MAJOR ARTICLE

Vivax Malaria: A Major Cause of Morbidity in Early Infancy

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Background. In areas where malaria is endemic, infants aged <3 months appear to be relatively protected from symptomatic and severe *Plasmodium falciparum* malaria, but less is known about the effect of *Plasmodium vivax* infection in this age group.

Methods. To define malaria morbidity in the first year of life in an area where both multidrug-resistant *P. falciparum* and *P. vivax* are highly prevalent, data were gathered on all infants attending a referral hospital in Papua, Indonesia, using systematic data forms and hospital computerized records. Additional clinical and laboratory data were prospectively collected from inpatients aged <3 months.

Results. From April 2004 through April 2008, 4976 infants were admitted to the hospital, of whom 1560 (31%) had malaria, with infection equally attributable to *P. falciparum* and *P. vivax*. The case-fatality rate was similar for inpatients with *P. falciparum* malaria (13 [2.2%] of 599 inpatients died) and *P. vivax* malaria (6 [1.0%] of 603 died; $P = .161$), whereas severe malarial anemia was more prevalent among those with *P. vivax* malaria (193 [32%] of 605 vs. 144 [24%] of 601; $P = .025$). Of the 187 infants aged <3 months, 102 (56%) had *P. vivax* malaria, and 55 (30%) had *P. falciparum* malaria. In these young infants, infection with *P. vivax* was associated with a greater risk of severe anemia (odds ratio, 2.4; 95% confidence interval, 1.03–5.91; $P = .041$) and severe thrombocytopenia (odds ratio, 3.3; 95% confidence interval, 1.07–10.6; $P = .036$) compared with those who have *P. falciparum* infection.

Conclusions. *P. vivax* malaria is a major cause of morbidity in early infancy. Preventive strategies, early diagnosis, and prompt treatment should be initiated in the perinatal period.

In sub-Saharan Africa, infants younger than 3–4 months of age who are infected with *Plasmodium falciparum* are less susceptible to clinical symptoms and severe disease, compared with older infected children [1, 2]. This protection has been argued to be due to innate mechanisms in infants rather than transfer of maternal antibody [3–5]. However, symptomatic malaria is not uncommon in young infants [6–8], and severe disease is frequently reported [6, 9].

The contribution of *Plasmodium vivax* to malaria in young infants is less well characterized [10, 11]. In areas where *P. falciparum* and *P. vivax* are prevalent, infants and young children are at greater risk of acquiring *P. vivax* infection than *P. falciparum* infection [12–15]; however, the contribution to morbidity in the first 3 months of life has been less well defined. In Timika, southern Papua, Indonesia, where multidrug-resistant *P. falciparum* and *P. vivax* are both prevalent, we define the epidemiology of symptomatic illness associated with *P. falciparum* and *P. vivax* infection in infancy, with a focus on the first 3 months of life.

METHODS

Study site. The study was conducted in southern Papua, Indonesia [16]. Malaria in this forested area has an annual incidence of 876 cases per 1000 person-years, with a 57:43 ratio for *P. falciparum* versus *P. vivax* infection. Transmission is restricted to the lowland

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areas. The Rumah Sakit Mitra Masyarakat Hospital in Timika is the only hospital in this district, servicing an area of 21,522 km^2 with a population of ~200,000 people. High levels of antimalarial drug resistance are present for both species, with the risk of failure within 28 days reaching 65% after chloroquine monotherapy for *P. vivax* malaria and 48% after chloroquine plus sulfadoxine and pyrimethamine for *P. falciparum* malaria; high-grade resistance of *P. vivax* occurred in 16% of patients [17].

Study population. The infant mortality rate in southern Papua is estimated to be 68 deaths per 1000 live births [18]. During the period 2004–2008, infants accounted for 7.4% of all hospital outpatient consultations, with malaria diagnosed in 14.4% of cases (P.S.; unpublished data). Because of economic migration, the ethnic origin of the local population is diverse, with highland Papuans, lowland Papuans, and non-Papuans all resident in the region. Hospital policy dictates that all patients presenting with a febrile illness should have blood film examination for malaria. Distribution of insecticide-treated nets specifically targeted to pregnant women and those aged <5 years started in 2007; however, there is no program for intermittent presumptive treatment for infants.

