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Effects of Different Antimalarial Drugs on Gametocyte Carriage in *P. Vivax* Malaria

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Abstract. The gametocytocidal and asexual stage activities of eight antimalarial and eight antibiotic-containing regimens were evaluated in 349 adult patients with *P. vivax* malaria. Gametocytemia was found in 63% of patients (22% before and 41% after treatment). The median (range) gametocyte clearance time was 24 hours (range, 2–504 hours) and correlated with asexual parasite clearance time ($r = 0.52$, $P < 0.001$). Gametocytemia in vivax malaria was more common in patients with admission parasitemia > 10,000/μL and after treatment with drugs which have weak antimalarial activity, and was also associated with an increased rate of vivax reappearance (29.4% versus 14.1%, $P = 0.002$). Sexual stage activities corresponded with asexual stage activity for all tested regimens. Treatment with potent antimalarial drugs reduces the transmission potential of *P. vivax.*

INTRODUCTION

Plasmodium vivax is the most prevalent human malaria species outside Africa, causing > 75 million acute malaria episodes per year in Central and South America and Asia, and it is increasingly recognized in Eastern Africa. Approximately 75% of *P. vivax* infections occur on the Asian continent with 15–20% in Central and South America and the remaining 5–15% in Africa. *P. vivax* is generally sensitive to chloroquine, although high level resistance is now found on the islands of New Guinea and Sumatra and lower levels of resistance have been reported from an increasing number of other geographic locations in Asia and the Americas.[1–4] In Thailand, where the current studies were performed, the prevalence of *P. vivax* is similar to that of *P. falciparum,* and mixed infection with the two species is common and underrecognized.

Malaria transmission is determined by the frequency with which Anopheline mosquito vectors feed on human hosts carrying sufficient densities of sexual stages (gametocytes) in their peripheral blood.[5,6] In falciparum malaria, gametocytogenesis is delayed with respect to asexual stage multiplication, whereas in the other three human malarias, sexual and asexual stage development are closer together.[7–10] In *P. falciparum* malaria, primaquine accelerates clearance of gametocytes and artemisinin derivatives prevent gametocyte development, whereas most of the other antimalarial drugs have little or no effects on the development or viability of mature gametocytes.[11–14] In *P. vivax* malaria, the antimalarial drugs are all considered to be effective against the sexual stages of the parasite,[15] although there have been no prospective studies on gametocytocidal activity or on the factors that influence the production of gametocytes *in vivo* in this infection. There is no *in vitro* model to test gametocytocidal drug activity against *P. vivax* directly because *ex vivo* culture is hampered by the requirement for special culture media[16,17] and the lack of reproducible continuous culture methods. This study, conducted outside a malaria transmission area, evaluated and compared the sexual and asexual stage activities of the major antimalarial drugs and of antibiotics with known antimalarial activities.

MATERIALS AND METHODS

Patients. The study was conducted in adult male patients with acute symptomatic *Plasmodium vivax* malaria admitted to the Bangkok Hospital for Tropical Diseases. The study took place during 1994–1998. In total 16 oral antimalarial regimens were tested for their asexual stage activity. Patients with microscopically detected asexual stages of both *Plasmodium vivax* and *Plasmodium falciparum* on admission (i.e., mixed infection) were excluded. Full details of the asexual stage antimalarial activities have been reported previously.[18,19] The oral treatments consisted of eight first-line antimalarial drugs either alone or in combination and eight regimens containing antibiotics with known antimalarial activities as follows: 1) artesunate (Guilin Pharmaceutical Co., Guilin, China) 3.3 mg/kg followed by 1.65 mg/kg for the next 4 days; 2) artemether (Kunming Pharmaceutical Co., Kunming, China) 2.7 mg/kg followed by 1.3 mg/kg daily for the next 4 days; 3) chloroquine (Government Pharmaceutical Organization, Bangkok, Thailand) 25 mg base/kg total dose given over 3 days; 4) chloroquine 25 mg base/kg total dose given over 3 days followed by primaquine (Government Pharmaceutical Organization) 15 mg base/d for 14 days; 5) mefloquine (Roche, Basle, Switzerland) 15 mg base/kg single dose; 6) halofantrine (Glaxo SmithKline Laboratories, Brentford, UK) 8 mg base/kg three times in 1 day; 7) primaquine (Government Pharmaceutical Organization) 15 mg base/d for 14 days; 8) quinine sulfate (Government Pharmaceutical Organization) 10 mg salt/kg three times daily for 7 days; 9) sulfadoxine/pyrimethamine (Roche) 25/1.25 mg/kg (adult dose three tablets) single dose; 10) clindamycin (Upjohn Pharmaceuticals, Kalamazoo, MI) 300 mg four times daily for 7 days; 11) tetracycline (Government Pharmaceutical Organization) 250 mg four daily for 7 days followed by primaquine 15 mg base/d for 14 days; 12) tetracycline 250 mg daily for 7 days; 13) doxycycline (Siam Pharmaceutical, Bangkok, Thailand) 200 mg/d for 7 days; 14) azithromycin (Pfizer, Sandwich, UK) 500 mg/d for 3 days; 15) rifampicin (Marion Merrell Dow Pharmaceuticals, Kansas City, MO) 20 mg/kg/d followed by 15 mg/kg for the next 4 days followed by primaquine 15 mg base/d for 14 days; and 16) rifampicin 20 mg/kg/d followed by

