# Vivax malaria: more severe and more resistant

The current dogma is that *Plasmodium falciparum* can lead to severe disease and death, whereas *Plasmodium vivax* is usually benign. Recent large prospective studies have demonstrated that *P. vivax* alone is associated with severe manifestations similar to those defining *P. falciparum* malaria. The proportion of severe malaria among *P. vivax* patients in Papua ranged from 3 to 23%, and the case-fatality rate from 0.8 to 1.6%. The prominent clinical features differ from site to site, severe anemia being the most common in Papua, respiratory distress in Papua New Guinea and hepatic failure and jaundice in India. This new paradigm is complicated by the spread of *P. vivax* resistance to chloroquine with rate of treatment failures as high as 50% in Indonesia and Papua New Guinea. Artemisinin-based combination therapies offer a good alternative to chloroquine, but further studies are needed to rationalize regimens containing both asexual and hypnozoite activity. The goal of malaria elimination will not be achieved without considering the specificities of *P. vivax*. New tools (drugs and vaccines) and innovative strategies to target the dormant forms of the parasites are required.

**KEYWORDS: clinical ■ malaria ■ resistance ■ severe ■ vivax**

**Blaise Genton[1†] & Ivo Mueller[2]**

*[†]Author for correspondence:*
*[1]Swiss Tropical Institute, Socinstrasse 57, Postfach, 4002 Basel, Switzerland*
*Tel.: +41 79 556 58 68*
*Fax: +41 21 314 48 57*
*blaise.genton@hospvd.ch*
*[2]Papua New Guinea Institute of Medical Research, Goroka, Papua New Guinea*

## The dogma

'Malignant tertian' and 'benign tertian' are words that have long been used for two of the major diseases we recognize as malaria. The former characterizes *Plasmodium falciparum,* and the latter *Plasmodium vivax* infection. As the names malignant and benign suggest, the current dogma is that *P. falciparum* can be severe and life-threatening, while *P. vivax* tends to be mild [1]. This consideration has driven much of the research interest and funding towards understanding *P. falciparum*, leaving *P. vivax* as a neglected disease. Only recently the old dogma has been revisited, and there is growing evidence that *P. vivax* causes significant morbidity, and even mortality in endemic areas. This new appreciation is probably the result of innovative approaches to estimate more precisely morbidity trends, such as a longitudinal surveillance system in endemic areas, availability of more accurate diagnostic tests such as species-specific PCR, spread of *P. vivax* resistance across Oceania and Southeast Asia and momentum towards malaria elimination, a concept that makes *P. vivax* a central component to consider.

## Epidemiology of *Plasmodium vivax*

*P. vivax* occurs throughout the tropics, except in western and central sub-Saharan Africa, where the absence of Duffy factor on the surface of red blood cells largely protects those populations. The geographical distribution of endemic vivax malaria overlaps with that endemic falciparum malaria, except in temperate zones, such as the Korean peninsula, where only vivax malaria occurs, and in much of sub-Saharan Africa, where Duffy negativity seems to exclude endemic vivax malaria. Guerra *et al.* recently reported estimates of people living at risk of falciparum and vivax malaria at 2.5 and 2.6 billion people, respectively [2]. Hay *et al.* estimated 130–435 million infections by *P. vivax* [3], in contrast to the previous figure of 70–80 million annual infections [4]. The major burden (approximately 80%) lies in South and Southeast Asia. In the Americas, *P. vivax* accounts for approximately 70% of the malaria infections, but the total burden is rather low. This potential huge number of *P. vivax* cases worldwide raises important issues as far as prospects of elimination are concerned. Even if benign, these infections still represent a considerable burden in terms of morbidity. In fact, numerous case reports, mainly from India and, more importantly, recent morbidity surveillance reports from Papua, Indonesia [5,6] and Papua New Guinea [7], demonstrate that a significant proportion of patients infected with *P. vivax* can only have a clinical picture similar to those defined as severe falciparum malaria cases. Moreover, their case-fatality rate can be as high as that of *P. falciparum* [6].