Data collection. Data were collected from all infants admitted to the wards of Rumah Sakit Mitra Masyarakat Hospital from 1 April 2004 through 30 April 2008. Demographic details and diagnosis were recorded for all inpatients using a computerized hospital records system (Q-Pro; PT Q-Pro Sukses Mandiri). In addition, patients who received a diagnosis of malaria were reviewed by a medically trained member of an onsite research team, and additional details about their hospitalizations were recorded on a standardized data form, as reported previously [19]. Standard care was provided according to hospital guidelines by the attending physician.

Substudy of young infants (0–3 months). The guardians of any infant aged <3 months admitted with *Plasmodium* parasitemia were invited to have their child enrolled in an additional study of young infants in which a research nurse completed a more detailed questionnaire documenting the history of illness in the infant. All young infants were examined by either the attending physician or a research clinician, and their clinical findings were documented. The presence of splenomegaly or hepatomegaly was determined by abdominal examination. Fever was defined as an axillary temperature >37.5°C, and respiratory insufficiency was defined on the basis of age-stratified criteria, as described elsewhere [19, 20]. Low weight for age was defined as 2 SDs below the median value of the reference (healthy) population and was further classified as severe if it was 3 SDs below [21].

Malaria was diagnosed at the hospital laboratory by microscopy of Giemsa-stained blood films and parasite density recorded as 1+ to 4+. Slides were considered to be negative for malaria after review of 100 high-power fields. Infants enrolled in the more detailed survey had an additional blood film taken, which was read by an expert microscopist; parasite counts were determined from the number of parasites per 200 white blood cells on Giemsa-stained thick films. Peripheral parasitemia was calculated from the recorded white blood cell count. Slides were considered to be negative for malaria after review of 200 high-power fields. A thin smear was also examined to confirm parasite species and used for quantification if the parasite count was >200 per 200 white blood cells. The hospital laboratory participates in ongoing training and quality control, with >90% of slide recordings confirmed on cross-checking by an independent expert microscopist [19].

Venous blood samples (1–5 mL) were obtained from infants with malaria admitted to the pediatric wards for measurement of complete blood cell counts and hemoglobin concentration (using an electronic counter [Coulter JT]).

Malaria was defined as a symptomatic illness associated with any peripheral parasitemia. The diagnosis of severe disease was made in accordance with the World Health Organization criteria for severe *P. falciparum* malaria [19, 20]. Other comorbidities (e.g., diarrhea, sepsis, pneumonia, and meningitis) were diagnosed on the basis of clinical, laboratory, and radiologic findings.

All infants with peripheral parasitemia received standard antimalarial therapy and supportive care, in accordance with hospital protocol. Before March 2006, the local protocol for newborn infants recommended 7 days of quinine for both *P. falciparum* and *P. vivax* infection. After March 2006, infants who weighed >5 kg were treated with dihydroartemisinin-piperaquine for uncomplicated malaria.

Statistical analysis. Data from the questionnaire and the laboratory were entered into an EpiData database, version 3.02 (EpiData Association). Data were analyzed using SPSS, version 15.0 for Windows software (SPSS). Infants with healthy deliveries and those with malaria diagnosed from active screening were excluded from the analysis. Normally distributed data were compared by Student's *t* test. Data that did not conform to a normal distribution were compared by the Mann-Whitney *U* test. Categorical data were compared by calculating the χ^2 with Yates' correction or by Fisher's exact test and the odds ratio (OR) with 95% confidence intervals (CIs).

Ethics approval. Ethics approval for this study was obtained from the ethics committees of the National Institute of Health Research and Development, Ministry of Health of Indonesia, and Menzies School of Health Research, Darwin, Australia.