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15 mg/kg for the next 4 days. Oral paracetamol (0.5–1 g four times daily) was given for fever ≥ 38°C.

These studies were approved by the ethics committee of the Faculty of Tropical Medicine, Mahidol University, Bangkok. Full informed consent was given by all patients.

Assessments of clinical response. Vital signs were recorded every 4 hours until resolution of fever and thereafter every 6–12 hours. Fever clearance time was defined as the time for body temperature to fall below 37.5°C and remain below this value for > 48 hours. Early treatment failure was defined as persistence of fever and parasitemia for > 7 days or persistence of parasitemia in the absence of fever for > 14 days. Reappearance of infection was assessed in patients who remained in Bangkok either in the hospital or at home (i.e., outside the malaria transmission area) for at least 28 days. Patients who failed to respond to the treatment or those who had recurrent vivax infections were treated subsequently with the standard regimen of chloroquine and primaquine at that time (Regimen 4). Patients with delayed appearance of *P. falciparum* were treated with a 7-day course of quinine (10 mg salt/kg every 8 hours) combined with tetracycline (250 mg every 6 hours).

Parasitologic assessment. Parasite counts of both sexual and asexual stages were measured every 2–12 hours in thin films and thick films until the parasitemia became detectable only in thick films, then every 12 hours until clearance, and thereafter daily for 28 days. Parasitemia was expressed as the number of parasites per microliter of blood (derived from the numbers of parasites per 1,000 red blood cells in the thin film stained with Giemsa or Field's stain or calculated from the white count and the numbers of parasites per 200 white blood cells in the thick film). Gametocytes and asexual stages were counted separately. Gametocyte counts were calculated from the thick film.

Gametocyte carriage was expressed as the proportion of patients with patent gametocytemia either before treatment (i.e., on admission) or at any time after initiation of treatment. The gametocyte clearance time (GCT) was defined as the interval from the first detection of gametocytes in peripheral blood films either before or immediately after treatment to the last detection of gametocytes. The variables describing parasite clearance were time taken until the asexual malaria parasite count fell by 50% (PC_{50}) and time to fall by 90% (PC90) of the pre-treatment admission value and the time to fall below detectable levels in a peripheral blood smear (PCT). Recurrence of vivax malaria could have resulted from recrudescence or relapse but not re-infection because these patients remained out of the transmission area. In an individual patient whose parasitemia cleared, recrudescence or relapse cannot be distinguished reliably.[20] Reappearance of parasitemia within 28 days was therefore considered together as treatment failure.

Statistical analysis. The data from each treatment group were compared by one-way analysis of variance with post hoc adjustment for multiple comparisons using the Bonferroni correction. Non-parametric data were compared by the Kruskal-Wallis test. A logistic regression model was used to determine factors related to gametocyte carriage using a forward stepwise analysis with the Wald statistic. The cumulative cure rates were calculated by Kaplan-Meier survival analysis and compared using the log rank test. Spearman rank correlation coefficient was used to evaluate the association between gametocyte counts, parasite counts, fever clearance, and parasite clearance times. All statistical analyses were performed using the statistical computing package, SPSS Version 11 for Windows (SSPS, Gorinchem, The Netherlands).