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## Severe vivax malaria

Few texts attribute to *P. vivax* the syndromes occurring in severe and complicated *P. falciparum* malaria. However, recent studies using PCR diagnostic technologies revealed that patients with vivax malaria can have cerebral malaria, acute respiratory distress syndrome (ARDS), liver dysfunction and renal failure, without evidence of falciparum malaria [8–10]. Contrary to common belief, ruptured spleen is not a prominent feature of severe *P. vivax* malaria. Baird has collected 108 cases of severe and complicated vivax malaria since 1998 from the literature, 17 of which proved fatal, and only two reports of three patients with ruptured spleens, who all survived [11]. A 2004 review of the literature reports that only 11 well documented cases of splenic rupture in vivax malaria have been published in the English medical literature since 1960 [12]. Therefore, it can be concluded that ruptured spleen is a minor contributor to the spectrum of severe disease and death caused by vivax malaria.

The turning point in terms of evidence for *P. vivax* being potentially severe was the publication of three large case series from Papua, Indonesia [5,6] and Papua New Guinea [7]. The first [5] was a retrospective analysis of nearly 6000 hospital admissions for malaria over 3 years at Jayapura in Papua, Indonesia. Among the 1135 patients admitted with a diagnosis of vivax malaria by microscopy, 38 (3.3%) were classified as having severe malaria (predominantly cerebral malaria), ARDS, liver dysfunction or renal failure. The case-fatality rate of 25% among these patients was identical to those among severe falciparum malaria patients. The other two studies were prospective studies, one in Timika, southern Papua in Indonesia [6], and the other in the Wosera region of Papua New Guinea [7]. The two studies were conducted in different settings, and the cultural and ethnic characteristics of the patient populations were also different. Tijtra *et al.* collected data from all patients attending the outpatient and inpatient departments of the only hospital in the region, using systematic data forms and computerized hospital records [6]. By contrast, Genton *et al.* investigated patients presenting at two rural health facilities [7]. In both settings, clinical and severe disease was most common in young children, with *P. vivax* cases peaking at an earlier age than those of *P. falciparum*. In Timika, in children under 5 years of age, approximately 30% of cases of either *P. falciparum* or *P. vivax* were classified as severe, and approximately 80% of such cases were accompanied by severe anemia (hemoglobin less than 5 g/dl). In total, 2.0% of the malaria patients died during admission: 2.2% with *P. falciparum*, 1.6% with *P. vivax* and 2.3% with mixed infections. In the Wosera, in children under 5 years attending the health center, approximately 9% of vivax and 12% of falciparum infections were classified as severe malaria. Among those infected with both *P. vivax* and *P. falciparum*, 17% had severe malaria. *P. vivax* was responsible for 21% of all severe malaria, *P. falciparum* for 71% and mixed *P. vivax* and *P. falciparum* infections for 5%. Approximately 60% of the severe *P. vivax* patients were defined as such because of respiratory distress, versus 40% for *P. falciparum*.

It is interesting to note that the relative proportion of severe disease in *P. vivax* and *P. falciparum* infections in each setting was comparable. There were differences in the prevalence of the components of severe disease in the two locations, and a notable disparity in the overall rates of severe disease. Thus, in Timika, anemia defined severe malaria more often than in Wosera, where anemia was rather infrequent in severe vivax. The reason for this difference might have been a higher level of *P. vivax* chloroquine resistance in Timika, which led to persistent blood infections, increased destruction of erythrocytes and hence more severe anemia.

