base taken daily beginning on the day of exposure and continued for 5 days following exposure to infection prevents primary attacks and relapses [24•,37,38].

The recommended dose of primaquine for prophylaxis is well tolerated in people who take the dose with a snack or meal (to prevent gastrointestinal upset). Primaquine is contraindicated in pregnant women and people having an inborn deficiency of glucose-6-phosphate dehydrogenase (G6PD) or methemoglobin reductase. It causes a mild to moderate methemoglobinemia (typically < 6g%) in most people, which persists for as long as the drug is taken daily. Methemoglobinemia resolves within 2 weeks of ceasing the medication [29]. Use of daily primaquine in well-controlled trials ranged from 11 to 52 weeks in people of both sexes ranging from 7 to 60 years of age [24•].

Treatment

Acute attack

Chloroquine

Chloroquine has been first-line therapy for acute attacks of vivax malaria since 1946 [39]. Early clinical investigators developed the recommended adult dose of 1.5 g base delivered over 48 hours for effective cure of falciparum malaria, which was five times the dose needed to cure infections by *P. vivax* (ie, 0.3 g) [18]. This may in part explain the apparently long lag between finding chloroquine-resistant *P. falciparum* in the late 1950s, and finding chloroquine-resistant *P. vivax* in the late 1980s [18]. Another explanation may be the exquisite sensitivity of gametocytes (the only stage capable of infecting mosquitoes) of *P. vivax* to chloroquine, whereas the gametocytes of *P. falciparum* seem unaffected.

For chloroquine-sensitive *P. vivax*, standard chloroquine therapy clears the blood of asexual parasites within 72 hours. However, primaquine is required to prevent late relapses, which is termed "radical-cure" or antirelapse therapy, described later.

The emergence of chloroquine-resistant *P. vivax* threatens the sustained utility of this drug against vivax malaria. In eastern Indonesia, more than half of infections with *P. vivax* appear resistant, and the prevalence of resistance in western Indonesia is about 20%. Resistance has been reported from elsewhere in Southeast Asia, South Asia, and in South America, but it is of much lower prevalence (< 5%) [18].

Chloroquine plus primaquine

When primaquine is combined with chloroquine against chloroquine-resistant *P. vivax*, efficacy against blood stages dramatically improves [40]. In fact, primaquine alone clears blood-stage infections by chloroquine-sensitive *P. vivax* [41]. The efficacy of chloroquine combined with primaquine against chloroquine-resistant strains is important, because this combination is the recommended first-line therapy against chloroquine-sensitive *P. vivax*, offering clinical and radical cure. Thus, it may continue to serve as the first-line therapy against chloroquine-resistant vivax malaria. Although laboratory studies suggest a similar synergy between these drugs against chloroquine-resistant *P. falciparum* [42], clinical studies showed only the most modest effect [40]. Chloroquine with or without primaquine should never be used as the primary blood schizonticide against chloroquine-resistant *P. falciparum*.

Other treatments

Other drugs commonly used to treat falciparum malaria are uniformly effective against acute attacks of *P. vivax*, with the exception of sulfadoxine-pyrimethamine [43]. In northeastern Indonesian New Guinea, where chloroquine-resistant *P. vivax* dominates, standard mefloquine therapy proved more than 95% efficacious [44]. Atovaquone-proguanil proved similarly effective in this region [45].

Antirelapse therapy (radical cure)

At the outbreak of the Second World War, no licensed tissue schizonticide (anti–liver-stage drug) existed. American scientists in the 1940s found primaquine to have the best therapeutic index against liver stages, and it was available during the Korean War, where it saw use in many thousands of soldiers. After more than 50 years, primaquine remains the only licensed drug for the prevention of relapse in vivax malaria. Remarkably, our knowledge regarding mechanism of action is minimal, and our knowledge regarding its efficacy is limited.

Mechanism of action of antirelapse therapy

Ultrastructural studies suggest primaquine may act against mitochondrial membranes and disrupt respiration. Other than the fact that that it has 10 putative metabolites, we know little more about the activity of primaquine or its metabolites. A key attribute of primaquine activity is the total dose concept. Although primaquine is rapidly eliminated (plasma half-life of 4 hours), its efficacy appears to depend almost entirely on total dose with little or no impact from the schedule of its delivery. Whether administered daily over 7, 14, or 21 days, or weekly over 8 weeks, similar total doses exert similar efficacy.

