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(2007) Vivax malaria: neglected and not benign. *The American journal of tropical medicine and hygiene*, 77 (6 Supp). pp. 79-87. ISSN  
0002-9637

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## Vivax Malaria: Neglected and Not Benign

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**Abstract.** *Plasmodium vivax* threatens almost 40% of the world's population, resulting in 132–391 million clinical infections each year. Most of these cases originate from Southeast Asia and the Western Pacific, although a significant number also occurs in Africa and South America. Although often regarded as causing a benign and self-limiting infection, there is increasing evidence that the overall burden, economic impact, and severity of disease from *P. vivax* have been underestimated. Malaria control strategies have had limited success and are confounded by the lack of access to reliable diagnosis, emergence of multidrug resistant isolates, the parasite's ability to transmit early in the course of disease and relapse from dormant liver stages at varying time intervals after the initial infection. Progress in reducing the burden of disease will require improved access to reliable diagnosis and effective treatment of both blood-stage and latent parasites, and more detailed characterization of the epidemiology, morbidity, and economic impact of vivax malaria. Without these, vivax malaria will continue to be neglected by ministries of health, policy makers, researchers, and funding bodies.

### INTRODUCTION

The past decade has brought fresh impetus to the fight against malaria, driven by a growing appreciation of the humanitarian and economic magnitude of the problem and access to new funding sources.<sup>1</sup> For the most part this resurgence of interest has focused on infections with *Plasmodium falciparum*, which is associated with the greatest mortality and, in sub-Saharan Africa, intensity of transmission. In contrast *P. vivax*, the other major species infecting humans, is usually considered a “benign” infection receiving lower priority from researchers, policy makers, and funding bodies. Although the emphasis on *P. falciparum* is appropriate, the burden of vivax malaria should not be underappreciated and exacts a significant toll on almost 40% of the world's population. In this article we examine new evidence highlighting the magnitude of this burden and discuss major challenges to achieving a successful control strategy.

### EPIDEMIOLOGY

Using national statistics reported by regional offices of the World Health Organization, the 1999 World Health Report estimated that there are between 72 and 80 million cases of malaria due to *P. vivax* each year with the greatest burden observed in South and East Asia (52%), Eastern Mediterranean (15%) and South America (13%).<sup>2</sup> Recently these statistics have been challenged by an analysis using a combination of geographic information systems, malaria epidemiology, historical maps, and information on population densities, environment, and vector limits.<sup>3</sup> Revised estimates of the global malaria burden were found to be up to 2.5-fold higher than that derived from national statistics.<sup>4</sup> In preliminary work, Hay and colleagues also found that non-falciparum malaria, predominantly *P. vivax*, accounts for 25–40% of the

global malaria burden with between 132 and 391 million cases per year (Table 1). When the population density of areas endemic for *P. vivax* is taken into consideration, the number of people at risk of infection reaches 2.6 billion, slightly greater than that for *P. falciparum*.<sup>3</sup> Although the debate over methodologies continues,<sup>5,6</sup> it is likely that the true burden of vivax malaria has been grossly underappreciated and is probably in the region of a quarter of a billion clinical cases a year.

In South and Southeast Asia, where the majority of vivax malaria occurs, *P. vivax* accounts for up to 50% of malaria cases with prevalence rates between 1% and 6% of the population.<sup>7–9</sup> The proportional burden of vivax is even greater in Central and South America, reaching 71–81% of all malaria cases.<sup>10</sup> In eastern and southern Africa only 5% of malaria infections are attributable to *P. vivax*, although this still accounts for between 6 and 15 million cases per year.<sup>2</sup> The emergence of chloroquine-resistant *P. falciparum* has tended to reduce the proportion of malaria cases due to *P. vivax*<sup>11</sup>; nevertheless the absolute numbers of *P. vivax* remain high. Conversely, where successful malaria control strategies have been used the ratio of *P. falciparum* to *P. vivax* infections has fallen.<sup>12</sup>