Both studies, inevitably, have limitations. First, co-morbidities, including concomitant bacterial or viral infections, that could have decreased the malaria-attributable fraction of disease [13], were not actively investigated. Second, microscopy was used for parasite detection and speciation, which routinely leads to marked underestimation of mixed infections in particular [14]. Some severe vivax cases may actually have been mixed infections. The concurrent publication of these two studies conducted by different research groups makes the findings less likely to be due to selection bias or be isolated observations. Certainly, both studies come from the same geographical areas and it may well be that there are some regional factors that can play a role. However, a recent prospective observational study adds to the evidence from the South-West Pacific [15]. It addresses the two concerns of geographical specialty and imperfect parasitological diagnosis. Indeed, this study was conducted in India, and *P. vivax* monoinfection was confirmed by microscopy, rapid diagnostic tests and PCR. Of all patients with *P. vivax* malaria, 9% had severe manifestations. The most frequent complication was hepatic dysfunction and jaundice in 58% of patients. Taken together, there is no doubt that *P. vivax* contributes to the high burden

of malaria morbidity, whether mild or severe. Clinicians should be aware that complications can occur in patients infected with *P. vivax* only. They should search for danger signs and manage patients appropriately, irrespective of the species.

## Type of severe manifestations in vivax malaria

Reported severe manifestations with *P. vivax* monoinfection are similar to those of severe *P. falciparum* infection, and include cerebral malaria with generalized convulsions and status epilepticus [8,9,15–17], severe anemia [6–8,15,16], hepatic dysfunction and jaundice [8,15,16], acute lung injury, ARDS and pulmonary edema [6–8,10,15,16,18–22], splenic rupture [23], acute renal failure [8,15,16,24,25] and severe thrombocytopenia with or without bleeding from different parts of the body [8,15,23,24,26–28].

The type of clinical manifestations defining severe *P. vivax* malaria differed from site to site, as shown in Table 1. The reasons for these differences are not all clear. As mentioned above, the high proportion of severe anemia in Timika may be attributed to a higher level of parasite resistance to chloroquine. Respiratory distress was the primary severe manifestation observed in Papua New Guinea. Since severe malaria was mostly encountered in children less than 2 years of age, it is possible that concurrent respiratory tract infections might have contributed to the respiratory distress and acidosis. In addition, there might be biases due to the fact that not all laboratory tests were available in all sites. Hepatic and renal function tests were not available in Papua New Guinea for example, which hindered the assessment of their prevalence, and hence can change the relative proportions.

**Table 1. Summary of the findings in the four main studies conducted in endemic areas.**

| Study characteristics and outcomes | Barcus *et al.* [5] | Genton *et al.* [7] | Tijtra *et al.* [6] | Kochar *et al.* [15] |
|---|---|---|---|---|
| Country | Jayapura, Papua | Wosera, PNG | Timika, Papua | Bikaner, India |
| Design | Retrospective | Prospective | Prospective | Prospective |
| Total number patients investigated | –* | 17,201 | 37,800 | – |
| ***Malaria*** | | | | |
| Total number malaria | 5936 | 9537 | 12,171 | 1091 |
| Total number *P. falciparum* | 3976 | 6886 | 7817 | 635 |
| Total number *P. vivax* | 1135 | 1946 | 2937 | 456 |
| Total number mixed infections | 817 | 350 | 1273 | – |
| ***Severity*** | | | | |
| *P. falciparum* severe (%) | 7 | 11‡ | 20 | – |
| *P. vivax* severe (%) | 3 | 9‡ | 22 | 9 |
| Mixed infections severe (%) | 6 | 17‡ | 31 | – |
| ***Case-fatality rate*** | | | | |
| CFR among all *P. falciparum* | 1.6%§ | – | 2.2 | – |
| CFR among all *P. vivax* | 0.79% | – | 1.6 | 4% |
| CFR among all mixed | 1.6%§ | – | 2.3 | – |
| ***Severe manifestations among all severe* P. vivax *malaria*** | | | | |
| Severe anemia (%) | 67 | 19‡ | 87 | 33 |
| Impaired consciousness (%) | 14 | 26‡ | 6 | 13 |
| Coma¶ (%) | 8 | 4‡ | – | 5 |
| Respiratory distress (%) | 14# | 61‡ | 12 | 10 |
| Shock (%) | 3 | – | – | 8 |
| Hepatic failure (%) | 28 | – | – | 58 |
| Renal failure (%) | 11 | – | – | 45 |
| Severe thrombocytopenia (%) | – | – | – | 23 |
| Severe hypoglycemia (%) | – | – | – | 3 |
| Multiorgan failure (%) | – | – | – | 48 |