Dosing of antirelapse therapy

Since the 1950s, the standard recommended dose of primaquine for prevention of relapse by *P. vivax* has been 15 mg daily for 14 days (2.8 mg/kg for a 75-kg individual total dosage). This schedule was extensively studied in American soldiers during the Korean War and found to be efficacious for *P. vivax* in Korea [46–48]. However, in the early 1950s, it became obvious that this dosage regimen was not adequate for eliminating Chesson strain *P. vivax* from New Guinea, with an efficacy of typically 80% or less. Chesson strain required a total dosage of

6 mg/kg of primaquine (30 mg per day for 14 days). Since then, there have been increasing reports of failure of the 15 mg/day for 14 days regimen in hospitalized patients in Thailand [49] and travelers all over the world [50]. Thus, the recommendation for the 15 mg/day regimen has been re-evaluated and altered [24•,37]. Most experts would now recommend 0.5 mg/kg/day for 14 days with a maximum dose of 30 mg/day for Oceania and Southeast Asia, and lower doses in parts of the world such as Ethiopia [51]. For heavy patients (> 80 kg) in Oceania and Southeast Asia, we recommend administering 30 mg daily to achieve a total dose of 6 mg/kg over as many days as is required [24•]. For an 85-kg individual, this would mean 17 days of treatment instead of 14.

Glucose-6-phosphate dehydrogenase–deficient patients

During the 1950s, investigators identified "primaquine sensitivity" to be caused by an inborn deficiency of G6PD. In studies on G6PD-deficient African Americans, they determined the primaquine-induced hemolysis to be mild and self-limited, even with continued dosing. Primaquine destroyed only senescent red blood cells in the African A-negative variant of G6PD (typically having > 15% residual activity). These investigators found 45 mg primaquine given once a week for 8 weeks was better tolerated among A-negative G6PD-deficient subjects and had good efficacy [52]. Primaquine is contraindicated in individuals with variants (eg, Mediterranean and Asian) of G6PD deficiency associated with less than 5% of residual G6PD activity because of the danger of life-threatening hemolysis. Thus, if the G6PD status cannot be determined, we do not recommend radical cure, but rather continued follow-up and re-treatment upon relapse.

Tolerance and resistance

The term tolerance to primaquine emerged from the early experience with the Chesson strain of *P. vivax*. The standard regimen of 15 mg daily for 14 days showed only 80% efficacy against this strain. It proved fully susceptible to the doubled dose of 30 mg daily. In the absence of selection pressure with a drug that did not yet exist, scientists considered the strain inherently tolerant rather than having an acquired resistance to primaquine. Whether tolerant or resistant to primaquine, *P. vivax* from New Guinea and Southeast Asia typically exhibit poor responses to the 15 mg per day regimen. A study of travelers documented travel to New Guinea as a significant risk factor for relapse following therapy with 15 mg per day of primaquine [50], causing most experienced clinicians to recommend 30 mg per day.

The burden of proof for resistance to primaquine is heavy. Many potential confounders must be addressed. First, reinfection must be ruled out as the source of parasitemia after primaquine treatment. Unlike with *P. falciparum*, genetic markers of strain identity are not helpful in *P. vivax*.

Second, proof of compliance with prescribed therapy must support a claim of resistance. Blood levels of primaquine at time of recurrent parasitemia are not helpful because it has been fully eliminated by the time relapse occurs. A documented record of witnessed compliance represents an essential element of evidence for resistance to primaquine.

The third confounding factor to be considered is recrudescence. If a patient was given chloroquine for the acute attack, a subsequent parasitemia within a month of treatment may represent failure of the blood schizonticide rather than the tissue schizonticide. Chloroquine resistance may create a false conclusion of primaquine resistance. Conversely, lingering blood levels of chloroquine may kill off parasites that relapse within 35 days of treatment. In other words, primaquine may appear effective when it is not.

