Relapses Contribute Significantly to the Risk of *Plasmodium vivax* Infection and Disease in Papua New Guinean Children 1–5 Years of Age

Inoni Betuela,[1,2,a] Anna Rosanas-Urgell,[1,2,a] Benson Kiniboro,[1] Danielle I. Stanisic,[1,4] Lornah Samol,[1] Elisa de Lazzari,[2] Hernando A. del Portillo,[2,3] Peter Siba,[1] Pedro L. Alonso,[2] Quique Bassat,[2] and Ivo Mueller[1,2,4]

[1]Papua New Guinea Institute of Medical Research, Madang, Papua New Guinea; [2]Barcelona Centre for International Health Research (CRESIB, Hospital Clínic-Universitat de Barcelona), and [3]Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain; and [4]Infection and Immunity Division, Walter and Eliza Hall Institute, Parkville, Victoria, Australia

Background. *Plasmodium vivax* forms long-lasting hypnozoites in the liver. How much they contribute to the burden of *P. vivax* malaria in children living in highly endemic areas is unknown.

Methods. In this study, 433 Papua New Guinean children aged 1–5 years were Randomized to receive artesunate (7 days) plus primaquine (14 days), artesunate alone or no treatment and followed up actively for recurrent *Plasmodium* infections and disease for 40 weeks.

Results. Treatment with artesunate-primaquine reduced the risk of *P. vivax* episodes by 28% ($P = .042$) and 33% ($P = .015$) compared with the artesunate and control arms, respectively. A significant reduction was observed only in the first 3 months of follow-up (artesunate-primaquine vs control, −58% [$P = .004$]; artesunate-primaquine vs artesunate, −49% [$P = .031$]) with little difference thereafter. Primaquine treatment also reduced the risk of quantitative real-time polymerase chain reaction– and light microscopy–positive *P. vivax* reinfections by 44% ($P < .001$) and 67% ($P < .001$), respectively. Whereas primaquine treatment did not change the risk of reinfection with *Plasmodium falciparum*, fewer *P. falciparum* clinical episodes were observed in the artesunate-primaquine arm.

Conclusions. Hypnozoites are an important source of *P. vivax* infection and contribute substantially to the high burden of *P. vivax* disease observed in young Papua New Guinean children. Even in highly endemic areas with a high risk of reinfection, antihypnozoite treatment should be given to all cases with parasitologically confirmed *P. vivax* infections.

In areas that are coendemic for *Plasmodium falciparum* and *Plasmodium vivax*, the burden of infections and disease caused by *P. vivax* peaks at an earlier age than that due to *P. falciparum* [1–6]. In Papua New Guinea (PNG), highly endemic for malaria caused by all 4 *Plasmodium* species that infect humans [7], *P. vivax* is the most common cause of malarial illness in infants [8] and toddlers [9], but its incidence decreases rapidly after that age and clinical disease is rare in children >5 years old [3], even though *P. vivax* infections remain common throughout childhood and into adulthood [10, 11]. The burden of *P. falciparum,* on the contrary, continues to rise through early childhood, with incidence of *P. falciparum* malaria peaking in children 3–7 years old [9, 12, 13] and *P. falciparum* infections remaining prevalent in school-aged children [10, 11].

In PNG, *P. vivax* and *P. falciparum* are transmitted by the same mosquito vectors and studies in different PNG lowlands population reported comparable sporozoite rates for *P. falciparum* and *P. vivax* in the local vector populations [3, 14, 15]. An important characteristic of *P. vivax* is related to its capacity to generate long-lasting liver stages (ie, hypnozoites) that after varying periods of dormancy [16] can cause relapsing malaria infection and clinical disease. As a consequence of this ability, a single mosquito inoculation may result in several blood-stage infections, during the

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[a]I. B. and A. R. U. contributed equally to this study.

Correspondence: Ivo Mueller, PhD, Vector Borne Disease Unit, PNG Institute of Medical Research, PO Box 60, Goroka, EHP 441, Papua New Guinea (ivomueller@fastmail.fm).

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following months or even years. Although such relapsing infections are an important source of illness in nonimmune travelers [17], it is unclear how much they contribute to the burden of *P. vivax* malaria in perennially exposed children living in (highly) endemic countries.

Currently primaquine is the only licensed radical treatment for hypnozoites [18, 19]. Because of the concern that primaquine can cause potentially life-threatening hemolysis in Glucose-6-phosphate dehydrogenase (G6PD)-deficient individuals [20], the lack of reliable parasitological diagnosis at most PNG health facilities, and the prevailing perception that given the high transmission level treating hypnozoites may be of little benefit, meant that primaquine treatment was not formally adopted as part of the PNG treatment guidelines until 2010. As a consequence, up to 87% of children with *P. vivax* malaria experience a recurrent *P. vivax* infection within 6 weeks of treatment [21] with approximately 25% of these infections associated with clinical symptoms. It has been suggested that relapses are responsible for the vast majority of these recurrent infections [22] and that in addition to being the predominant cause of blood-stage infections, they may contribute significantly to *P. vivax* clinical malaria and transmission [16].