In most areas the burden of disease is greatest in young children and infants with immunity usually developing by 10 to 15 years of age.<sup>13</sup> In a longitudinal study from Thailand, incidence rates varied from over 800 per 100 person-years in children under 5 years to 200 per 100 person-years in older adults. In these low-transmission settings premonition and asymptomatic carriage occur,<sup>14</sup> although overall 82% of patients with *P. vivax* parasitaemia were still found to be symptomatic.<sup>7</sup> Extrapolating this figure to the estimated total number of *P. vivax* infections presented in Table 1 suggests that there are between 106 and 313 million clinical cases of vivax malaria each year.

### PATHOBIOLOGY

Compared with *P. falciparum*, *P. vivax* has a slightly longer incubation period (12 days to several months), a similar eryth-

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TABLE 1  
Estimates of population at risk of *P. vivax* and number of clinical cases per year (in million)

| WHO Regional Offices | Population at risk of <i>P. vivax</i> infection (millions) |                     | Number of <i>P. vivax</i> infections per year (millions) |                   |         |
|----------------------|--|---------------------|--|-------------------|---------|
|                      | Mendis <sup>2</sup>  | Guerra <sup>3</sup> | Mendis <sup>2</sup>                                      | Hay <sup>4*</sup> |         |
| Africa               | AFRO   | 550                 | 50   | 6–15              | —       |
| America              | AMRO   | 87.7                | 78   | 11.1              | 10–28   |
| East Mediterranean   | EMRO   | 64.6                | 211  | 11.7              | 11–34   |
| Europe               | EURO   | —                   | 20   | —                 | 1.4–4.2 |
| Central Asia         |  | 8.5                 | —  | 0.17              | —       |
| Sea East Asia        | SEARO  | 1,284               | 1,347  | 42.1              | 90–248  |
| Western Pacific      | WPRO   |                     | 89   |                   | 20–77   |
| Total                |  | 1,995               | 2,596  | 71–80             | 132–391 |

\* Adapted from estimates on non-falciparum malaria, assuming that *P. vivax* constitutes the 90% of these infections.

rocytic cycle (42–48 hours), and produces fewer merozoites per schizont.<sup>15</sup> It is generally believed that *P. vivax* merozoites require a single cell receptor, the Duffy antigen, to invade host erythrocytes. Humans lacking this antigen are not susceptible to infection, explaining why *P. vivax* is largely absent from West Africa, a highly malarious region where the Duffy negative blood group is ubiquitous.<sup>16</sup> Recently this paradigm has been challenged by observations in East Africa, demonstrating *P. vivax* transmission in a population found to be Duffy antigen negative, although further studies are needed to elucidate the epidemiology.<sup>17</sup> *P. vivax* is further limited by its apparent preference for invading young red cells, whereas *P. falciparum* invades a broader range of erythrocyte ages.<sup>18</sup> This selective preference for red cell invasion is an important factor limiting the growth of *P. vivax* both *in vitro* and *in vivo*. The latter was noted over 100 years ago by Ross who commented upon the lower levels of parasitemia observed in febrile patients with benign tertian malaria (*P. vivax*) compared with those with malignant tertian (*P. falciparum*).<sup>19</sup> *P. vivax* is capable of inducing fever at levels of parasitemia lower than those causing fever in *P. falciparum* infection. In western Thailand, a region of low endemicity, the pyrogenic density was 180 parasites/ $\mu$ l, compared with 1000 parasites/ $\mu$ l observed in *P. falciparum* infection.<sup>7</sup> These estimates are similar to those observed in volunteers and malariatherapy patients.<sup>20</sup> In keeping with this the host inflammatory response is activated to a greater extent during infections with *P. vivax*, with plasma levels of fever-inducing cytokines such as TNF- $\alpha$  being higher in vivax malaria compared with *P. falciparum* infections with similar parasitemia.<sup>21,22</sup>