RESULTS

Patients. In total, 349 patients with acute vivax malaria 14–64 years of age (mean ± SD = 24 ± 9 years) were included in 16 treatment regimens. The majority of the patients came from the western border of Thailand (N = 277; 65%). Multidrug resistance in *P. falciparm* is a major problem in this area. These patients (N = 217; 62%) usually had at least one malaria infection in the past (median = 1 attack; range = 1–12 attacks). All patients presented with a history of fever (median = 4 days; range = 1–21 days) before hospital admission. The overall geometric mean (range) peripheral blood *P. vivax* asexual parasite count was 8,161/μL (41–107,765/μL). Of the 349 patients, 77 (22%) had detectable gametocytemia at presentation. In these, the median (range) gametocyte count was 24/μL (2–504/μL), and the median (range) ratio of sexual to asexual parasites was 0.3% (0.07–6.2%). The mean (SD) admission hematocrit was 36% (6.8%). Comparison between the different treatment groups did not show a significant difference in the age distribution of the patients, numbers of past malaria attacks, duration of fever before admission, or admission parasite counts ($P \geq 0.08$).

Clinical and parasitologic responses. All enrolled patients recovered fully and were discharged from the hospital as reported previously. Clinical recovery after study treatment occurred in all except nine patients who had early treatment failures after sulfadoxine/pyrimethamine (N = 5) or rifampicin (N = 4) treatment as described previously. The mean (SD) parasite clearance time of cases with clinical recovery was 98.4 hours (51.1 hours). Fever clearance times ranged from 2 to 169 hours (median = 31 hours). Detailed clinical and parasitologic follow-up was obtained in 271 patients (78%). These patients were either followed up outside the malaria transmission area for 28 days or remained in the hospital until the subsequent appearance of vivax or falciparum malaria (Table 1). In total, 170 patients (62.7%) had a complete clinical and parasitologic recovery, 83 patients (30.6%) had either treatment failure or reappearance of vivax malaria, and 18 patients (6.6%) had appearance of *P. falciparum* parasites in the peripheral blood smear after clearance of *P. vivax* parasitemia. Reappearance of vivax malaria after initial cure during the 28-day follow-up was observed in all treatment groups except for the patients treated with long half-life drugs (chloroquine or mefloquine) or tetracycline plus primaquine. All patients with incomplete cure responded to re-treatment with the standard regimens for vivax malaria or falciparum malaria.

***Plasmodium vivax* gametocytemia.** On admission, 22% (N = 77) of patients had patent gametocytemia and a further 41% (N = 144) developed gametocytemia after treatment (Table 1; Figure 1). The overall gametocyte carriage rate varied between treatment groups from < 50% in the chloroquine alone and chloroquine plus primaquine groups to all patients (100%) in the pyrimethamine-sulfadoxine group (which had a very high rate of early treatment failure). The pre-treatment gametocyte carriage of patients treated with the eight major antimalarial drugs (artesunate, artemether, chloroquine, chlo-

TABLE 1

Clinical data in patients with *P. vivax* malaria treated with different drug regimens showing gametocytemia rates, gametocyte clearance times (GCTs), and clinical outcome

Treatment groups	Total	No. (%) of patients with gametocytemia			GCT (hours) [median (range)]	No. with subsequence appearance of malaria/total follow-up (%)	
		Before treatment	After treatment	Total		*P. vivax*	*P. falciparum*
Antimalarials							
Artesunate	20	6 (30.0)	4 (20.0)	10 (50.0)	4 (2–24)	12/19 (63.2)	0
Artemether	20	3 (15.0)	9 (45.0)	12 (60.0)	8 (2–32)	9/17 (52.9)	0
Chloroquine	49	14 (28.6)	6 (12.2)	20 (40.8)	20 (2–56)	0/33	7 (21.2)
Chloroquine + primaquine	26	3 (11.5)	8 (30.8)	11 (42.3)	2 (2–43)	0/20	0
Mefloquine	16	2 (12.5)	9 (56.3)	11 (68.8)	24 (2–72)	0/14	0
Halofantrine	23	11 (47.8)	9 (39.1)	20 (87.0)	30 (2–76)	9/17 (52.9)	2 (11.8)
Primaquine	30	2 (6.7)	15 (50.0)	17 (56.7)	24 (2–72)	3/26 (11.5)	3 (11.5)
Quinine	22	5 (22.7)	15 (68.2)	20 (90.9)	26 (2–88)	11/17 (64.7)	0
Total	206	46 (22.3)	75 (36.4)	121 (58.7)	20 (2–88)	44/163 (30.0)	12
Antibiotics and SP							
Clindamycin	19	7 (36.8)	8 (42.1)	15 (78.9)	62 (2–115)	5/12 (41.7)	0
Tetracycline + primaquine	16	4 (25.0)	7 (43.8)	11 (68.8)	55 (2–144)	0/12	0
Tetracycline	24	3 (12.5)	12 (50.0)	15 (62.5)	48 (12–132)	4/17 (23.5)	0
Doxycycline	25	8 (32.0)	11 (44.0)	19 (76.0)	62 (2–189)	8/18 (44.4)	0
Azithromycin	19	2 (10.5)	8 (42.1)	10 (52.6)	67 (12–180)	9/17 (52.9)	6 (35.5)
Rifampicin + primaquine	24	2 (8.3)	13 (54.2)	15 (62.5)	12 (2–208)	1/18 (5.6)	0
Rifampicin	4	0	3 (75.0)	3 (75.0)	300 (163–504)	4*/4 (100)	0
Sulfadoxine-pyrimethamine	12	5 (41.7)	7 (58.3)	12 (100)	46 (2–172)	3 + 5*/10 (80.0)	0
Total	143	31 (21.6)	69 (48.3)	100 (69.9)	48 (2–504)	39/108 (36.1)	6 (5.6)
Overall totals	349	77 (22.1)	144 (41.3)	221 (63.3)	24 (2–504)	83/271 (30.6)	18 (6.6)