Companion blood schizonticide

In a series of experimental challenges during the 1950s, Alving et al. [53] demonstrated very poor efficacy when low-dose primaquine was not given with either quinine or chloroquine, and much better efficacy (75%–95%) when the same doses were given concurrently (with either chloroquine or quinine). Chloroquine or quinine alone has no known activity against hypnozoites. These studies suggested that the activity of primaquine against hypnozoites is enhanced when given with either chloroquine or quinine. Unfortunately there have been no studies in over 50 years of this phenomenon and no studies in the field to assess these findings. Thus, these observations have had little impact on clinical practice.

Nonetheless, the practical lesson from from the study mentioned earlier about the synergistic effect of primaquine and chloroquine is that concurrent administration of both drugs may enhance the activity of chloroquine against the blood-stage parasites and enhance the primaquine effect against the liver stage of the parasite. Thus, starting primaquine early during the treatment course (immediately after having G6PD results) for vivax malaria may be beneficial for both clearing the parasitemia and killing the hypnozoites.

Vaccine

There are three distinct approaches to vaccine development for *P. falciparum* [54,55]. The first is to immunize to prevent asexual erythrocytic-stage infection in entirety, thereby preventing all clinical manifestations of the disease. This requires protective immune responses against the sporozoite and/or liver stages of the life cycle. The second is to immunize to reduce the incidence of severe disease and mortality without preventing infection. This approach could involve immune responses against the sporozoite, liver, and/or asexual erythrocytic stages of the life cycle. The third approach is to immunize to

Table 2. Results of experimental challenge in a single research subject immunized with irradiated sporozoites from the El Salvador and Chesson strains of *Plasmodium vivax*

	Immunization		Challenge	
	El Salvador strain	Chesson strain	El Salvador strain	Chesson strain
Week 1	728 infectious mosquito bites			
Week 2			Not protected	
Week 5		1251 infectious mosquito bites		
Week 6				Protected
Week 29				Not protected
Week 33				Protected
Week 46			Protected	

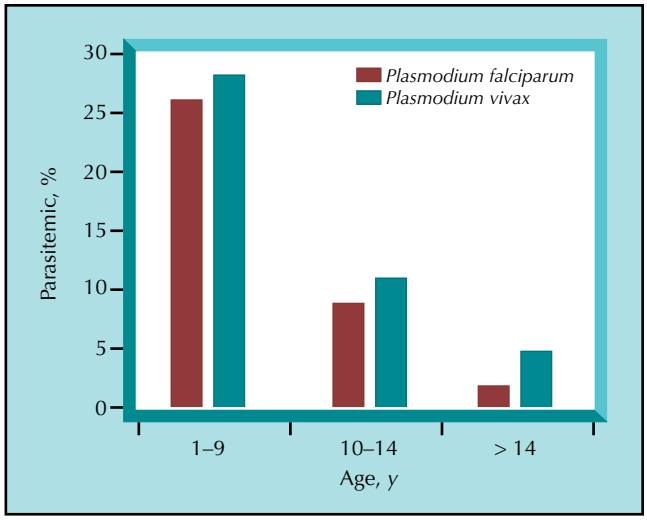

Figure 2. Rates of parasitemia found in cross-sectional surveys on the island of Flores in eastern Indonesia showing an age-dependent distribution of risk of parasitemia likely reflecting onset of naturally acquired immunity to *Plasmodium vivax* (Hoffman, unpublished data).

reduce transmission of the infection by inducing immune responses against the stages of the parasite life cycle that develop in the mosquito. This approach would not protect an individual, but would protect an entire community.

There are groups working on all three types of vaccines for *P. vivax* [56]. However, since *P. vivax* is rarely associated with severe disease and death, it is unlikely that there will be a large market for a vaccine to prevent severe disease and death. Furthermore, with the exception of epidemic control or use on small islands, it is difficult to envision large-scale deployment of a transmission-blocking vaccine. Thus, we think that primary efforts to develop a *P. vivax* vaccine should be directed at the sporozoite and liver (pre-erythrocytic) stages so as to entirely prevent infection.

Unfortunately, there are few data demonstrating the feasibility of protecting against *P. vivax* by immunization. One individual was reported to have been protected by immunization with radiation-attenuated *P. vivax* sporozoites delivered by the bite of infected mosquitoes (Table 2) [57].