In addition to lower peripheral parasitemias, patients with *P. vivax* infections also tend to present with all parasite stages visible on the peripheral blood film. In contrast the late stages of *P. falciparum* are usually absent or present in low numbers, reflecting cytoadherence in the postcapillary venules. The latter is fundamental to the etiology of severe and placental malaria in *P. falciparum* infections.<sup>23</sup> In contrast *P. vivax*-infected red blood cells become increasingly more deformable as they mature<sup>24</sup> and are usually considered not to cytoadhere or sequester in the microvasculature. These characteristics underlie the reason why severe pathology in vivax infections is much less common than with *P. falciparum* infection. Interestingly recent studies have challenged this paradigm by suggesting that *P. vivax*-infected red cells may sequester in organs such as the lung.<sup>25</sup>

One of the most important differences between the plasmodial species infecting humans lies in the ability of *P. vivax*

and *P. ovale* to relapse after the cure of the original infection. A proportion of sporozoites do not undergo immediate development in the invaded hepatocytes. Instead they remain dormant in the liver, as hypnozoites, for prolonged periods of time before developing and causing recurrent infection. *P. vivax* strains from different geographic areas display widely different relapse patterns, reflecting evolutionary adaptation to local environmental conditions that optimize transmission potential of the parasite. Strains from tropical areas are characterized by early primary infection followed by frequent (10–14) relapses 3–6 weeks apart.<sup>26</sup> Whereas in temperate areas primary infection tends to occur later with intervals up to 1 year and fewer and later relapses to overcome prolonged periods of the year when transmission to the mosquito vector is unfavorable.<sup>27</sup> The ability to relapse renders *P. vivax* resilient to eradication from both the human host and the environment.

## CLINICAL MANIFESTATIONS

Clinical disease is associated with chills, vomiting, malaise, headache, fever, and myalgia. These symptoms are non-specific and cannot be distinguished reliably from other febrile illnesses or other malarias.<sup>7</sup> High fever and rigors are more common in vivax than falciparum malaria, reflecting synchronicity of schizont rupture. The classic paroxysms of fever lasting 4–8 hours and occurring with 48–56 hour periodicity, take several asexual cycles to develop in primary infections, although relapses often start synchronously with rigors.<sup>28</sup> *Plasmodium vivax* has a reputation as a benign infection, when compared with the severe manifestations frequently observed with untreated *P. falciparum*. However, in the pre-antibiotic era vivax malaria resulted in a chronic debilitating febrile illness that could last for years and was associated with hypoproteinemia and edema and dramatic weight loss akin to kwashiorkor.<sup>26</sup> Even today with access to effective antimalarials, severe and fatal infections can occur with *P. vivax*. It has long been recognized that splenic rupture is a life-threatening, though rare, complication.<sup>29</sup> More recently *P. vivax* has been shown to cause severe anemia, respiratory distress, malnutrition,<sup>30</sup> and possibly coma.<sup>31–33</sup>

In areas endemic for *P. vivax*, prevalence usually reaches a peak in young infants and children. In impoverished communities, anemia from malnutrition, worm infestations and falciparum malaria can be near-universal in this age group. Recurrent hemolysis (of both parasitized and non-parasitized

red cells)<sup>34</sup> and dyserythropoiesis from relapsing vivax malaria exacerbate this multifactorial anemia. Although most studies have not quantified the proportion attributable to vivax malaria, in some areas *P. vivax* infections are likely to be the most important determinant of anemia in infants. A case in point comes from southern Papua, Indonesia where almost 38% of patients hospitalized with malaria are anemic (Hb < 7 g/dl). In this region, 40% of severe anemia (Hb < 5g/dl) in infants can be attributed to infections with *P. vivax*, a rate almost 3-fold higher than that for *P. falciparum*.<sup>8</sup> Similar findings in Venezuela also suggest that anemia may be more severe and frequent in *P. vivax* infections than in *P. falciparum*.<sup>35</sup> When compounded by even mild respiratory dysfunction and malnutrition, such degrees of anemia are likely to be an important contributor to morbidity, hospital stay, and even mortality.<sup>30</sup>