The development of high-throughput genotyping methods [23, 24] has greatly increased our ability to study the longitudinal dynamics of *P. falciparum* infections [25, 26] and differentiate new from ongoing or recrudescent infections [27, 28]. Although similar methods now exist for *P. vivax* [29], genotyping cannot differentiate relapses from new infections [30], because relapses are usually genetically distinct from the primary infection [31, 32]. It is therefore not possible to directly quantify the contribution of relapses to the burden of *P. vivax* reinfection and disease by genotyping individual infections in longitudinal studies of participants living in areas of high transmission and thus high reinfection risk. Such a direct estimation is possible only with use of an imaginative study design, wherein relapses are deliberately prevented in a portion of study subjects. Therefore, to assess the contribution of hypnozoites to the burden of *P. vivax* reinfection and disease, we conducted a longitudinal cohort study in children aged 1–5 years old in a hyperendemic area of PNG, where we selectively treated preexisting hypnozoites in a subset of the children.

MATERIALS AND METHODS

Study Description

This study was conducted in 11 villages in the Ilaita area of Maprik District, East Sepik Province, a highly endemic area where all 4 human malaria species coexist, with *P. falciparum* the most common parasite in all age groups except among children ≤4 years, in whom *P. vivax* predominates [9, 11]. Malaria transmission is moderately seasonal, with transmission peaking in the early wet season (ie, December through March) [25]. The study area is serviced by a single health subcenter and an aid post. A more detailed description of the study areas is given elsewhere [9].

All children aged 1–5 years living in study villages, whose parents consented to their participation, were tested for G6PD deficiency (OSSMR-D G6PD Assay; R&D Diagnostics). All G6PD-normal children were subsequently randomized to 1 of the 3 groups: (1) artesunate (4 mg/kg/d for 7 days) plus primaquine (0.5 mg/kg/d for 14 days), (2) artesunate alone (4 mg/kg/d for 7 days), or (3) no treatment (control). Owing to a concurrently ongoing mass-distribution of long-lasting insecticide-treated nets (LLINs), which resulted in nearly universal LLINs coverage, treatment of the cohort was delayed until after the LLIN campaign finished in early April 2008.

Immediately before treatment administration, children were assessed for symptoms of febrile illness, a detailed history of bed net use and recent antimalarial treatment was obtained, and a venous blood sample was collected for immunological and molecular studies. Children in control and artesunate arms found to be parasitemic were treated with arthemeter-lumefantrine (Coartem; Novartis). All treatment doses for the cohorts were administered as direct observed therapy and monitored for side effects.

After completion of treatment children were followed up for the presence of febrile illness actively every 2 weeks and passively throughout the study at the local health center and aid post for the duration of the follow-up (40 weeks). Finger-prick blood samples were collected every 2 weeks for the first 12 weeks and every 4 weeks thereafter from all children seen during active follow-up (active detection of infection, see Supplementary Figure 1). Malaria infection was investigated in all symptomatic children using a rapid diagnostic test (RDT) for malaria (ICT Diagnostics) and 250-μL finger-prick blood samples were collected for confirmation of infection by light microscopy (LM), and quantitative real-time polymerase chain reaction (qPCR). Only RDT-positive and LM-confirmed, RDT-negative symptomatic children were treated with arthemeter-lumefantrine . All other illness episodes detected were referred to local health center and treated in accordance with PNG treatment guidelines.

The study received ethical clearance by the PNG Institute of Medical Research Institutional Review Board (IRB 07.20) and the PNG Medical Advisory Committee (07.34).

Laboratory Methods

All blood films were read independently by 2 expert microscopists. Slides with discrepant results were reread by a third microscopist. Thick blood films were examined for 100 thick-film fields (under ×100 oil immersion lens) before being declared negative for infection. Parasite densities were recorded

as the number of parasites per 200 white blood cells and converted to parasites per microliter of blood, assuming counts of 8000 white blood cells/μL [33]. Slides were scored as LM positive for an individual *Plasmodium* species if the species was detected independently by ≥2 microscopists and/or if subsequent qPCR diagnosis confirmed the presence of the species. Densities were calculated as the geometric mean densities of all positive readings.