RESULTS

Inpatient malaria in first year of life. During the period from April 2004 through April 2008, 4976 (12.4%) of 40,035 patients

admitted to the hospital were infants, and 1560 (10.0%) of 15,582 patients admitted to the hospital had malaria. In total, 1560 (31.4%) of 4976 infants admitted to hospital had malaria, with infection attributable to *P. falciparum* in 662 infants (42.4%), *P. vivax* in 668 infants (42.8%), and mixed species in 222 infants (14.2%). Eight infants were infected with *Plasmodium malariae.* Patients of Papuan origin were more likely to have malaria than non-Papuans (OR, 3.1; 95% CI, 2.5–3.9; $P < .001$), and this was apparent for all species of infection. Although there was an overall predominance of all-cause admissions for male infants throughout infancy (54.6%; 95% CI, 53.3%–56.0%), female infants were at greater risk of *P. vivax* infection (OR, 1.25; 95% CI, 1.06–1.48; $P = .009$) but not for any other species of infection. Infants admitted to the hospital at <1 month had a 9.0% (87 of 967) prevalence of malaria, which increased throughout the first year of life to 54% (792 of 1476) in the last quarter. *P. vivax* was the predominant species from birth to 8 months of age (figure 1 and table 1).

Additional clinical details were available in 1424 (91.2%) of the 1560 infants with malaria, with severe disease (defined as severe anemia, coma, or respiratory distress) present in 547 (38.4%) of 1424. The overall risk of severe malaria decreased with age ($P < .001$), with the risk of respiratory distress significantly greater in infants <3 months, compared with older infants (OR, 9.2; 95% CI, 4.5–7.5; $P < .001$) (table 1). The mean hemoglobin concentration in infants who were admitted to the hospital with malaria was 6.7 g/dL (95% CI, 6.6–6.9 g/dL), compared with 9.7 g/dL (95% CI, 9.6–9.9 g/dL) for 1389 infants who were admitted to the hospital without malaria during the same period ($P < .001$). The corresponding rates of severe anemia were 30% (420 of 1424 infants) and 3.9% (54 of 1389 infants; OR, 13.7; 95% CI, 10.1–18.6; $P < .001$). Infants with pure *P. vivax* infection were at greater risk of severe anemia (193 [31.9%] of 6605) than were those with *P. falciparum* malaria (144 [24%] of 601; OR, 1.3; 95% CI, 1.04–1.7; $P = .025$), and this risk remained after controlling for age (adjusted OR, 1.5; 95% CI, 1.16–1.95; $P = .002$). The risk of severe anemia in infants was (81 [38.6%] of 210) with mixed infections, significantly greater than that with pure *P. falciparum* infection ($P < .001$) but not *P. vivax* infection ($P = .093$).

During the study period, 173 deaths among infants aged >1 week were reported at the hospital, of which 23 (13.9%) were associated with malaria. The risk of death was significantly greater for infants without malaria (150 [4.4%] of 3416) than for those with malaria (23 [1.6%] of 1474; OR, 2.9; 95% CI, 1.8–4.6; $P < .001$). The overall infant mortality rate associated with *P. falciparum* malaria was 2.2% (13 of 599 infants), which is similar to the rate for *P. vivax* malaria (6 [1.0%] of 603) and mixed-species malaria (4 [1.9%] of 210; $P = .258$).

Substudy of malaria in young infants (0–3 months old). Of the 234 infants 3 months or younger who were admitted to the hospital with malaria, 187 (76%) were enrolled in the additional study with more detailed data collection (figure 2). No significant difference was found in the age and sex distribution of infants enrolled compared with those not enrolled in the nested study. Microscopic reexamination of the admission blood film revealed concordance between first and second readings of 88% (134/152), with 6 patients (3.2%) found to be blood smear negative. Of the 181 young infants with confirmed malaria, *P. falciparum* was present in 55 (30%), *P. vivax* in 102 (56%), mixed infections in 22 (12%), and *P. malariae* in 2 (1%).

Most infants were treated with intravenous quinine alone (93 [51%] of 181 patients), with the remaining receiving intravenous artesunate followed by oral dihydroartemisinin-piperaquine (46 [25%]), oral dihydroartemisinin-piperaquine alone (7 [4%]), oral artesunate (18 [10%]), and oral artesunate-amodiaquine (13 [7%]). Antimalarial treatment was not doc-