Pregnant women are particularly vulnerable to malaria. *Plasmodium falciparum* sequesters in the placenta resulting in pathologic changes and compromise of materno-fetal transport, resulting in adverse outcomes in both mother and baby. The burden of *P. vivax* malaria in pregnancy is less well described. *P. vivax* does not appear to sequester in the placenta<sup>36</sup> and is associated with less pronounced histologic changes in the placenta, the main process being increased hemozoin deposition.<sup>36</sup> However *P. vivax* may still exert an adverse effect on the fetus through maternal anemia and the induction of a strong local inflammatory response, both of which interfere with utero-placental hemodynamics.<sup>37</sup> Clinical findings from Thailand and India have shown that vivax malaria during pregnancy causes maternal anemia and a significant reduction in mean birthweight (about 110 g), which is about 60% of that observed with falciparum malaria<sup>38,39</sup>; this almost certainly contributes to infant mortality. Interestingly, in contrast with falciparum malaria, the birthweight reduction is greater in multigravidae than primigravidae.

There have now been at least 18 case reports of non-cardiogenic pulmonary edema/acute lung injury in vivax malaria, almost all of which have excluded concurrent infection with *P. falciparum*.<sup>25,40,41</sup> All of the cases developed after commencement of antimalarial chemotherapy, raising the possibility of a pulmonary inflammatory response to parasite killing.<sup>42</sup> The possible sequestration of *P. vivax* in the pulmonary microvasculature<sup>25</sup> may target this inflammatory response to the lung. Although further studies are needed, these findings and the observation that over 50% of patients with vivax malaria present with cough<sup>25,42</sup> suggest that, as with *P. falciparum*,<sup>43</sup> there may be an important overlap between the clinical features of acute respiratory infections and acute vivax malaria. There have also been several reports of coma associated with vivax malaria<sup>31–33</sup> though most have not excluded concurrent infection with *P. falciparum* or other pathogens with central nervous system manifestations.

These reports of severe manifestations after vivax malaria challenge the usual perception of *P. vivax* as a benign infection. The spectrum of disease caused by *P. vivax* in Papua New Guinea and Papua, Indonesia, appear particularly bad; indeed in southern Papua 16% of all cases of severe malaria admitted to hospital were attributable to *P. vivax*.<sup>8</sup> Reports from India and Sri Lanka also highlight the broad range of pathology associated with *P. vivax*.<sup>2,33</sup> However, these rates may not necessarily be extrapolated to other endemic areas. Differences in parasite virulence, host susceptibility, age of

exposure as well as parasite factors such as antimalarial drug resistance may play a crucial role in modulating the clinical presentation. Alternatively the spectrum of disease in other areas may simply be underreported, particularly if severe pathology is mistakenly attributed to co-infection or misdiagnosis in speciation.

## MIXED INFECTIONS

In regions where *P. falciparum* and *P. vivax* coexist, mixed-species infections are common and yet rarely reported. Surveys usually report rates less than 2% and yet careful clinical studies record rates up to 30% and this figure is even higher when PCR detection methods are used.<sup>44</sup> Concurrent infections with different plasmodium species may have important implications on the host response and development of cross-species immunity.<sup>45</sup> Indeed in Thailand where this has been particularly studied, mixed infections with *P. vivax* appear to attenuate the severity of disease with *P. falciparum* reducing the risk of severe malaria,<sup>46</sup> decreasing the risk of treatment failure,<sup>47</sup> lowering gametocyte carriage,<sup>48</sup> and reducing the prevalence of anemia.<sup>49</sup> However in higher-transmission areas and areas of emerging drug resistance, the additive burden of severe malarial anemia and maternal malaria has not been addressed in detail. The potential for *P. vivax* to attenuate falciparum malaria requires further characterization, and has significant implications for vivax-only vaccination strategies, and the deployment of drugs such as chloroquine, which have lost efficacy against *P. falciparum* but still retain it against *P. vivax*.