* Early treatment failure.

roquine plus primaquine, mefloquine, halofantrine, primaquine, or quinine) was similar to those treated with the regimens containing antibiotics (22.3% versus 21.7%; $P = 0.50$), but the post-treatment gametocyte carriage rates, and thus the overall gametocyte carriage, were significantly higher in the less effective antibiotic groups (48.3% versus 36.4% and 69.9% versus 58.7%, respectively; $P \leq 0.042$).

Duration of *P. vivax* gametocyte carriage. The median gametocyte carriage of all studied patients (i.e., including those without gametocytemia) was 4 person.h (range, 0–504 hours), reflecting considerable inter-individual variation and the low pre-treatment counts. The duration of gametocyte carriage was significantly less for patients treated with antimalarial drugs (median = 2 person.h; range = 0–88 person.h) compared with those treated with the antibiotic containing regimens (median = 24 person.h; range = 0–504 person.h; $P < 0.001$). After treatment, the median time taken for gametocyte clearance of all gametocytemic patients was 24 hours, ranging from 2 to 504 hours. Thus, the overall gametocyte clearance times (GCTs) of patients treated with the eight major antimalarial drugs were significantly shorter compared with the antibiotic group (median = 20 hours; range = 2–88 hours versus median = 48 hours; range = 2–504 hours; $P < 0.001$; Table 1). These significant differences between the two groups in GCT were observed in patients with gametocytemia detected both before and after treatment (before; median = 23 hours; range = 2–88 hours versus median = 93 hours; range = 2–189 hours and after; median = 20 hours; range = 2–72 hours versus median = 36 hours; range = 2–504 hours, respectively; $P < 0.001$). The sexual and asexual stage activities of all 16 regimens show similar orders of their relative activities as reflected by GCT and PCT (Figure 1). The overall GCT correlated significantly with PCT ($R = 0.52$, $P < 0.001$) and with fever clearance times ($R = 0.36$, $P < 0.001$).

Relationship between *P. vivax* sexual and asexual parasitemia. On admission, the overall median gametocyte count in gametocytemic patients ($N = 77$) was 0.3% (range = 0.07–6.2%) of the corresponding admission asexual parasite counts. This ratio was slightly higher in patients with gametocyte counts of > 50/μL (Table 2), which may simply reflect numeric instability at very low counts. The highest gametocyte proportion was 2.2% (range = 0.1–5.6%). The overall time to peak gametocytemia was 1 day (range = 0–5 days). The median delay after time to peak parasitemia was 12 hours (range = 15 hours to 4 days).