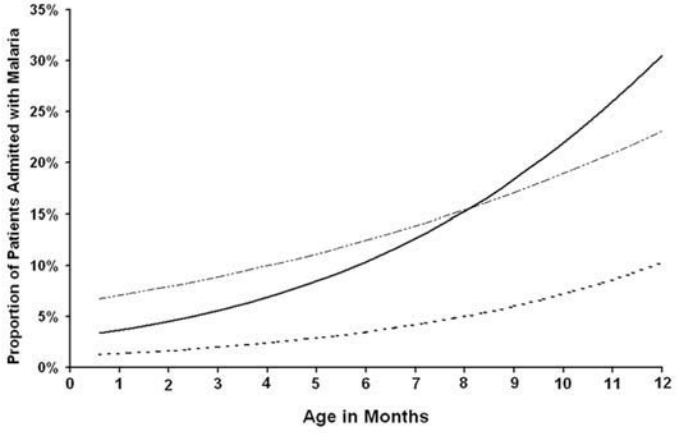

Figure 1. Age-specific risk of malaria in patients admitted to hospital with *Plasmodium falciparum (bold line), Plasmodium vivax (hatched line),* and mixed *(dotted line)* infections. Lines represent predicted values from a logistic regression model in which age was entered as a linear effect.

Table 1. Characteristics of infants admitted to the Rumah Sakit Mitra Masyarakat Hospital (Timika, southern Papua, Indonesia) with malaria.

Characteristic	Patient age, months					Total	*P*
	0–1	>1 to 3	>3 to 6	>6 to 9	>9 to 12		
Proportion of infants with malaria (%)	87/967 (9.0)	147/693 (21.2)	254/933 (27.2)	280/907 (30.9)	792/1476 (53.7)	1560/4976 (31.4)	<.001[a]
Etiology of malaria							
Plasmodium falciparum	34 (39.1)	48 (32.7)	81 (31.9)	124 (44.3)	375 (47.3)	662 (42.4)	<.001[b]
Plasmodium vivax	42 (48.3)	85 (57.8)	132 (52.0)	122 (43.6)	287 (36.2)	668 (42.8)	
Plasmodium malariae	0 (0)	2 (1.4)	0 (0)	1 (0.4)	5 (0.6)	8 (0.5)	
Mixed infection	11 (12.6)	12 (8.2)	41 (16.1)	33 (11.8)	125 (15.8)	222 (14.2)	
Hemoglobin concentration, mean g/dL (95% CI)[c]	7.9 (7.2–8.6)	6.5 (6.2–6.9)	6.4 (6.1–6.7)	6.9 (6.6–7.2)	6.7 (6.5–6.9)	6.7 (6.6–6.9)	<.001[d]
Signs of severity[c]							
Severe anemia[e]	16 (14.2)	41 (29)	75 (33)	67 (28)	221 (30)	420 (30)	.32[a]
Respiratory distress	31 (14.2)	61 (44)	22 (9.7)	19 (8.0)	44 (6.0)	177 (12.4)	<.001[a]
Coma	1 (1.2)	6 (4.3)	5 (2.2)	4 (1.7)	4 (0.5)	22 (1.5)	.02[a]
Mortality[c]	2 (2.4)	4 (4.3)	3 (1.3)	3 (1.3)	11 (1.5)	23 (1.6)	.349[a]

NOTE. Data are no. (%) of infants, unless otherwise indicated.

[a] Determined by χ^2 for trend.
[b] Determined by overall χ^2 test.
[c] Data restricted to 1424 infants (91%) for whom further details were available.
[d] Determined by 1-way analysis of variance.
[e] Hemoglobin concentration, <5 g/dL.

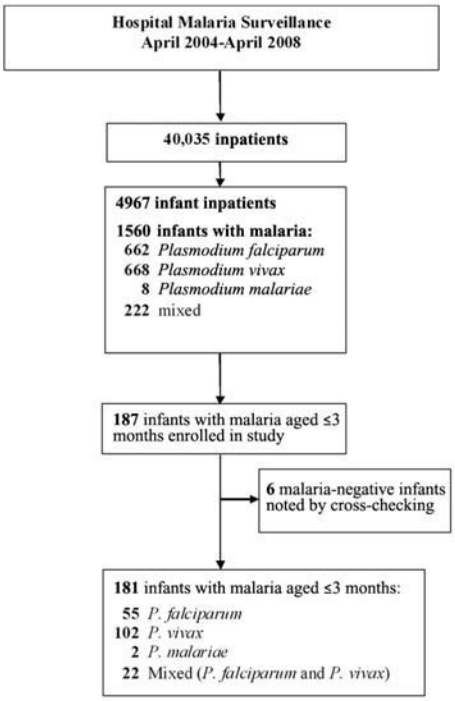

Figure 2. Profile of a study of *Plasmodium vivax* malaria in early infancy.

umented in 4 young infants. Almost one-half (73 [40%] of 181 patients) of the young infants also received antibiotic treatment.