Plasma and peripheral blood mononuclear cells were collected from all venous blood samples. The remaining red blood cells were pelleted and aliquoted. Finger-prick blood samples were separated into plasma and cell pellets. DNA was extracted from the cell pellet fraction of all samples using the QIAamp 96 DNA Blood kit (Qiagen), and *Plasmodium* sp. infections were detected using a 4-species qPCR assay [34]

Statistical Analyses

For analysis purposes, clinical malaria was defined as fever (axillary temperature ≥37.5°C) or history of febrile illness within the last 48 hours in the presence of a concurrent *Plasmodium* sp. infection of any density or *P. falciparum* >2500/μL and *P. vivax* >500/μL [35]. The associations between the incidence of clinical malaria and treatment as well as other covariates were assessed by negative binomial regressions. Children were considered at risk from the first day after the last primaquine or artesunate dose until they withdrew, were lost to follow-up, or completed the study. Children were not considered at risk for 14 days after each recurring or new episode. The time to the first *P. vivax* episode or infection and its association with treatment and covariates were modeled using Cox regression and the proportional-hazards assumption was checked using the test based on the Schoenfeld residuals. The log-rank test was used to test differences between survival curves. In all survival analyses, children were considered at risk until they reached the end point of interest, withdrew, were lost to follow-up or completed the study. Differences between treatment groups at baseline were investigated using χ^2 and Fischer's exact tests for categorical characteristics and the Kruskal–Wallis test for continuous variables. Tests were 2 tailed, and the confidence level was set at 95%. All analyses were performed using Stata 12 software (StataCorp 2011, release 12; StataCorp).

RESULTS

Of 463 children screened, 449 (97.0%) G6PD-normal children were randomized to artesunate (7 days), artesunate plus primaquine (14 days), or no treatment (Figure 1). Sixteen children were withdrawn from the study or migrated out of the study area between randomization (late January) and the start of the study (mid-April). Therefore, a total of 433 children 1.1–5.6 years old were treated and followed up actively and passively for 40 weeks.

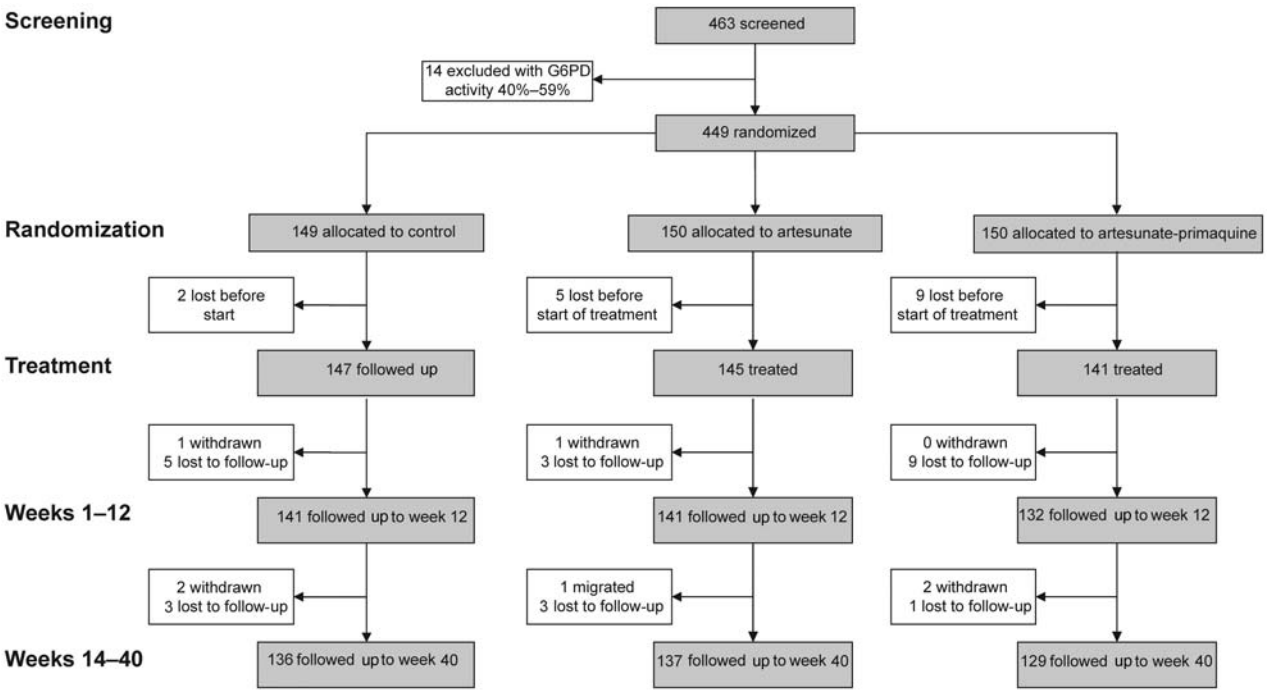

Figure 1. CONSORT study design, randomization, and retention of study participants during follow-up.