No other human data indicate that protective immunity against infection with *P. vivax* can be generated by vaccination. However, it has been shown that passive transfer of a monoclonal antibody against the *P. vivax* circumsporozoite protein (PvCSP) can prevent sporozoite-induced infection in *Saimiri* monkeys [58], and that pre-incubation of *P. vivax* sporozoites with anti-PvCSP monoclonal antibody can prevent infection in chimpanzees [59]. Also, several vaccine trials in *Saimiri* and *Aotus* monkeys suggest low-level protection can be elicited [60,61].

Data from studies in the field and experimental and therapeutic infection with *P. vivax* indicate that immunity to the asexual erythrocytic stages develop after repeated infections. In areas with significant transmission of *P. vivax*, the prevalence and density of *P. vivax* infection decrease with increasing age (Fig. 2).

It has also been shown that humans experimentally infected with *P. vivax* rapidly develop acquired immunity that limits the peak parasite density and the extent of clinical symptoms after challenge with the same isolate of *P. vivax*. However, this effect is reduced significantly with challenge with a heterologous isolate of *P. vivax* [62].

In the past 2 to 3 years, interest has been renewed in vaccines for *P. vivax* [56]. There is significant work on the primary candidate antigens for pre-erythrocytic antigens (PvCSP and Pv sporozoite surface protein/thrombospondin-related anonymous protein), asexual erythrocytic stage antigens (Pv merozoite surface protein 1, Pv apical membrane antigen 1, and Pv Duffy binding protein), and sexual stage antigens (PvS25, PvS28, and PvS48. Only PvCSP and PvS25 have entered phase 1 clinical trials. There is also interest in developing a Pv radiation-attenuated sporozoite vaccine.

Conclusions

Travelers using blood-stage prophylaxis alone often suffer late relapse by *P. vivax*. Presumptive primaquine therapy (30 mg/d for 14 days, or a total dose of 6 mg/kg given as 30 mg/day) must immediately follow exposure to infection. Alternatively, travelers may use 30 mg primaquine

daily while exposed to risk of infection and for 5 days following exposure to prevent both primary attacks and relapses. Treatment of acute attacks with standard chloroquine therapy remains the first-line treatment, except in eastern Indonesia and Papua New Guinea, where resistance predominates. Standard mefloquine therapy is completely effective against chloroquine-resistant vivax malaria. Simultaneous dosing of chloroquine therapy with primaquine radical cure (30 mg/d for 14 days, or a total dose of 6 mg/kg given 30 mg/day) improves efficacy against chloroquine-resistant strains, and may improve the efficacy of primaquine against hypnozoites. In the absence of a vaccine in the foreseeable future, primaquine remains a vital tool against vivax malaria, and reliable assessments of its current therapeutic efficacy are sorely needed.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Mendis K, Sina BJ, Marchesini P, Carter R: **The neglected burden of Plasmodium vivax malaria.** *Am J Trop Med Hyg* 2001, **64(1-2 Suppl):**97–106.
2.• Kochar DK, Saxena V, Singh N, et al.: **Plasmodium vivax malaria.** *Emerg Infect Dis* 2005, **11:**132–134.

Uses polymerase chain reaction diagnostics to rule out coinfection with falciparum malaria in a series of 11 severely ill patients with vivax malaria.