At hospital admission, 152 (84%) of 181 young infants had fever or a history of fever, with a median duration of symptoms before admission of 3 days (interquartile range, 2–7 days). Severe disease was present in 128 (70%) of the 181 young infants, splenomegaly in 86 (48%) of 181 patients, and malnutrition in 31 (20%) of 154 patients. No significant difference was found in the prevalence of signs or symptoms, nutritional status, or markers of severity according to the species of infection (table 2) or between neonates and infants 1–3 months old.

Laboratory investigations. The geometric mean parasite count was moderately high in both patients infected with *P. falciparum* (8046 μL^{-1}; 95% CI, 3103–20,827 μL^{-1}) and in those infected with *P. vivax* (5814 μL^{-1}; 95% CI, 4179–8425 μL^{-1}) (table 2). The mean hemoglobin concentration was 6.8 g/dL (95% CI, 6.4–7.2 g/dL), with severe anemia present in 52 (29%) of 176 infants and severe thrombocytopenia (thrombocyte count, <50,000 cells/mm^3) in 33 (21%) of 159 infants. Compared with infants who had *P. falciparum* malaria, young infants with *P. vivax* malaria were at greater risk of severe anemia (OR, 2.4; 95% CI, 1.03–5.9; $P = .041$) and severe thrombocytopenia (OR, 3.3; 95% CI, 1.07–10.6; $P = .036$) (table 2); both ORs remained statistically significant after we controlled for age (adjusted OR, 2.2 and 3.1, respectively; $P = .04$). The median white blood cell count was 8500 cells/mm^3 (range, 1300–62,400 cells/mm^3) and did not differ according to the species of infection.

Outcome. The median duration of hospitalization for young infants with malaria was 4 days (range, 1–38 days). In total, 7 infants (4%) died, 5 of whom had *P. falciparum* malaria, and 2 of whom had *P. vivax* malaria. Three of these infants died ⩽24 h after admission to hospital. Additional details are provided in table 3.

DISCUSSION

In Papua, severe disease and hospitalization are observed after infection with multidrug-resistant strains of both *P. falciparum* and *P. vivax* [19]. Previous studies in this region have demonstrated that, although the prevalence of *P. falciparum* infection peaks among young adults aged 15–25 years, the burden of *P. vivax* is predominantly in children aged <5 years [16, 19]. In the present study, we highlight that the risk of admission to the hospital with malaria with either species starts in early infancy and is associated with hospitalization, severe disease, and death. At the Rumah Sakit Mitra Masyarakat Hospital, one-third of all infant admissions are associated with malaria, with *P. vivax* the predominant species up to 8 months of age (figure 1).

These findings mirror those of an associated community-based survey in which *P. vivax* infection accounted for 67% of malaria infections in infancy [16]. Prospective studies from both Papua New Guinea and Vanuatu have previously described the importance of *P. vivax* infection in young children with symptomatic disease uncommon in adults [12, 14, 15], suggesting the rapid development of immunity [22].

In regions of high *P. falciparum* endemicity, the risk and morbidity from malaria in early infancy (the first 3 months of life) are relatively low [5, 8]. In contrast, in Papua, where *P. vivax* is highly prevalent, we found that malaria was present in almost one-fifth of all-cause hospital admissions in young infants, with a risk of severe disease similar to that of older infants. Our study was restricted to infants who presented to the hospital and is thus likely to have preferentially selected those with clinical complications; nonetheless, the degree of morbidity was striking and suggests a significant risk of infection and susceptibility to severe disease. The low prevalence of severe malaria in infants has been attributed to passive immunity from maternal antibodies and a degree of innate immunity [4, 8]. However, despite the high prevalence of maternal malaria in this region (17%) [23] and the high prevalence of antibodies to both *Plasmodium* species in adults [24], we found that immunity had a limited effect in preventing severe malaria from either species in early life.