**Not available.*
*‡Subsample of children aged <5 years.*
*§CFR aggregated between* P. falciparum *and mixed.*
*¶Coma included also in percentage with impaired consciousness.*
*#Including acidosis.*
*CFR: Case-fatality rate;* P. falciparum*:* Plasmodium falciparum*;* P. vivax*:* Plasmodium vivax*; PNG: Papua New Guinea.*

## Severe anemia

*P. vivax* contributes to severe anemia (hemoglobin concentration <5 g/dl) in vivax-endemic areas, particularly in young children. Severe anemia was most prominent in Papua (60–80% of the cases) [6], and accounted for a third of severe cases in India [7,15]. There are numerous possible etiologies for anemia, such as infection with *P. falciparum*, helminth infections, nutritional deficiencies and hemoglobinopathies, but in equatorial regions where more than 80% of *P. vivax* infections relapse at 3–4-week intervals, anemia is associated with recurrent bouts of hemolysis and dyserythropoiesis. It is not only the parasitized red cells that are destroyed, but also the uninfected ones. For each infected erythocyte destroyed, there are 32 noninfected ones that are removed from the circulation, a ratio much higher than for *P. falciparum* [29,30]. A study in Venezuela found even anemia to be more severe in *P. vivax* compared with *P. falciparum* [31]. Cytokine-related dyserythropoieis also probably contributes to anemia [32].

## Respiratory distress & acute lung injury

Nonsevere respiratory involvement manifesting as cough is well recognized in patients with *P. vivax* malaria. It has been reported in case series in 53% of nonimmune travelers and 63% of adults living in an endemic area [33,34]. Recent detailed studies of individuals with uncomplicated *P. vivax* infection have contributed to the understanding of the pathophysiology of lung injury [33,34]. At presentation, patients with *P. vivax* malaria had substantially reduced pulmonary capillary vascular volume compared with healthy controls. This reduction was unrelated to the parasite density in the blood, and was similar to that found in uncomplicated *P. falciparum* malaria. It is therefore likely that *P. vivax*-infected red blood cells are sequestering in the pulmonary capillary bed, even if it is contrary to the dogma that *P. vivax* is not able to mediate cytoadherence and microvascular sequestration [34]. There are data *in vitro* suggesting that *P. vivax*-infected red cells can cytoadhere to the ligand chondroitin sulfate A, which is expressed in pulmonary [35], placental [36] and cerebral [37] microvasculature. After treatment, pulmonary capillary vascular volume progressively improved in patients with *P. vivax* malaria, which is consistent with clearance of sequestered parasitized cells. However, the alveolar–capillary membrane component of gas transfer, which was normal at baseline, progressively fell. A likely explanation is a post-treatment intravascular inflammatory response to the death of parasites or reperfusion, or both. Increased pulmonary phagocytic cell activity has been shown 1–2 days after starting treatment for *P. vivax* malaria [33]. Together, sequestration of *P. vivax* in the lungs, followed by a post-treatment inflamatory response, might explain the delayed lung injury in *P. vivax* malaria, with acute lung injury or ARDS representing the most severe end of the clinical spectrum.

In adults, acute lung injury has been described as the cause of acute respiratory distress in returning travellers with vivax malaria [21,34]. In endemic areas, the majority of vivax-associated respiratory distress occurs in children, an age group in which acute lung injury is rare. This suggests that other causes such as anemia, acidosis and concurrent respiratory tract infections are likely to contribute to vivax-associated respiratory distress in children, a severe manifestation that was found in 5% of all children infected with *P. vivax* and in 60% of the severe cases in Papua New Guinea [7].