Table 1. Demographic and other Key Characteristics of Treatment Groups Before Start of Treatment

Characteristic	Artesunate		Artesunate-Primaquine		Control		*P*
Male patients, No.	75	52	68	49	75	51	.79
Age, mean (SD), y	3.1	(1.1)	3.2	(1.2)	3.3	(1.2)	.57
Village of residence, No. (%)							.64
Ilaita 1	5	3	5	4	8	5	
Ilaita 2–4	27	19	29	21	27	18	
Ilaita 5	8	6	3	2	5	3	
Ilaita 6	5	3	6	4	6	4	
Ilaita 7	5	3	8	6	13	9	
Ingamblis	31	21	26	19	19	13	
Kamanokor	14	10	21	15	17	12	
Sunuhu	38	26	28	20	37	25	
Utamup	12	8	14	10	14	10	
Currently ill, No. (%)	17	12	31	22	27	19	.059
Slept under net, No. (%)	133	94	120	86	130	90	.053

Abbreviation: SD, standard deviation.

No significant differences in demographic characteristics and infection status were observed at baseline (ie, before the start of treatment) between treatment groups, nor was there any difference in the distribution of children in each group among study villages (Table 1). There was a tendency for a higher LLIN use in the artesunate group than in the artesunate-primaquine and control groups ($P = .053$) at baseline. Reported rates of LLIN use during follow-up were comparable ($P = .74$).

During follow-up, 92% (range 74%–98%; interquartile range [IQR], 92%–95%) of children were seen at active detection of infection time points (Figure 1). There was no difference in the average number of study contact between treatment arms (likelihood-ratio (LR), 0.21; $df = 2$; $P = .90$).

During 40 weeks of follow-up, a total of 271 febrile episodes with *P. vivax* of any density (incidence rate [IR], 0.89) and 115 episodes with *P. vivax* >500/μL (Incidence rate (IR), 0.37) were detected; 132 children (30%) had 1 *P. vivax* malaria episode (any density), and 60 (14%) had ≥2 episodes (maximum, 4). The incidence of *P. vivax* malaria decreased strongly with age (Incidence rate ratio (IRR) for *P. vivax* episodes of any density, 0.81 [95% confidence interval (CI), .73–.91; $P < .001$]; IRR for *P. vivax* >500/μL, 0.60 [95% CI, .50–.72; $P < .001$]) and varied between villages (LR for episodes of any density, 16.0; $df = 8$; $P = .042$).

The incidence of *P. vivax* malaria of any density differed significantly between the 3 treatment arms (Table 2). Treatment with artesunate-primaquine reduced the risk of *P. vivax* episodes of any density during 40 weeks of follow-up by 28% (95% CI, 1%–52%; $P = .042$) compared with the artesunate arm and by 33% (95% CI, 8%–52%; $P = .015$) compared with the control arm. The differences were almost entirely due to a strong reduction in incidence in the first 3 months of follow-up (Figure 2) (IRR for artesunate-primaquine vs control, 0.42 [95% CI, .23–.76; $P = .004$]; IRR for artesunate-primaquine vs artesunate, 0.51 [95% CI, .27–.94; $P = .031$]), with little or no difference during the rest of the follow-up (Table 2). In multivariate analyses, only treatment and age were significant predictors of risk of malaria, and adjustment for age did not alter the observed differences between treatment arms (Supplementary Table 1). Similar differences were observed for the time to first or only *P. vivax* episode (Table 2; Figure 2). Interestingly, neither treatment resulted in a significant reduction in the incidence of *P. vivax* malaria episodes with a density >500/μL (Table 2).

In children in the artesunate-primaquine and artesunate arms who successfully cleared preexisting blood-stage infections, differences in the time to first *P. vivax* infection were investigated (Table 3; Figure 2). When diagnosed with qPCR, new *P. vivax* blood-stage infections were detected very rapidly, with 50% of children in artesunate and artesunate-primaquine groups infected by day 23 (IQR, 14–30 days) and day 30 (IQR, 15–56 days), respectively. It took significantly longer until infection became patent by LM, with the difference between treatment arms becoming even more pronounced (median, 29 days for artesunate [IQR, 16–55 days] vs 78 days for artesunate-primaquine [IQR, 42–280]). Overall, the elimination of liver stages through primaquine treatment was found to reduce the risk of qPCR- and LM-positive recurrent blood-stage parasitemia by 44% (95% CI, 28%–57%; $P < .001$) and 67% (95% CI, 55%– 75%; $P < .001$), respectively. The risk of *P. vivax* parasitemia did not vary with age (LR for qPCR, 1.93 [$df = 1$; $P = .16$]; LR for LM, 0.53 [$df = 1$; $P = .47$]) but differed significantly among children living in different villages