Severe anemia was the most frequent manifestation of severity for both *P. falciparum* and *P. vivax* infections and was more prevalent among infants with *P. vivax* infection than

Table 2. Admission characteristics and laboratory investigation of young infants (age, <3 months) admitted to the hospital with malaria.

Characteristics	*Plasmodium falciparum* infection (n = 55)	*Plasmodium vivax* infection (n = 102)	Mixed infection (n = 22)	P[a]
Male sex	30/55 (55)	58/102 (57)	14/22 (67)	.77
Papuan ethnicity	41/55 (75)	85/102 (83)	19/22 (86)	.32
Symptoms and signs				
Fever and/or history of fever	46/55 (84)	85/102 (83)	19/22 (86)	.94
Splenomegaly	26/55 (47)	45/101 (45)	14/22 (64)	.27
Hepatomegaly	16/55 (29)	29/101 (29)	8/22 (36)	.77
Sign of severity				
Hemoglobin concentration, <5 g/dL	10/54 (18)	35/98 (36)	7/22 (32)	.08[a]
Respiratory distress	29/54 (54)	62/101 (61)	12/21 (57)	.64
Coma	1/54 (2)	2/102 (2)	0/22 (0)	.81
Underweight[b]	13/44 (29)	16/90 (18)	2/18 (11)	.16
Geometric mean parasite count, μL^{-1} (95% CI)	8046 (3103–20,827)	5814 (4179–8425)	1990 (619–6393)	.10
Hemoglobin concentration, mean g/dL (95% CI)	7.8 (7.1–8.5)	6.5 (5.9–6.9)	6.3 (5.2–7.4)	.005[c]
Anemia[d]	49/54 (91)	94/98 (96)	21/22 (95)	.41
Platelet count				
Median platelets/mm^3 (range)	113,500 (32,000–685,000)	72,500 (23,000–962,000)	63,000 (35,000–116,000)	.002[e]
<100,000 cells/mm^3	24/51 (47)	57/88 (65)	13/18 (72)	.06
<50,000 cells/mm^3	5/51 (10)	23/88 (26)	5/18 (28)	.06[a]
White blood cell count, median cells/mm^3 (range)	9850 (2500–60,000)	8050 (1300–62,400)	7600 (4200–12,700)	.06[a]
Leukopenia[f]	6/44 (14)	5/74 (7)	4/18 (22)	.14
Leukocytosis[g]	10/44 (23)	7/74 (9)	0/18 (0)	.02

NOTE. Data are proportion of infants (%), unless otherwise indicated.

[a] $P < .05$ for *Plasmodium vivax* versus *Plasmodium falciparum*.

[b] Weight for age 2 SDs below the median value of the reference (healthy) population [21].

[c] $P \leqslant .001$ for *P. vivax* versus *P. falciparum*.

[d] Hemoglobin concentration, <11 g/dL.

[e] $P = .003$ for *P. vivax* versus *P. falciparum*.

[f] White blood cell count, <5000 cells/mm^3.

[g] White blood cell count, >25,000 cells/mm^3 in neonates and >15,000 cells/mm^3 in children aged 1–3 months.

among those with pure *P. falciparum* infection (OR, 1.3). Although severe anemia associated with *P. falciparum* in Africa generally manifests after 4 months of age [25], almost one-third of young infants in Papua were severely anemic. This is likely to reflect a number of factors. Hookworm infection and malnutrition reduce mean hemoglobin concentrations; however, the rates of severe anemia in infants admitted without malaria was only 3.9% and that of aparasitemic infants in a house to household survey was 0.6% [16], suggesting that, in this age group, malaria was a major contributory factor. Both *P. vivax* and *P. falciparum* cause dyserythropoiesis and hemolysis, resulting in a combination of impaired red blood cell production and loss of parasitized and unparasitized erythrocytes [26–28]. Community studies conducted in parallel highlighted that only one-third of infants with malaria infections were symptomatic [16], making it likely that many infections remain undetected or undertreated before presentation with worsening anemia. Persistent and recurrent infections are also important components arising from the emergence of multidrug-resistant strains of both *P. falciparum* and *P. vivax* [17], associated with repeated bouts of malaria from vivax relapses and *P. falciparum* reinfections. Because severe anemia has been shown to be an important determinant of infant mortality [6, 8], the prevalence and degree of anemia in Papua are likely therefore to be major factors in the high infant mortality rates reported locally (68 deaths per 1000 live births).