## Cerebral malaria

Coma associated with *P. vivax* is rather rare, and its etiology is the least well-characterized of the syndromes associated with *P. vivax*. In Papua New Guinea, 26% of the severe malaria cases presented with neurological signs, whether coma or repeated convulsions [7]. In Papua, approximately 5% presented with impaired consciousness; coma was more frequent in adults [6]. As mentioned earlier, these large prospective studies did not exclude co-infection with *P. falciparum* by PCR, or other (e.g., bacterial or viral) infections or comorbidities. However, it is likely that *P. vivax* alone can lead to coma, since Kochar reported nine cases in India where PCR was used to exclude *P. falciparum* [8,15].

Most of the research into cerebral malaria assumes the primary event to be vascular obstruction by parasitized red blood cells. The cytoadherence phenomena, described above, is believed to be central to the etiology of coma in falciparum malaria [38–40], but their role remains speculative in vivax-associated coma. Other potential factors include: concurrent infections, occult mixed plasmodium infections, metabolic changes, reversible local microvascular dysfunction, endothelial activation and injury, and microvascular thromboinflammatory responses [29]. Actually, the evidence that *P. vivax* malaria can alter brain function to the same degree as *P. falciparum* may question the

hypothesis of vascular obstruction as the primary cause of coma. It might favor the hypothesis that suggests enhancement of brain-origin cytokines, such as TNF, by nonbrain systemic inflammation as the cause of cerebral malaria [41].

### Hepatic & renal failures

The most common complications observed in India were jaundice and hepatic dysfunction, which was found in 58% of the severe cases. The second most frequent severe manifestation was renal failure, seen in 45% of the patients [15]. These observations are commonly found in the Indian subcontinent, but were not reported in Papua New Guinea for the simple reason that liver and renal function tests were not available. This means that eventually the proportion of severe cases might be even more important than the 9% reported in children aged under 5 years [7].

## Severe vivax malaria: old disease newly recognized or new disease?

It is not clear whether *P. vivax* severity is a newly recognized phenomenon or is a brand new disease presentation [1]. Price *et al.* hypothesize that the increase of chloroquine-resistant *P. vivax* parasites in recent years is one of the main drivers of the new severe vivax malaria [42]. It is based on their observation that severe anemia is the most frequent manifestation of severe malaria in Papua [6]. This may be true, but is definitely not the only reason, since severe vivax malaria has been newly recognized in India where no resistant parasites are circulating. In the latter setting, more accurate diagnostic methods certainly play a central role in better ascertaining the species responsible for severe malaria. The recent establishment of demography surveillance systems has proved a useful tool to improve our understanding of the respective contribution of falciparum and vivax parasites in the development of severe malaria. Published literature shifted from case reports or case series to longitudinal morbidity surveillance system reports with accurate denominators that allow precise estimation of the rates of severe malaria, and thus disease burden.

## *P. vivax* resistance to chloroquine & primaquine

Chloroquine has been the therapy of choice for the treatment of acute vivax malaria since 1946. Chloroquine was, in almost every way, the ideal drug for treating acute malaria in endemic settings. It was cheap, universally effective against all plasmodia species, deliverable in few doses, and safe for pregnant women and small children. No drug like this had appeared before, and none like it has appeared since, with these uniformly superior characteristics for a drug used in areas where medical supervision is scarce. The first report of *P. vivax* resistance appeared from Papua New Guinea in 1989 [43]. Today, eastern Indonesia presents the highest level of *P. vivax* resistance, with less than 50% probability of therapeutic success [44], followed by Papua New Guinea [45,46]. There is a gradient of less *P. vivax* resistance to chloroquine when going north east. For example, recent reports from Southern Myanmar [47] and Vietnam [48,49] showed a rate of treatment failure within a range of 10–25%. A number of reliable studies from Thailand [44] and India [50] have shown an almost uniform susceptibility of *P. vivax* to chloroquine. Systematic surveys in South America showed evidence of low risk of resistance [51,52].