Table 2. Incidence of *Plasmodium vivax* and *Plasmodium falciparum* Malaria in Treatment Groups

	Placebo			Artesunate				Artesunate-Primaquine				
	Events	PYR	Incidence	Events	PYAR	Incidence	IRR (95% CI)	Events	PYAR	Incidence	IRR (95% CI)	*P*
P. vivax malaria												
Any density												
9-mo follow-up	105	102.2	1.03	99	103.9	0.93	0.91 (0.69– 1.24)	67	97.8	0.69	0.67 (.48–.92)	.037
0–3 mo	37	33.3	1.11	31	33.9	0.91	0.82 (.51–1.31)	15	32.3	0.46	0.42 (.23–.76)	.009
>3 to 9 mo	68	68.9	0.99	68	70.0	0.97	0.98 (.70–1.39)	52	65.4	0.76	0.81 (.56–1.16)	.446
P. vivax >500/μL												
9-mo follow-up	42	104.6	0.40	42	106.1	0.40	0.98 (.62–1.57)	31	99.1	0.31	0.78 (.47–1.28)	.549
P. falciparum malaria												
Any density												
9-mo follow-up	69	103.6	0.67	55	105.4	0.52	0.79 (.52–1.18)	34	98.9	0.34	0.51 (.32–.81)	.015
0–3 mo	11	34.4	0.32	8	34.9	0.23	0.71 (.28–1.83)	2	32.9	0.06	0.19 (.04–.87)	.041
>3 to 9 mo	58	69.2	0.84	47	70.6	0.67	0.80 (.51–1.25)	32	66.0	0.48	0.57 (.35–.94)	.083
P. falciparum >2500/μL												
9-mo follow-up	42	104.6	0.40	32	106.3	0.30	0.75 (.47–1.20)	21	99.5	0.21	0.53 (.31–.89)	.053
First or only malaria episode												
P. vivax, any density	73	73.3	1.00	74	78.1	0.95	0.95 (.69–1.31)	45	82.2	0.55	0.55 (.38–.80)	<.001
P. vivax >500/μL	34	91.8	0.37	35	92.3	0.38	1.04 (.59–1.83)	25	90.3	0.28	0.70 (.38–1.29)	.379
P. falciparum, any density	50	88.0	0.57	39	92.7	0.42	0.74 (.49–1.13)	30	90.6	0.33	0.58 (.37–.92)	.017
P. falciparum >2500/μL	35	94.4	0.37	29	96.4	0.30	0.81 (.50–1.33)	19	94.8	0.20	0.54 (.31–.95)	.085

Abbreviations: IRR, ; PYAR, ; PYR.

(LR for qPCR, 19.1 [$df = 8$; $P = .008$]; LR for LM, 49.4 [$df = 8$; $P < .001$]). Adjustment for village differences did not significantly change the treatment effects.

The treatment had no significant effect on the likelihood of being reinfected with *P. falciparum,* as detected with either qPCR (Table 3) ($P = .85$) or LM ($P = .40$). During follow-up, only 158 children experienced febrile episodes with any concurrent *P. falciparum* parasitemia (IR, 0.51), and 95 with *P. falciparum* >2500/μL (IR, 0.30). Thirty children had >1 *P. falciparum* episode (any density). Children in the artesunate-primaquine arm were significantly less likely to become ill with *P. falciparum* malaria than those in the control arm (Table 2) (IRR for all *P. falciparum,* 0.51 [95 CI , .32–.81; $P = .004$]; IRR for *P. falciparum* >2500/μL, 0.53 [95% CI, .31–.89; $P = .018$]), but not those in the artesunate arm (all *P. falciparum,* $P = .61$; *P. falciparum* >2500/μL, $P = .22$). The incidence of *P. falciparum* malaria of any density varied significantly among villages ($P < .001$) but showed no association with age ($P = .86$), whereas *P. falciparum* >2500/μL showed a nonlinear association with age ($P = .005$) but did not vary among villages. Adjustment for village of residence or age did not significantly change the associations of treatment with incidence of *P. falciparum* malaria (data not shown).