## SOCIO-ECONOMIC BURDEN

The appreciation of the socio-economic burden of malaria has risen over the past decade and has been a major factor in raising its global profile and the funds dedicated to combating the disease. Falciparum malaria alone is estimated to have reduced the Gross Domestic Product of 31 African countries by almost 10%.<sup>50</sup> Although neglected, a number of observations suggest that *P. vivax* is also likely to exert a considerable economic toll. The incidence of *P. vivax* varies between regions, and age groups, with *P. vivax* relapses occurring in 20–80% of patients.<sup>27</sup> This ensures that even in low-transmission areas, up to 20% of the population can have a symptomatic infection each year with a cumulative experience of 10–30 episodes of malaria during a lifetime.<sup>2</sup>

The socio-economic burden of *P. vivax* infection is not known. Based on the estimated number of clinical episodes per year (106–313 million), assuming full treatment coverage with drug costs of \$0.1 per course of chloroquine and non-drug treatment costs of \$8.3,<sup>51</sup> the direct cost of treatment is between US\$0.9 and 2.7 billion per year. Because each symptomatic infection is associated with at least 3 days of absence from school or work (unpublished data), the overall global cost of *P. vivax* infection to the individual in terms of lost productivity (assuming a daily wage of US\$1.5 per day), healthcare costs and transport to clinics can be conservatively estimated as being between US\$1.4 and 4.0 billion per year.

These immediate costs are likely to be augmented by recurrent *P. vivax* infections in children. Longitudinal studies from Sri Lanka suggest that repeated attacks of malaria have

an adverse impact on the school performance of children.<sup>52,53</sup> Intuitively, recurrent vivax malaria will also result in anemia, malnutrition, growth retardation, stunting of development, and impaired economic productivity later in life, though detailed studies are lacking.

The burden of vivax malaria is felt not only at the individual level but also by healthcare providers. In many parts of Asia and South America, where *P. vivax* accounts for more than half of the cases of malaria, institutional healthcare costs are appreciably higher due to high rates of clinic attendance and hospitalization. In Thailand and Indonesia almost 30% of patients hospitalized with malaria are associated with pure *P. vivax* infections.<sup>8,12</sup> Again further studies are needed to quantify these costs more precisely.

#### DIAGNOSIS AND MANAGEMENT OF VIVAX MALARIA

Although microscopy remains the mainstay of diagnosis of vivax malaria, lack of access to good quality microscopy services in many endemic regions limits the reliability of diagnosis (as well as contributes to the underestimation of cases). HRP-2-based rapid diagnostic tests (RDTs) are usually sensitive for the diagnosis of *P. falciparum*, although aldolase-based and parasite lactic dehydrogenase-based RDTs have suboptimal sensitivity for *P. vivax*,<sup>54,55</sup> limiting the utility of RDTs for vivax diagnosis.<sup>56</sup>