The methodology for diagnosing resistance to chloroquine [53] is not straightforward, since recurrent parasitemia may be due to recrudescence, relapse or reinfection. Ideally, the diagnosis of resistance to chloroquine involves the measurement of chloroquine and its metabolite in blood on the day of reappearing parasitemia. This does not allow for distinguishing between recrudescence, relapse or reinfection, but it indicates that the parasite has broken through concentrations of the drug in the blood that ordinarily eliminate parasites of the chloroquine sensitive phenotype. This currently stands as the only functional definition of resistance to chloroquine in vivax malaria [44].

*In vitro* drug susceptibility assays provide an alternative method to assess drug susceptibility of *Plasmodium spp*. free from the confounders of host immunity, relapse and reinfection. However, as we lack a stable, continous *in vitro* culture system, standard *in vitro* drug assays cannot be applied to *P. vivax*. Recently, some success has been achieved in evaluating the inhibitory effect of antimalarials on fresh asexual stages of the parasite from the human host after short-term cultivation [54–56]. Results from *in vitro* susceptibility testing of *P. vivax* parasites were correlated with differing levels of clinical efficacy of chloroquine in different populations [57].

The investigation of the molecular profile of the *P. vivax* parasites can also provide additional useful information on chloroquine resistance. Suwanarusk *et al.* identified the Y976F mutations in *Pvmdr1* as highly prevalent in parasite populations originating from areas with high

level of clinical resistance [58]. This mutation correlated with *in vitro* [57] and *in vivo* susceptibilities [59], and could be therefore of interest to track the dynamic *P. vivax* resistance. In addition, a recent report suggested that clinical severity could be associated with increased expression levels of parasite genes likely involved in chloroquine resistance, namely *pvcrt-o* and *pvmdr 1* [60].

The diagnosis of resistance of *P. vivax* to primaquine is difficult, and there have been extensive discussions on which benchmark of primaquine sensitivity should be used. Confounders such as reinfections and recrudescences are not easy to handle to ascertain true primaquine resistance. Southeast Asian strains have shown consistently poor therapeutic responses to primaquine as far back as 1944, when the Chesson strain of *P. vivax* infected an American soldier in New Guinea [61]. Objective assessments of the risk of therapeutic failure in any given region remain elusive. Most of the data of poor responsiveness of *P. vivax* to primaquine in Southeast Asia rests largely upon evidence from clinical trials in Thailand [62,63]. Relapses of *P. vivax* after primaquine treatment were also frequent in travelers returning from the island of New Guinea [64,65]. Data from other places, such as the Korean Peninsula, India, Afghanistan, Africa and South America, also show a certain degree of resistance of *P. vivax* to primaquine. Since no molecular marker of liver-stage *P. vivax* resistance to primaquine has been identified, and considering the frequent relapses observed worldwide, it is probably wise to use a 30 mg daily regimen for 14 days. For those with glucose-6-phosphate dehydrogenase (G6PD) deficiency, alternative regimens over extended periods of time are explored (e.g., 0.75 mg/kg weekly for 8 weeks) [66].

## Which drug to use next?

With declining efficacy of chloroquine and almost universal use of artemisinin-based combinations therapies (ACTs) for the management of malaria (whatever the species), there is a need to precisely know the efficacy of the different drugs. Amodiaquine monotherapy appears to be compromised [46,67]. Mefloquine and atovaquone–proguanil have an excellent efficacy against highly chloroquine-resistant *P. vivax* [68,69]. Of the ACTs, dihydroartemisinin–piperaquine, produces the lowest failure rates at day 28 [70–72]. By contrast, artesunate–sulfadoxine/pyrimethamine is associated with recurrence rates of over 10% at day 28 [70,73], and this rises to over 20% for artemether–lumefantrine [70,72]. As none of these antimalarial drugs has any efficacy on the hypnozoite stages of *P. vivax*, the difference in recurrence rates is likely to be a consequence of the post-treatment prophylactic effect on relapses of drugs with different terminal elimination half-lives: approximately 4 days for lumefantrine, 18 days for amodiaquine and 28–35 days for piperaquine (28–35 days). An alternative might be to use three drugs instead of two, as *P. vivax* has partial resistance.