DISCUSSION

By selectively removing liver stages from some but not all children, we demonstrated that relapses cause approximately 50% of infection and more than 60% of clinical episodes in the first 3 months of follow-up, with little effect thereafter. The Chesson strain of *P. vivax* [36] that is present in the Southwest Pacific is known to have a short relapse frequency

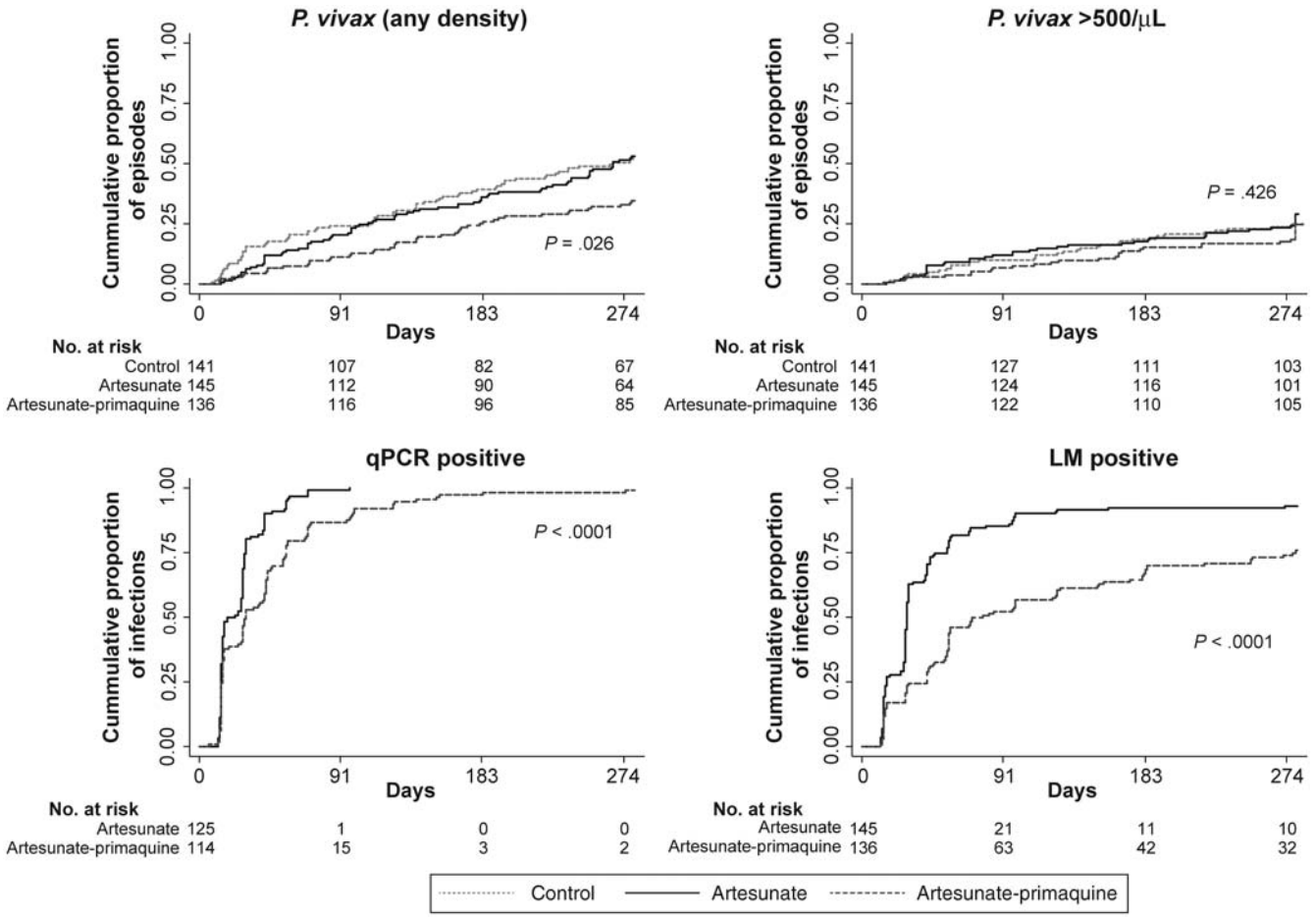

Figure 2. Time to first *Plasmodium vivax* clinical episode (any density) and reinfection as demonstrated by quantitative real-time polymerase chain reaction (qPCR) and light microscopy (LM). Differences between groups were tested by log-rank tests.