3. Krotoski WA, Collins WE, Bray RS, et al.: **Demonstration of hypnozoites in sporozoite-transmitted Plasmodium vivax infection.** *Am J Trop Med Hyg* 1982, **31:**1291–1293.
4. Glynn JR, Bradley DJ: **Inoculum size, incubation period and severity of malaria. Analysis of data from malaria therapy records.** *Parasitology* 1995, **110(Pt 1):**7–19.
5. Church LW, Le TP, Bryan JP, et al.: **Clinical manifestations of Plasmodium falciparum malaria experimentally induced by mosquito challenge.** *J Infect Dis* 1997, **175:**915–920.
6. Cogswell FB: **The hypnozoite and relapse in primate malaria.** *Clin Microbiol Rev* 1992, **5:**26–35.
7. Schwartz E, Praise M, Kozarsky P, Cetron M: **Delayed onset of malaria: in travelers: Implications for chemoprophylaxis.** *N Engl J Med* 2003, **349:**1510–1516.
8. Hemmer CJ, Holst FG, Kern P, et al.: **Stronger host response per parasitized erythrocyte in Plasmodium vivax or ovale than in Plasmodium falciparum malaria.** *Trop Med Int Health* 2006, **11:**817–823.
9. Ravichandiran K, Sumitha K, Selvam RJ: **Liver function tests in recurrent P. vivax malaria.** *Commun Dis* 1996, **28:**231–240.
10. Lomar AV, Vidal JE, Lomar FP, et al.: **Acute respiratory distress syndrome due to vivax malaria: case report and literature review.** *Braz J Infect Dis* 2005, **9:**425–430.
11. Rodriguez-Morales AJ, Sanchez E, Vargas M, et al.: **Anemia and thrombocytopenia in children with Plasmodium vivax malaria.** *J Trop Pediatr* 2006, **52:**49–51.
12. Mohapatra MK, Padhiary KN, Mishra DP, Sethy G: **Atypical manifestations of Plasmodium vivax malaria.** *Indian J Malariol* 2002, **39:**18–25.
13. Beg MA, Khan R, Baig SM, et al.: **Cerebral involvement in benign tertian malaria.** *Am J Trop Med Hyg* 2002, **67:**230–232.
14. Mehta KS, Halankar AR, Makwana PD, et al.: **Severe acute renal failure in malaria.** *J Postgrad Med* 2001, **47:**24–26.
15. Gockel HR, Heidemann J, Lorenz D, Gockel I: **Spontaneous splenic rupture in tertian malaria.** *Infection* 2006, **34:**43–45.
16. Oh MD, Shin H, Shin D, et al.: **Clinical features of vivax malaria.** *Am J Trop Med Hyg* 2001, **65:**143–146.
17. Baird JK: **Resurgent malaria at the millennium: control strategies in crisis.** *Drugs* 2000, **59:**719–743.
18. Baird JK: **Resistance to chloroquine by Plasmodium vivax.** *Antimicrob Agents Chemother* 2004, **48:**4075–4083.
19. Ling J, Baird JK, Fryauff DJ, et al.: **Randomized, placebo-controlled trial of atovaquone/proguanil for the prevention of Plasmodium falciparum or Plasmodium vivax malaria among migrants to Papua, Indonesia.** *Clin Infect Dis* 2002, **35:**825–833.
20.• Soto J, Toledo J, Luzz M, et al.: **Randomized, double-blind, placebo-controlled study of malarone for malaria prophylaxis in non-immune colombian soldiers.** *Am J Trop Med Hyg* 2006, **75:**430–433.

Evidence of good efficacy of Malarone® (GlaxoSmithKline, London, UK) for preventing acute attacks of vivax malaria. Only the second such trial published.

21. Ohrt C, Richie TL, Widjaja H, et al.: **Mefloquine compared with doxycycline for the prophylaxis of malaria in Indonesian soldiers. A randomized, double-blind, placebo-controlled trial.** *Ann Intern Med* 1997, **126:**963–972.
22. Taylor WR, Richie TL, Fryauff DJ, et al.: **Malaria prophylaxis using azithromycin: a double-blind, placebo-controlled trial in Irian Jaya, Indonesia.** *Clin Infect Dis* 1999, **28:**74–81.
23. Boudreau E, Schuster B, Sanchez J, et al.: **Tolerability of prophylactic Lariam regimens.** *Trop Med Parasitol* 1993, **44:**257–265.
24.• Hill DR, Baird JK, Parise ME, et al.: **Primaquine: report from CDC expert meeting on malaria chemoprophylaxis I.** *Am J Trop Med Hyg* 2006, **75:**402–415.

An authoritative assessment of the available clinical data pertaining to the use of primaquine to prevent primary attacks and relapses by vivax malaria in travelers to endemic areas.

25.• Baird JK, Hoffman SL: **Primaquine therapy for malaria.** *Clin Infect Dis* 2004, **39:**1336–1345.

A review of the available data on the use of primaquine as anti-relapse therapy for vivax malaria.