Activity of primaquine against sexual stages of *P. vivax*. Primaquine has significant asexual stage activity against *P. vivax*.[21] The addition of primaquine to other drugs had no significant effects on the overall gametocyte carriage rates ($P \geq 0.48$; Table 1). Excluding patients with pre-treatment gametocytemia, there were no significant differences in the post-treatment gametocyte carriage rates of the following paired comparisons; primaquine-chloroquine versus chloroquine alone (35% versus 17%, $P = 0.22$), primaquine-tetracycline versus tetracycline alone (58% versus 57%, $P = 0.76$), and primaquine-rifampicin versus rifampicin (59% versus 75%, $P = 0.97$). However, the addition of primaquine did result in significantly shorter median overall GCT in two comparisons: primaquine-chloroquine versus chloroquine (2 versus 19.5 hours, $P = 0.022$) and primaquine-rifampicin versus rifampicin (12 versus 300 hours, $P = 0.010$) but not in the primaquine-tetracycline versus tetracycline regimens (55 versus 48 hours, $P = 0.50$). The primaquine alone regimen did not show different sexual stage activity compared with the other antimalarial drugs (Table 1; Figure 1). Taken together, these data do not indicate any preferential effect of primaquine on the sexual stages of *P. vivax*, although there may be asexual stage synergy with chloroquine.

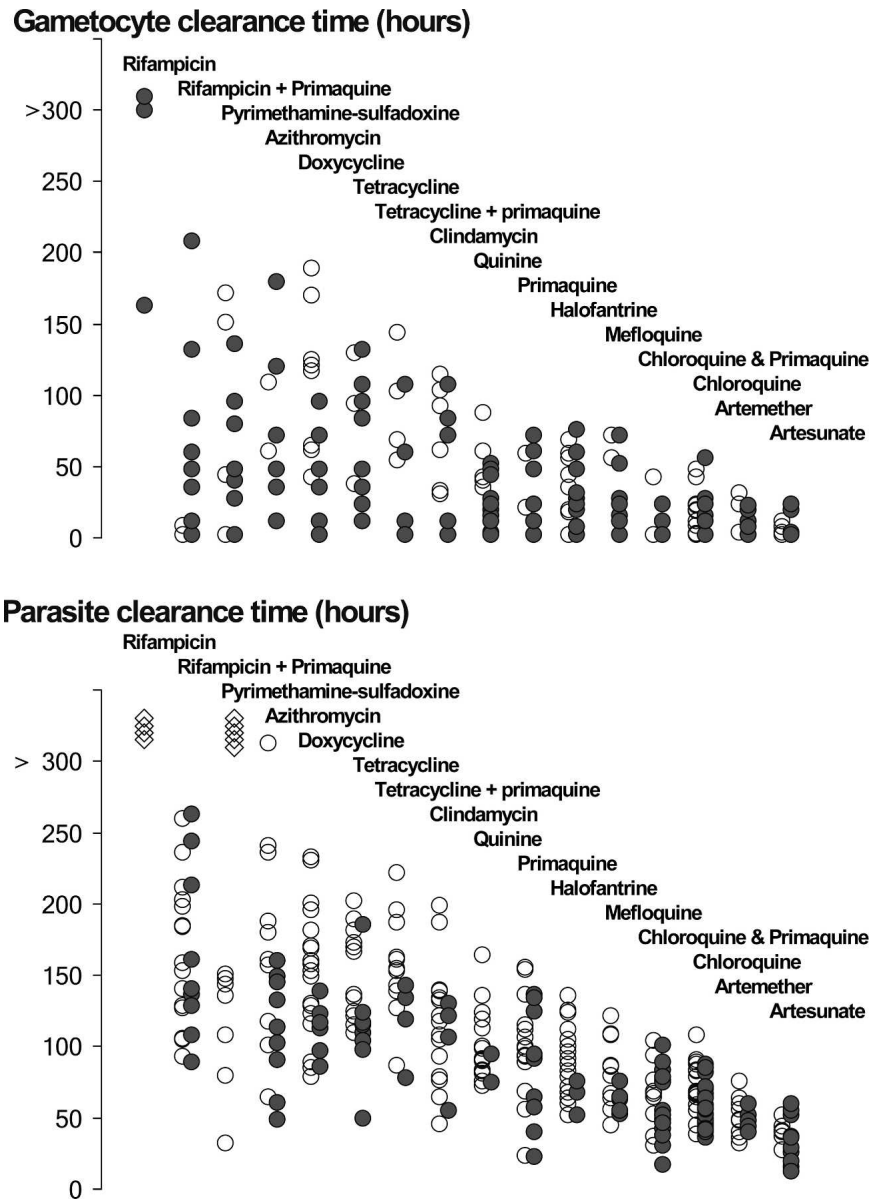

FIGURE 1. Gametocyte and parasite clearance times in the 16 treatment groups of patients with *P. vivax* malaria. Gametocyte clearance times in patients with gametocytemia appearing before and after starting treatment are shown as open and closed circles, respectively in the upper figure. Parasite clearance times in patients with and without gametocytemia are shown as open and closed circles, respectively in the lower figure.