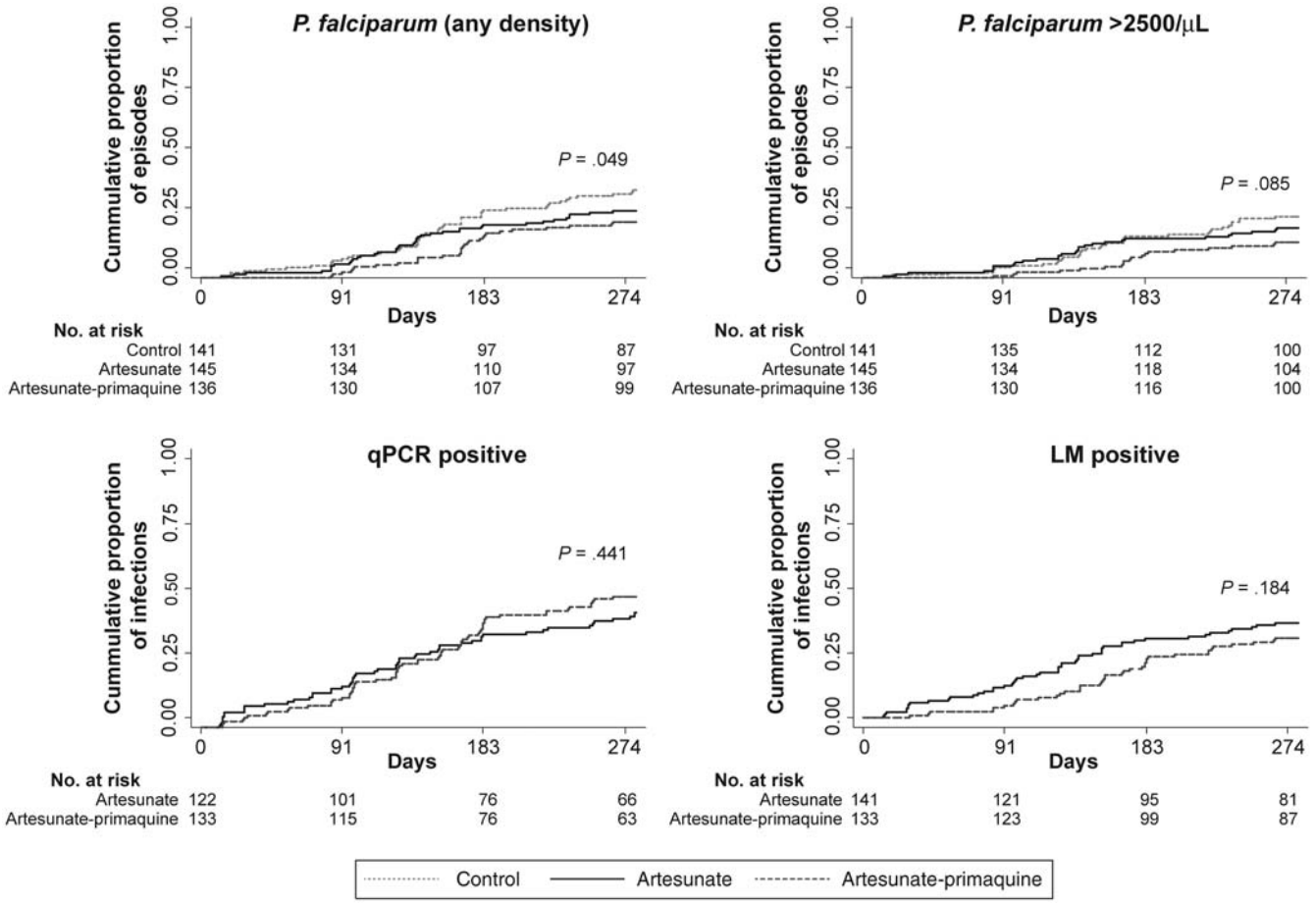

Figure 3. Time-to-first *Plasmodium falciparum* clinical episode (any density) and reinfection as demonstrated by quantitative real-time polymerase chain reaction (qPCR) and light microscopy (LM). Differences between groups were tested by log-rank tests.

Table 3. Incidence of New *Plasmodium vivax* and *Plasmodium falciparum* Infections in Artesunate and Artesunate-Primaquine Treatment Groups

	Artesunate				Artesunate-Primaquine					
	No.	PYR	ST, Median, d	Incidence	No.	PYAR	ST, Median, d	Incidence	HR	*P*
Incidence of first or only *P. vivax* (re)infection										
LM	145	21.7	30	6.14	139	45.9	79	2.18	0.43 (0.33–0.56)	<.001
PCR	125	8.5	17	14.62	117	12.2	28	9.16	0.66 (0.50–0.86)	.002
Incidence of first or only *P. falciparum* (re)infection										
LM	141	83.5	…	0.61	136	85.0	…	0.45	0.73 (0.48–1.12)	.147
PCR	122	64.3	…	0.85	135	70.6	253	0.92	1.06 (0.74–1.52)	.750

Abbreviations: d, days; HR, Hazard ratio; LM, light microscopy; PYAR, Person-year-at-risk; PYR, Person-year-at-risk; qPCR, quantitative real-time polymerase chain reaction; ST, median: median survival time.

(approximately 1 month [16, 37]). Consequently, in the artesunate-only arm, 71% and 85% of children had recurrent LM-detectable *P. vivax* infection by 6 and 12 weeks respectively. This finding resembles previous reports of the rate of recurrent *P. vivax* parasitemia after arthemeter-lumefantrine treatment [21], suggesting that most children in the cohort were likely to have had hypnozites in their livers at the time of treatment. This fast relapse pattern of residual hypnozoites in the artesunate and control arms plus the acquisition of new infections (and consequent establishment, or reestablishment, of new cohorts of hypnozoites) could explain the limited effect of primaquine beyond 3 months.