26. Baird JK, Fryauff DJ, Basri H, et al.: **Primaquine for prophylaxis against malaria among nonimmune transmigrants in Irian Jaya, Indonesia.** *Am J Trop Med Hyg,* 1995, **52:**479–484.
27. Fryauff DJ, Baird JK, Basri H, et al.: **Randomized, placebo-controlled trial of primaquine for prophylaxis of falciparum and vivax malaria in Indonesia.** *Lancet* 1995, **346:**1190–1193.
28. Weiss WR, Oloo AJ, Johnson A, et al.: **Daily primaquine is effective for prophylaxis against falciparum malaria in Kenya: comparison with mefloquine, doxycycline, and chloroquine plus proguanil.** *J Infect Dis* 1995, **171:**1569–1575.
29. Baird JK, Lacy MD, Basri H, et al.: **Randomized, parallel placebo-controlled trial of primaquine for malaria prophylaxis in Papua, Indonesia.** *Clin Infect Dis* 2001, **33:**1990–1997.
30. Soto J, Toledo J, Rodriquez M, et al.: **Primaquine prophylaxis against malaria in nonimmune Colombian soldiers: efficacy and toxicity. A randomized, double-blind, placebo-controlled trial.** *Ann Intern Med* 1998, **129:**241–244.
31. Schwartz E, Regev-Yochay G: **Primaquine as prophylaxis for malaria for non-immune travelers; comparison to mefloquine or doxycycline.** *Clin Infect Dis* 1999, **29:**1502–1506.
32. Berman JD, Nielsen R, Chulay JD, et al.: **Causal prophylactic efficacy of atovaquone-proguanil (Malarone) in a human challenge model.** *Trans R Soc Trop Med Hyg* 2001, **95:**429–432.
33. Arnold J, Alving AS, Hockwald RS, et al.: **The effect of continuous and intermittent primaquine therapy on the relapse rate of Chesson strain vivax malaria.** *J Lab Clin Med* 1954, **44:**429–438.