Chloroquine has been the mainstay of treatment of acute vivax malaria for more than 50 years with dosing recommendations generally similar to those for *P. falciparum* (25 mg base/kg up to 1.55 g, given in 3 or 4 doses over 3 days). After eradication of the asexual stages of *P. vivax* from the peripheral blood, patients are at risk of relapse from the dormant liver stage. In equatorial regions such relapses occur in 20–80% of patients.<sup>27,57</sup> Chloroquine has potent activity against asexual stages, but no activity against hypnozoites. However, its long terminal elimination ensures that plasma concentrations of chloroquine are sustained above the minimum inhibition concentration for at least 28 days and thus are capable of suppressing the first relapse, which in tropical zones occurs at about 21 days.<sup>58</sup> The prevention of further relapses necessitates eradication of the dormant liver stages; however, only one antimalarial agent is registered with such activity, the 8-aminoquinoline primaquine. The standard recommendation for radical cure of *P. vivax* has been 15 mg primaquine daily over 14 days.<sup>27</sup> In some areas, particularly the Indian subcontinent, 5-day courses are recommended despite there being no evidence that they prevent relapse. The efficacy of the 14 day regimen varies considerably with relative resistance documented in Oceania and parts of Asia.<sup>59,60</sup> Several unsubstantiated reports also suggest that primaquine efficacy may be waning elsewhere.<sup>27</sup> The problem is particularly bad in Papua and Papua New Guinea where *P. vivax* demonstrates marked tolerance to primaquine.<sup>61,62</sup> Higher doses or longer courses have been advocated and may be more effective<sup>63</sup>; however, in practice, long courses of unsupervised therapy are rarely adhered to and thus likely to be ineffective. Furthermore, primaquine is contraindicated in infancy and pregnancy and causes hemolysis in G6PD-deficient individuals. In endemic settings, shorter alternatives are needed urgently. Short-course tafenoquine has potential,<sup>64</sup> but is not

registered and concerns about its prolonged hemolytic potential have tempered enthusiasm for its use in endemic areas where routine screening for G6PD deficiency is not possible.

#### CHLOROQUINE RESISTANCE (CQR)

Whereas chloroquine-resistant *P. falciparum* was first documented over 50 years ago, drug-resistant strains of *P. vivax* have taken much longer to emerge. This may reflect species differences in the underlying molecular mechanisms of resistance or lower selection pressure because of differences in the biology of gametocytogenesis. Gametocytogenesis in *P. falciparum* occurs after the appearance of symptoms and is refractory to schizontocidal drugs, thus favoring the transmission of resistant genotypes. In contrast gametocytes occur earlier in *P. vivax* compared with *P. falciparum* infections and are eliminated rapidly by schizontocidal agents, ensuring early transmission prior to selection.

The first case of CQR *P. vivax* (CQRPV) was reported in 1989 from Papua New Guinea<sup>65</sup> and was soon followed by reports from northern Papua, Indonesia.<sup>66–68</sup> By 1995, in some parts of Papua almost all patients with vivax malaria treated with chloroquine monotherapy failed therapy within 28 days.<sup>69</sup> Other studies subsequently confirmed a high prevalence of chloroquine resistance elsewhere in Papua,<sup>70</sup> and other parts of Indonesia.<sup>71,72</sup> Sporadic cases have also been reported from Burma,<sup>73</sup> South America,<sup>74,75</sup> Vietnam,<sup>76</sup> and Turkey<sup>77</sup>; see Figure 1. In contrast, chloroquine mostly retains its efficacy against *P. vivax* in Thailand and India.<sup>57,78,79</sup>

Despite these reports, the global prevalence of CQRPV is still poorly defined. In a recent systematic review only 11% (47/435) of published antimalarial drug trials between 1966 and 2002 addressed the efficacy of antimalarial drugs against *P. vivax*.<sup>80</sup> This reflects both the inherent difficulties associated with the *in vivo* test for relapsing malarial and, in the absence of any empirical evidence, the belief that established protocols continue to be effective. The latter was a major reason why policies were so slow to respond to the collapse of chloroquine efficacy against *P. falciparum* in sub-Saharan Africa a decade ago. The WHO 1999 Guidelines recommended a 14-day follow-up for the *in vivo* diagnosis of CQR *P. vivax* and such a short duration is incapable of detecting early decline in antimalarial therapeutic efficacy.<sup>81</sup> The 2005 WHO guidelines have extended follow-up to 28 days, which improves the sensitivity of the test, but at the expense of increasing confounding results from reinfection and relapse. Parasite genotyping has been useful in discriminating reinfection and recrudescence in *P. falciparum*, but the use of a similar strategy in *P. vivax* is more complex.<sup>82</sup> Relapses can occur either from the primary infection (in which case they are identical to recrudescence infections) or from a previous infection (in which case they may be misclassified as a reinfection); allocating a treatment outcome to a recurrent parasitemia is therefore not possible. In practice, recurrent infections occurring within 28 days of supervised chloroquine administration will be growing in the presence of chloroquine concentrations normally considered above those required to inhibit parasite multiplication and thus can be considered resistant.<sup>83</sup> Monitoring the uncorrected cure rate at day 28 is therefore a reasonable indicator of declining chloroquine efficacy, which can be confirmed by analysis of whole blood