Early work showed that primaquine apparently requires an appropriate companion drug to achieve clearance of hypnozoites in the liver [44]. This consideration adds considerable complexity to the development of appropriate therapies for vivax malaria. Further studies are needed to rationalize regimens containing asexual and hypnozoite activity [44].

## Implication for the management

The observation that *P. vivax* can lead to severe disease calls for a revision of the case management. In most endemic places, the standard first-line regimen for *P. vivax* is still chloroquine (total 60 kg adult dose of 1.5 g over 3 days). It is likely that this drug will achieve sufficient reduction of the parasite biomass in areas with low levels of resistance. If G6PD status is known, primaquine is the best option, since it has proved to be more effective against relapses when administered simultaneously with chloroquine or quinine (reviewed in Baird [44]). To be effective, the adult dose of primaquine should be 30 mg for 14 days. However, in areas where treatment failure with chloroquine exceeds 10%, it would be reasonable to switch to an ACT. Up until results of studies with ACTs as companion drugs for primaquine are available, it may be safe to administrate primaquine at a later stage (eventually with chloroquine) to achieve radical cure. There is no proof that drugs administered intravenously are superior to those administered orally, as is the case for high-density *P. falciparum* patients, but no study has been conducted among severe *P. vivax* patients. Such a study may be difficult (impossible?) to perform due to the large sample size needed to demonstrate a reduction in case-fatality rate. However, similarly to *P. falciparum* cases, when danger signs are identified, it would be reasonable to use quinine administered intravenously (with primaquine given orally if G6PD status is known).

The prospective clinical studies in endemic areas have shown that the severe cases were at this stage upon admission. This is probably

due to the fact that most of them experienced delay in treatment initiation. This was not always the case for nonimmune travelers that tended to have poor outcome after several days of treatment, especially so for respiratory complications [21]. The implications of that is first to improve access to prompt diagnosis and appropriate treatment in endemic areas, and second to monitor carefully *P. vivax* malaria patients, as it is done for *P. falciparum*. This does not mean hospitalization for all, but strict follow-up, as advised for *P. falciparum* [74]. Such procedures are easy to implement in industrialized countries where patients have relatively easy access to health facilities. In endemic areas, clinicians should be aware that they need to carefully assess danger signs upon admission and, if possible, check hemoglobin to identify those patients that have, or are likely to develop, severe malaria. This last point is actually a matter for further research, since there is no good prognostic factor for poor outcome that has been identified and/or validated for *P. vivax*.

## Momentum for eradication: *Plasmodium vivax* cannot continue to be neglected

When speaking about shrinking the malaria map [75], scientists and public health authorities tend to believe that they have in hand the necessary tools to achieve elimination, thanks to effective and safe drugs, powerful vector control measures such as long-lasting impregnated bednets and indoor residual spraying. Even a malaria vaccine against *P. falciparum* may complement these effective strategies. This optimism does not take into account the specificity of the *P. vivax* lifecycle, which includes dormant hypnozoites that are not killed by conventional blood schizonticides. Primaquine, a very old drug, is actually the only currently available weapon against the hypnozoite reservoir. The armentarium is thus quite meager, and threatens the prospect of malaria elimination in areas where *P. vivax* coexists with *P. falciparum*. Primaquine may progressively lose its effectiveness; in addition, it may cause potentially fatal hemolytic anemia in some individuals with a G6PD deficiency. At present, there is a gap in knowledge on which G6PD-deficient persons are threatened by primaquine. The failure to improve or replace primaquine secures *P. vivax* as a persistent and severe challenge to public health. Elimination of *P. vivax* malaria requires the deployment of fixed-dose combinations effective against the drug-resistant *P. falciparum* and *P. vivax* parasites, including the dormant forms. The absence of such a tool renders prospects for elimination questionable at this stage. Indeed, one of the strategies could be to add mass drug administration to the current available malaria control measures. The ideal drugs for mass drug administration would be administered as a single dose, would have an excellent safety profile, including in pregnant women and small children, and would not need laboratory screening for contraindicating risk factors. Such a drug combination does not yet exist. Tafenoquine, a 8-aminoquinoline invented by the US Army and later developed by GlaxoSmithKline (London, UK), was intended first to be a drug for prophylaxis, then was proposed to replace primaquine for the prevention of relapses. This drug has an exceptional broad spectrum of activity against blood and tissue stages of *P. falciparum* and *P. vivax*, killing liver-stage schizonts and hypnozoites, sexual and asexual blood stages and stages in the mosquito host. Its half-life is extremely long (14 days) and provides incidental prophylactic protection lasting for several months [76]. These characteristics are ideal to serve as a complementary tool for malaria elimination. Indeed, theoretically, a single course of therapy could eliminate disease, relapse and further transmission. Unfortunately, tafenoquine did not prove to be as safe as expected, especially for persons with G6PD deficiency or pregnant women.