Factors associated with gametocyte carriage. The first gametocyte count correlated positively with pre-treatment asexual parasitemia ($R = 0.23$, $P = 0.001$). The admission asexual parasite count was significantly higher in patients with gametocytemia ($N = 221$) compared with those without ($N = 128$; geometric mean = 10,381/μL versus 5,386/μL; $P = 0.003$). There were no significant differences in the numbers of previous malaria attacks, duration of fever, or admission hematocrit values in patients with and without gametocytemia (Table 3). Fever clearance times and parasite clearance times and profiles (PCT, PC_{90}, and PC_{50}) were all significantly longer in patients with patent gametocytemia ($P \leq 0.010$), presumably reflecting the higher asexual densities. Patients with patent gametocytemia had higher rates of subsequent vivax reappearance compared with those without gametocytemia (29.4% versus 14.1%, $P = 0.002$; Figure 2). This significantly higher cumulative rate of subsequent vivax reappearance seen in the gametocytemic patients was observed both for those with gametocytemia detected on admission (28.6% versus 14.1%, $P = 0.007$) and after treatment (29.9% versus 14.1%, $P = 0.004$) and was also seen in the subgroup treated with antimalarial drugs (28.1% versus 11.8%, $P = 0.001$). This remained true after adjusting for initial parasitemia and type of treatment: hazard ratio (HR) = 1.90 (1.07–3.38), $P = 0.028$ for gametocytemia present at admission and HR = 2.03 (1.07–3.84), $P = 0.030$ for gametocytemia presenting after treatment and before Day 7.

***Plasmodium falciparum* co-infections.** Gametocytes of *P. falciparum* were detected in 19 patients, of whom 18 completed their follow-up. The majority of them ($N = 16$) had complicated clinical outcomes including delayed appearance of falciparum malaria ($N = 13$), reappearance of vivax ($N =$

TABLE 2
Relationship between sexual and asexual parasitemia in patients with *P. vivax* gametocytemia

	Patients with > 50/μL gametocyte count	All patients with gametocytemia
Gametocyte/parasite counts before treatment (%)	0.4 (0.1–8.3) $N = 35$	0.3 (0.07–6.2) $N = 77$
Peak gametocyte/peak parasite counts (%)		
Gametocytemia before treatment	0.7 (0.1–3.5) $N = 55$	0.5 (0.07–4.0) $N = 79$
Gametocytemia after treatment	0.6 (0.1–3.7) $N = 74$	0.4 (0.07–3.7) $N = 141$
All patients with gametocytemia	0.6 (0.1–3.7) $N = 129$	0.4 (0.07–3.7) $N = 220$
Peak gametocyte/corresponding asexual parasite counts (%)		
Gametocytemia before treatment	1.1 (0.1–4.0) $N = 55$	1.0 (0.1–4.0) $N = 79$
Gametocytemia after treatment	3.0 (0.3–6.0) $N = 72$	2.9 (0.2–6.7) $N = 136$
All patients with gametocytemia	1.9 (0.2–5.6) $N = 127$	2.2 (0.1–5.6) $N = 215$
Days of peak parasitemia	0 (0–3) $N = 130$	0 (0–3) $N = 221$
Days of peak gametocytemia	0.5 (0–4) $N = 130$	1 (0–5) $N = 221$
Lag time (days) between peaks of gametocytemia and parasitemia		
Gametocytemia before treatment	0.25 (–0.5 to 3) $N = 55$	0.25 (–0.5 to 3) $N = 79$
Gametocytemia after treatment	0.63 (–0.25 to 3.5) $N = 74$	0.75 (–0.75 to 4.5) $N = 141$
All patients with gametocytemia	0.5 (–0.25 to 3) $N = 129$	0.5 (–0.63 to 4) $N = 220$

All data are presented as median (90% range).