FIGURE 1. Published reports of treatment failure after chloroquine monotherapy (25 mg base/kg up to 1.55 g over 3 days) for *P. vivax* infections. Large white stars = clinical trials of chloroquine monotherapy with > 10% recurrence rate by day 28; small black stars = case series with < 5 recurrences before day 28 (with or without chloroquine plasma drug levels); black circles = clinical trials after 2000, with no recurrences by day 28.

chloroquine concentrations to ensure adequate drug absorption.

*In vitro* susceptibility assays provide another means of assessing drug susceptibility of *Plasmodium* spp. free from the confounders of host immunity, relapse, and reinfection. Although these tests have been used in *P. falciparum* for more than 30 years, their application in *P. vivax* has been more difficult to develop because of the inability to culture the parasite through schizogony in an ex-vivo assay. Recently several groups from Thailand, where *P. vivax* responds well to chloroquine, have reported successful adaptation of schizont maturation assays deriving IC<sub>50</sub> values for *P. vivax* to chloroquine in the range of 30–120 nM.<sup>79,84,85</sup> Preliminary studies from Papua, Indonesia, where clinical studies have established the presence of high-grade CQR, demonstrate that chloroquine susceptibility of *P. vivax* is 5-fold lower than that reported in Thailand.<sup>86</sup> These findings suggest that *in vitro* testing may prove useful in monitoring for the emergence of resistance.

The other important tool for monitoring antimalarial drug resistance is tracking the prevalence of genetic markers of resistance. However, our current understanding of the molecular mechanisms of CQR in *P. vivax* is limited and preliminary studies suggest that resistance mechanisms may be different from that seen in *P. falciparum*.<sup>87</sup> Renewed interest in identifying putative molecular markers of CQRPV has been stimulated by the recent completion of the vivax genome project.

#### MANAGEMENT OF RESISTANT *P. VIVAX*.

*In vivo* drug studies on strains of *P. vivax* sensitive to chloroquine have demonstrated the efficacy of artemisinin derivatives, mefloquine, quinine, and halofantrine<sup>88</sup>; however, few studies have addressed suitable treatment regimens for CQR vivax malaria.<sup>83</sup> *P. vivax* has previously been regarded as intrinsically resistant to antifolates. It is not; but resistance develops readily,<sup>68,89</sup> through the sequential acquisition of muta-

tions in *Pvdhfr*.<sup>68,90,91</sup> The prevalence of antifol resistance is similar to that of *P. falciparum* with high levels of resistance in much of Southeast Asia<sup>92</sup> (Laos is a notable exception) and lesser degrees of resistance in the Indian subcontinent.

In Indonesia the efficacy of amodiaquine is superior to that of chloroquine, but in regions where high levels of CQR predominate, day 28 failure rates exceed 25%, suggesting amodiaquine monotherapy is not a suitable alternative once high-grade resistance has been reached.<sup>93</sup> Better success in the same region has been obtained with mefloquine and halofantrine, which retain almost 100% cure rates by day 28.<sup>94,95</sup> Atovaquone–proguanil plus primaquine also showed excellent efficacy against CQR *P. vivax*<sup>96</sup>; however, the high cost of this regimen (~US\$40) virtually precludes its use in endemic communities.