Interestingly, primaquine reduced the incidence of only low-density but not high-density clinical infection. Although past genotyping studies showed that relapses are often genetically different from primary infections [31, 32] (but see [38]), in PNG where the mean multiplicity of *P. vivax* infection is approximately 3 [39], sexual recombination in the mosquito is likely to be common, and therefore different blood-stage infections that originate from a single infected mosquito bite are genetically often related. Partial immunity acquired against a related primary infection may therefore allow children to better control blood-stage parasite densities, as in observations of sequential, homologous infections among patients receiving malaria therapy [40], resulting in mild and probably mostly self-limiting clinical episodes (in patients receiving malaria therapy, reinfection with homologous strains resulted only in a few transient symptoms). Therefore, outside a research setting, many of these episodes might not lead to treatment seeking and might not be treated.

Although we showed directly for the first time the substantial contribution of relapses to the burden of *P. vivax* infection and disease, the estimated burden caused by relapses is subject to several potential uncertainties. First, local PNG *P. vivax* strains are relatively resistant to primaquine and thus require higher doses of primaquine to prevent relapses [18, 41]. Although the recommended daily primaquine dose was used [19], concurrent treatment with active schizonticide drugs, such as chloroquine or quinine [18], is required to be effective against Chesson strain parasites. Even then, 14-day high-dose primaquine has an efficacy of only approximately 80% against New Guinea vivax strains [41]. Although artesunate is a highly effective schizonticide, the efficacy of the artesunate-primaquine combination is unknown. As indicated by the much faster recurrence of *P. vivax* compared with *P. falciparum* blood-stage infections in the primaquine arm, it is therefore possible that the chosen treatment did not eliminate all hypnozoites and that the burden of hypnozoite-derived infections is underestimated.

Population-wide distribution of LLINs took place immediately before the study. Compared with a study conducted 2 years earlier [9], we observed an approximately 50% lower incidence of clinical malaria. The hypnozoites present at the time of the treatment would therefore have been acquired mostly under the higher transmission present before LLINS distribution. Similarly, the delayed LLINS distribution meant that the study was started toward the end of the high–transmission season and continued through the low-transmission season [9,25]. Both factors could have resulted in overestimating the contribution of relapses.

As expected, treatment with primaquine had no effect on the risk of acquiring new *P. falciparum* infections. However, significantly fewer of the *P. falciparum* infections in the artesunate-primaquine group were associated with clinical illness. Unfortunately, the low number of *P. falciparum* episodes and thus limited statistical power precluded a more in-depth investigation of this intriguing observation. Confirmation in a larger study will be required.

The demonstrated large contribution of relapses to the burden of *P. vivax* infections and (mild) disease not only leads to a better understanding of *P. vivax* epidemiology but also has important implications for clinical practice and formulation of treatment guidelines. The high rate of relapses is almost certainly the principal reason for the higher prevalence,

multiplicity, and incidence of *P. vivax* infection and disease in early childhood [8, 9, 39], contributing substantially to the much faster acquisition of immunity to *P. vivax* compared with *P. falciparum* [3]. Furthermore, relapses may significantly contribute to transmission, because *P. vivax* gametocytemia closely follows asexual parasitemia. It will therefore be difficult to achieve a sustained reduction in *P. vivax* transmission, leading to local elimination, without targeting the hypnozoite reservoir [42, 43]. Although relapses seem to be predominantly associated with mild disease, without appropriate antirelapse therapy, children will be exposed to chronic blood-stage infections (or reinfections) with *P. vivax* that can lead to severe anemia in their cumulative effect [44, 45].

These findings have important public health relevance: even in areas with intense transmission and thus high risk of reinfection, strong efforts should be made to eradicate *P. vivax* hypnozoites in all cases of parasitologically confirmed *P. vivax* infection. The only currently available drug that effectively attacks the dormant hepatic reservoir is primaquine. Although the effect of primaquine against hypnozoites has been known for >50 years [18] and radical cure with primaquine is part of World Health Organization and many national treatment guidelines [19], concerns about its safety in persons with (severe) G6PD deficiency have hampered its programmatic implementation. The recent development of RDTs that specifically detect *P. vivax* will facilitate the recognition and diagnosis of this species. Poor adherence to the current 14-day primaquine schedule, the lack of therapeutic alternatives, and the lack of reliable, point-of-care (rapid) tests for G6PD deficiency remain major obstacles, which urgently need to be addressed if the recent reductions in global *P. vivax* burden are to be sustained and local elimination achieved [43, 46].

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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