2), or vivax treatment failure ($N = 1$). In 13 patients with subsequent falciparum malaria, *P. falciparum* gametocytemia was detected before ($N = 9$), at the same time ($N = 2$), or after ($N = 2$) the delayed appearance of asexual falciparum parasitemia. In these 13 patients, the median interval between first appearance of sexual and asexual forms of *P. falciparum* was 216 hours (range = 96–439 hours). In the nine cases whose *P. falciparum* gametocytemia preceded the asexual parasitemia, the median (range) interval was 11 days (48–439 hours). The incidence of cryptic falciparum malaria was significantly higher among patients with emergence of *P. falciparum* gametocytes compared with those without (72.2% versus 2.0%; $P < 0.001$). The cumulative appearance of cryptic *P. falciparum* malaria is shown in Figure 3 ($P < 0.001$). Detection of *P. falciparum* gametocytemia without asexual stages gave an 18.4-fold (95% confidence interval = 8.7–38.9) increased risk for the subsequent development of detectable asexual *P. falciparum* parasitemia ($P < 0.001$).

DISCUSSION

Malaria transmission depends on a feeding anopheline mosquito ingesting sexual stages of the parasite from one person and surviving long enough to transmit the sporozoite products of meiosis to another person.[5,6,14] *P. vivax* differs considerably from *P. falciparum* in the dynamics of this process. *P. vivax* is considerably more efficient. It generates sexual stages immediately in the blood stage infection, and therefore gametocytemia occurs early during the course of infection.[7–10] In this study, 22% of patients had gametocytemia on admission, which is similar to a previous report from Thailand (29%).[22] However, the post-treatment gametocyte carriage rates were much higher (41% compared with 11%), reflecting that this was a prospective study with frequent blood sampling and also that several relatively ineffective treatment regimens were evaluated. Because *P. vivax* gametocytemia was often transient, it is likely to be underestimated unless blood smears are taken frequently. Gametocyte densities were low and close to the limit of detection, which increases counting errors. This was partially offset by the large number of patients studied. The overall rates of gametocyte carriages in our study detected both before and after initiation of treatment was 63%. This is similar to reports from the Western border of Thailand (57%)[9] and Indonesia (65%).[2] In this detailed prospective series, there was an overall slight lag (median = 12 hours) between peak asexual and peak sexual stage parasitemia. In contrast, in *P. falciparum* infections, gametocytogenesis is often considerably delayed with respect to asexual parasite multiplication, and after the start of antimalarial treatment, peak densities of the sexual stages typically occur 1 week after peak asexual stage densities. In Thailand, admission gametocytemia rates in acute falciparum malaria are lower than in *P. vivax* malaria, with reported rates ranging from 2.5% to 15%.[9,13,23] *P. vivax* transmits effectively at

TABLE 3
Comparison between patients with and without patent *P. vivax* gametocytemia

	Patients with gametocytemia	Patients without gametocytemia	*P* values
No.	221	128	
Parasite count/μL (geometric mean; range)	10,381; 45–107,765	5,386; 41–77,370	0.003*
Previous malaria attack (numbers)	1 (1–10)	1 (1–12)	0.43
Duration of fever (days)	4 (1–20)	4 (1–21)	0.19
Hematocrit % (mean; SD)	35.3; 7.0	36.5; 6.6	0.12
Fever clearance time (hours)	35.0 (3–169)	27.0 (2–104)	0.001
PCT50 (hours)	14.5 (0–155)	11.0 (1–107)	0.010
PCT90 (hours)	39.0 (3–235)	23.0 (3–137)	< 0.001*
Parasite clearance time (hours)	99 (24–313)	67 (13–263)	< 0.001*
No. (%) of patients treated with antimalarial drugs	121/221 (54.8%)	85/128 (66.4%)	0.042
No of patient with *P. vivax* reappearance/FU patients	65/176 (36.9%)	18/92 (19.6%)	0.004

* Factors independently associated significantly with gametocytemia on admission.
FU = follow-up; PCT50 and PCT90 = times taken for the asexual parasite count to fall by 50%, and 90% of the admission values, respectively.

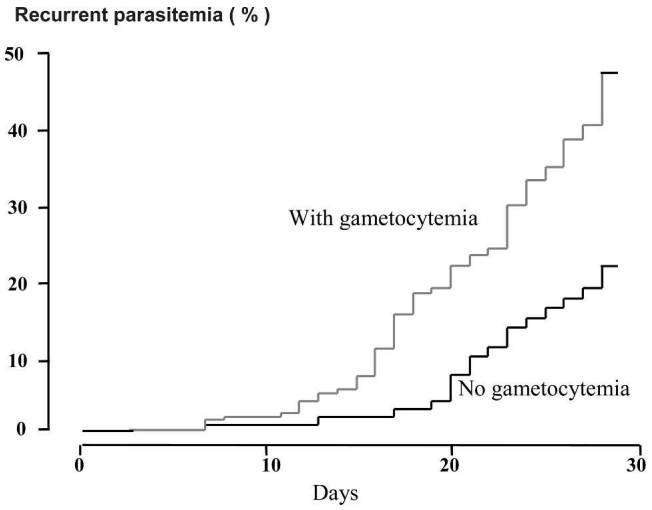

FIGURE 2. Recurrent parasitemia in patients with and without *P. vivax* gametocytemia.