## Future perspective

*P. vivax* control definitely benefits from this renewed interest, due to the momentum for elimination. A research agenda has been recently developed [77] and all areas are concerned. More should be known on basic parasite biology, including key steps in hypnozoite formation, metabolism and reactivation, investigation of cytoadherent properties of *P. vivax*, development of a continuous *in vitro* culture system for blood-stage parasites, and screening of potential targets for future vaccine and drug interventions. Advances are needed in determining burden (risk areas and spatial limits of transmission), epidemiology (distribution of inherited blood disorders linked to susceptibility of malaria or adverse events with drugs), clinical patterns (vivax malaria in pregnancy, definition of severe vivax malaria) and immunity (naturally acquired protective responses). New products need to be developed, such as blood schizonticides effective against resistant *P. vivax* parasites, tissue and liver schizonticides,

practical and affordable point-of-care diagnostics of G6PD deficiency, and vaccines against both *P. falciparum* and *P. vivax*. Current control strategies effective against *P. falciparum*, such as insecticide-impregnated bednets, indoor residual spraying and intermittent preventive treatment for pregnancy, infants and, eventually, children, need to be assessed for their impact on *P. vivax* [77]. A collaborative spirit and a considerable increase in investment are needed to address the crucial gaps in our knowledge on *P. vivax* that could accelerate the development of new diagnostic tools, new drugs and, eventually, new vaccines. These will need to be assessed for their efficacy and impact in areas where *P. falciparum* and *P. vivax* co-exist, in order to address the potential for synergy or detrimental effects between species, such as replacement or increased morbidity [78].

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**Executive summary**

- *Plasmodium vivax* is associated with severe manifestations similar to those defining severe *Plasmodium falciparum* malaria.
- The proportion of severe malaria among *P. vivax* patients ranges from 3 to 23% (vs 7–20% for *P. falciparum*), and case-fatality rate from 0.8 to 1.6% (vs 1.9–2.2% for *P. falciparum*).
- The relative proportion of manifestations defining severe malaria differ from site to site and among age groups.
- *P. vivax* resistance to chloroquine is widespread in Indonesia and the South Pacific, with the rate of treatment failures as high as 50%.
- Artemisinin-based combination therapies offer a good alternative to chloroquine to kill asexual blood stage parasites, but further studies are needed to rationalize regimens containing both asexual and hypnozoite activity.
- Considering the potential for poor outcome, patients with *P. vivax* malaria should be managed in the same way as those with *P. falciparum* – that is, prompt diagnosis, identification of danger signs, effective treatment and close follow-up.
- The goal of malaria elimination will not be achieved without considering the specificities of *P. vivax*; new tools (drugs and vaccines) and innovative strategies to target the dormant forms of the parasites are required.

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- ▪ of interest
- ▪▪ of considerable interest

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