34. Arnold J, Alving AS, Hockwald RS, et al.: **The antimalarial action of primaquine against the blood and tissue stages of falciparum malaria.** *J Lab Clin Med* 1955, **46:**391–397.
35. Alving AS, Rucker K, Flanagan CL, et al.: **Observations on primaquine in the prophylaxis and cure of vivax malaria.** *Proc. 6th International Congress of Tropical Medicine and Malaria* 1959, **7:**203–209.
36. Powell RD, Brewer GJ: **The effects of pyrimethamine, chloroquine and primaquine against exoerythrocytic forms of a strain of chloroquine-resistant Plasmodium falciparum from Thailand.** *Am J Trop Med Hyg* 1967, **16:**693–698.
37. Centers for Disease Control and Prevention: *Health Information for International Travel 2003–2004.* Atlanta: US Department of Health and Human Services, Public Health Service; 2003.
38. Baird JK, Fryauff DJ, Hoffman SL: **Primaquine for prevention of malaria in travelers.** *Clin Infect Dis* 2003, **37:**1659–1667.
39. Loeb RF, Clark WM, Coatney GR, et al.: **Activity of a new antimalarial agent, chloroquine (SN 7618).** *JAMA* 1946, **130:**1069–1070.
40. Baird JK, Wiady I, Sutanihardja A, et al.: **Short report: therapeutic efficacy of chloroquine combined with primaquine against Plasmodium falciparum in northeastern Papua, Indonesia.** *Am J Trop Med Hyg* 2002, **66:**659–660.
41. Pukrittayakamee S, Vanijononta S, Chantra A, et al.: **Blood stage antimalarial efficacy of primaquine in Plasmodium vivax malaria.** *J Infect Dis* 1994, **169:**932–935.
42. Bray PG, Deed S, Fox E, et al.: **Primaquine synergises the activity of chloroquine against chloroquine-resistant P. falciparum.** *Biochem Pharmacol* 2005, **70:**1158–1166.
43. Pukrittayakamee S, Imwong M, Looareesuwan S, White NJ: **Therapeutic responses to antimalarial and antibacterial drugs in vivax malaria.** *Acta Trop* 2004, **89:**351–356.
44. Maguire JD, Krisin, Marwoto H, et al.: **Mefloquine is highly efficacious against chloroquine-resistant Plasmodium vivax malaria and Plasmodium falciparum malaria in Papua, Indonesia.** *Clin Infect Dis* 2006, **42:**1067–1072.
45. Lacy MD, Maguire JD, Barcus, et al.: **Atovaquone/proguanil therapy for Plasmodium falciparum and Plasmodium vivax malaria in Indonesians who lack clinical immunity.** *Clin Infect Dis* 2002, **35:**92–95.
46. Alving AS, Hankey DD, Coatney GR, et al.: **Korean vivax malaria. II. Curative treatment with pamaquine and primaquine.** *Am J Trop Med Hyg* 1953, **6:**970–976.
47. Hankey DD, Jones Jr R, Coatney GR, et al.: **Korean vivax malaria. I. Natural history and response to chloroquine.** *Am J Trop Med* 1953, **2:**958–969.
48. Coatney GR, Alving AS, Jones R Jr, et al.: **Korean vivax malaria. V. Cure of the infection by primaquine administered during long-term latency.** *Am J Trop Med Hyg* 1953, **6:**985–988.
49. Wilairatana P, Silachamroon U, Krudsood S, et al.: **Efficacy of primaquine regimens for primaquine-resistant Plasmodium vivax in Thailand.** *Am J Trop Med Hyg* 1999, **61:**973–977.
50. Jelinek T, Nothdurft HD, Von Sonnenburg F, Loscher T: **Long-term efficacy of primaquine in the treatment of vivax malaria in nonimmune travelers.** *Am J Trop Med Hyg* 1995, **52:**322–324.
51. Schwartz E, Regev-Yochay G, Kurnik D: **Considering primaquine dose adjustment for radical cure of Plasmodium vivax malaria.** *Am J Trop Med Hyg* 2000, **62:**393–395.
52. Alving AS, Johnson CF, Tarlov AR, et al.: **Mitigation of the hemolytic effect of primaquine and enhancement of its action against exoerythrocytic forms of the Chesson strain of Plasmodium vivax by intermittent regimens of drug administration.** *Bull World Health Organ* 1960, **22:**621–631.
53. Alving AS, Arnold J, Hockwald RS, et al.: **Potentiation of the curative action of primaquine in vivax malaria by quinine and chloroquine.** *J Lab Clin Med* 1955, **46:**301–306.
54. Hoffman SL: *Malaria Vaccine Development: A Multi-Immune Response Approach.* Washington DC: American Society for Microbiology; 1996.
55. Miller LH, Hoffman SL: **Research toward vaccines against malaria.** *Nat Med* 1998, **4:**520–524.
56. Higgs ES, Sina B: **Plasmodium vivax vaccine research: steps in the right direction.** *Am J Trop Med Hyg* 2005, **73(5 Suppl):**1–2.
57. McCarthy VC, Clyde DF: **Plasmodium vivax: correlation of circumsporozoite precipitation (CSP) reaction with sporozoite-induced protective immunity in man.** *Exp Parasitol* 1977, **41:**167–171.
58. Charoenvit Y, Collins WE, Jones TR, et al.: **Inability of malaria vaccine to induce antibodies to a protective epitope within its sequence.** *Science* 1991, **251:**668–671.
59. Nardin EH, Nussenzweig V, Nussenzweig RS, et al.: **Circumsprozoite proteins of human malaria parasites Plasmodium falciparum and Plasmodium vivax.** *J Exp Med* 1982, **156:**20–30.
60. Collins WE, Nussenzweig RS, Ballou WR, et al.: **Immunization of protein of Plasmodium vivax.** *Am J Trop Med Hyg* 1989, **40:**455–464.
61. Collins WE, Sullivan JS, Morris CL, et al.: **Protective immunity induced in squirrel monkeys with a multiple antigen construct against the circumsporozoite protein of Plasmodium vivax.** *Am J Trop Med Hyg* 1997, **56:**200–210.
62. Collins WE, Jeffery GM, Roberts JM: **A retrospective examination of reinfection of humans with Plasmodium vivax.** *Am J Trop Med Hyg* 2004, **70:**642–644.