blood gametocyte densities close to or below the limit of microscopic detection,[7,8,24] whereas *P. falciparum* transmission is relatively inefficient and is less likely below the level of microscopic detection (roughly 20/μL; transmission requires at least two gametocytes of the opposite sex in a 2–3-μL blood meal). It has been assumed that because asexual and sexual stage parasitemias are closely associated before treatment and because *P. vivax* gametocytes are relatively drug sensitive (in contrast to those of *P. falciparum*), events after drug treatment might be similar, but this has not been examined previously. Assessment of asexual stage activity of antimalarial drug is usually measured by PCT (time to clear parasitemia after initiation of treatment). Gametocytes are nonpathogenic stages, dependent on previous asexual stage development, so assessment of sexual stage activity can be measured by both gametocyte appearance rates and clearance rates.

Antimalarial drugs reduce malaria transmission by reducing asexual parasitemia, by killing sexual stages directly, and by interfering with parasite development in the mosquito.[6–8,14,15,25] Resistance is usually associated with reduced

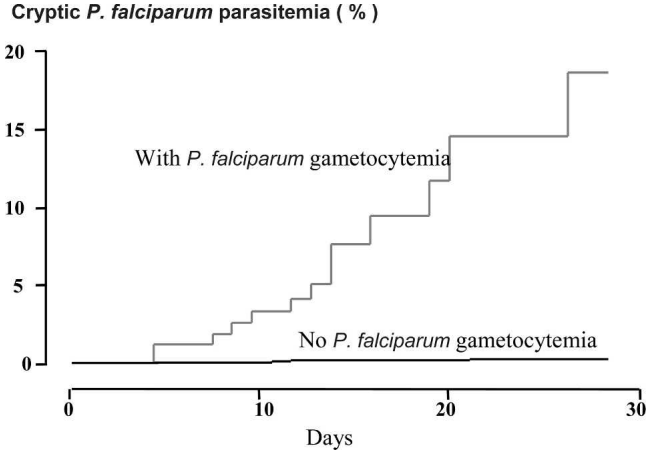

FIGURE 3. The development of cryptic *P. falciparum* malaria in patients with primary *P. vivax* malaria who did and did not have *P. falciparum* gametocytemia.

effects for all three. This large prospective study of different antimalarial compounds suggests that antimalarial effects on *P. vivax* gametocytes are similar to those on asexual stages and that marked differences in gametocyte carriage can be explained by differences in asexual stage activity. Thus, artemisinin derivatives do clear *P. vivax* gametocytemia rapidly, but this is associated with, and therefore presumably because of, their potent asexual stage activity. They do not have such a marked effect on overall gametocyte carriage in vivax malaria as in falciparum malaria because of the earlier appearance of gametocytemia and thus lower opportunity to prevent it. In contrast, sulfadoxine-pyrimethamine treatment and treatment with antibiotics gave slow or incomplete clinical and asexual stage responses[18,19] and concomitantly prolonged gametocyte carriage. In this area, *P. vivax* is highly resistant to sulfadoxine-pyrimethamine. Primaquine, which has a specific gametocytocidal effect against *P. falciparum*, but little asexual stage activity, did not have any specific effect against *P. vivax*. Its activity was explained adequately by asexual stage activity.[18,21] The possibility of synergistic asexual stage activity with chloroquine, analogous to that shown for liver stage activity,[26] was suggested by more rapid asexual and sexual stage activity with the combination, but further evidence on this is needed. These data suggest that treatment with artemisinin derivatives will limit *P. vivax* transmission by shortening gametocyte carriage but that the effect will be less than in *P. falciparum* malaria because more than one fifth of patients have gametocytemia before presentation, up to two thirds will have gametocytemia overall, and a further unknown proportion of patients will have sub-patent but transmissible densities. Gametocytemia is common in vivax malaria. Treatment with potent antimalarial drugs increases cure rates and reduces the transmission potential of *P. vivax*.

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