The artemisinin derivatives are highly potent antimalarials and are even more active against *P. vivax* than *P. falciparum*.<sup>97</sup> Artemisinin combination therapy (ACT) is now widely advocated for the management of *P. falciparum* infections. In practice only a minority of infections has correct species identification prior to treatment and therefore in Asia and South America it is highly likely that other species will also be treated with ACT. Despite this, only 3 studies have addressed the efficacy of these combinations against *P. vivax*. In the first, a 3-day course of artesunate plus sulfadoxine-pyrimethamine resulted in a recurrence rate of 10.5% by day 28.<sup>68</sup> In 2 subsequent studies of patients with pure *P. vivax* infections, recurrence rates by day 28 were significantly higher after artemether–lumefantrine (23%) and amodiaquine–artesunate (12%) than after dihydroartemisinin piperazine (3.6%).<sup>93,98</sup> None of these antimalarial drugs have any efficacy on the hypnozoite stages of *P. vivax* and hence the difference in cure rates is likely to be a consequence of the difference between the terminal elimination half life of lumefantrine (~4 days), amodiaquine (18 days) and that of piperazine (28–35 days). Piperazine, like chloroquine, suppresses the first relapse whereas lumefantrine and amodiaquine do not. In areas where primaquine cannot be super-

vised, such post-treatment prophylaxis afforded by drugs with long half lives will not prevent subsequent relapses, but will provide the only practical means currently available of delaying the timing of clinical illness from these relapses. The latter affords patients a longer period free from symptomatic malaria, decreases the risk of anemia and reduces significantly gametocyte carriage and thus the transmission potential to the mosquito vector.<sup>93</sup> Although longitudinal studies are needed to confirm these findings, when choosing an alternative to chloroquine in communities where CQR vivax malaria is endemic, the relevance of post-treatment prophylaxis should not be overlooked.

### CONTROL OF VIVAX MALARIA

Malaria control programs generally focus on providing good vector control, early diagnosis, and access to effective antimalarial regimens, preferably with anti-gametocyte activity to reduce transmission. In areas where both species are present, ACT-treatment-based programs have greater impact on *P. falciparum* than *P. vivax*.<sup>12,99</sup> Intensive eradication programs were successful in Europe, US, Australia, and in the 1940s–1960s both *P. falciparum* and *P. vivax* were almost eradicated from India with intensive DDT-based vector control and effective chloroquine chemotherapy.<sup>100</sup> The subsequent abandonment of DDT-based vector control led to a resurgence of both species in South Asia. Control measures remain limited in most areas of Asia, South America, and temperate regions of the middle and Far East and are compounded by political instability in central Asia where there has been a resurgence of vivax malaria. This lack of progress is of particular concern in view of the availability of both DDT and chloroquine, the latter remaining inexpensive and effective against vivax malaria in most areas. Chloroquine-resistant strains of the parasite are already firmly established in Papua New Guinea and eastern Indonesia and as they spread further afield will impact significantly on the current control program.

The drive to tackle *P. vivax* is very much dependent upon the perception of the threat that it poses. The latter has been hampered by an under-appreciation of the morbidity and mortality from vivax malaria, and the paucity of literature focused on this species. A crucial step in recruiting the interest of ministries of health, policy makers, researchers, and funding bodies will be the detailed characterization of the clinical epidemiology and economic burden of *P. vivax* in different geographical areas. From here our knowledge and experience with *P. falciparum* provides a useful framework with which to tackle perhaps the greater challenges that we face in controlling *P. vivax*.

Received October 25, 2006. Accepted for publication February 24, 2007.

Acknowledgments: We thank Simon Hay, Kathryn Maitland, and Bob Snow for their helpful comments on the manuscript. RP is funded by a Wellcome Trust Career Development Award (074637). CAG is supported by a Wellcome Trust Project grant (#076951) attached to the Malaria Atlas Project (MAP, <http://www.map.ox.ac.uk>). NJW is a Wellcome Trust Principal Fellow. NA is supported by an NHMRC Practitioner Fellowship.

No conflict of interests declared.

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