Another notable finding of our study was the high level of peripheral parasitemia in the youngest infants with *P. vivax* infection. *P. vivax* is capable of inducing fever at parasite levels lower than those necessary to cause fever in *P. falciparum* infection. Indeed, in associated community surveys and clinical studies in the same area, the geometric mean *P. vivax* parasite counts in clinical infections were generally 1500–2000 per μL^{-1} [29, 30], with the pyrogenic threshold estimated at ~400–600 per μL^{-1} [16, 23]. In infants younger than 3 months the geometric mean parasite count was significantly higher (5814 per

Table 3. Details of young infants (<3 months) admitted to the hospital with malaria who died.

Patient	Age	Sex	Nutritional status	*Plasmodium* species	Other medical condition	Malaria treatment	Intravenous antibiotic treatment	Time before death
1	6 days	Female	Severely underweight	*Plasmodium falciparum*	Neonatal sepsis (clinical diagnosis)	Intravenous quinine	Ampicillin	38 days
2	2 months	Male	Not recorded	*P. falciparum*	Bronchopneumonia	Intravenous quinine	Ampicillin, gentamicin	4 days
3	2 months 17 days	Male	Not recorded	*P. falciparum*	Bacterial meningitis (cerebrospinal fluid confirmed)	Intravenous quinine	Ampicillin, gentamicin	6 days
4	2 months 21 days	Female	Severely underweight	*P. falciparum*	Coma, severe anemia, hypoglycemia, metabolic acidosis	Intravenous quinine	Ceftriaxone	Within 24 h
5	3 months	Male	Normal	*P. falciparum*	Severe anemia with metabolic and respiratory acidosis	No record of malaria treatment	Ceftriaxone and gentamicin	Within 24 h
6	1 month 11 days	Male	Normal	*Plasmodium vivax*	Coma	Intravenous artesunate	Ampicillin, gentamicin, ceftriaxone	Within 24 h
7	2 months 16 days	Male	Underweight	*P. vivax*	Respiratory distress and severe anemia	Intravenous artesunate and then oral dihydroartemisinin-piperaquine	Ampicillin	4 days

μL^{-1}) and similar to that observed with *P. falciparum*, suggesting an inherent susceptibility to infection in early infancy, which may reflect a lack of immunity and/or a greater propensity for parasite multiplication.

In southern Papua, malnutrition generally manifests in infants 5–6 months old, when mothers stop breast-feeding their children. In household surveys, the overall prevalence of underweight infants is ~8% in the first year of life (M. Karyana; unpublished data) but was significantly higher in young infants hospitalized with malaria in our study (28% with *P. falciparum* and 18% with *P. vivax*), a finding consistent with either *P. vivax* and *P. falciparum* malaria contributing to malnutrition in these young infants or with malnutrition increasing susceptibility to malaria. Although the relationship between malaria and low nutritional status is complex and likely bidirectional [31], our results in young infants concur with previous studies in children aged <2 years [32].

A limitation of the present study was the unavailability of related details on associated comorbidities, particularly routine microbiology. A proportion of infants with malaria are likely to have been admitted to the hospital with alternative diagnoses and incidental parasitemia [33]. Approximately 40% of infants hospitalized with malaria had either leukocytosis or leukopenia, and this did not differ significantly among species of infection. Although sepsis itself may also have contributed to anemia [34], malaria coinfection and its associated anemia will have undoubtedly contributed to the underlying associated morbidity.

In conclusion, *P. vivax* is associated with major morbidity in early infancy. Malaria prevention strategies, such as insecticide-treated nets and intermittent presumptive treatment for infants, are mainly targeted at reducing the burden of *P. falciparum* infection [35]. However, the chronic and relapsing nature of *P. vivax* infection and its early acquisition are likely to undermine the effectiveness of these approaches. Additional studies are needed to confirm whether the degree of morbidity observed in southern Papua can be generalized to other vivax endemic settings. However, in regions with mixed *P. vivax* and *P. falciparum* endemicity, improved strategies are needed urgently to reduce infection from all *Plasmodium* species, especially *P. vivax*. Our study suggests that these interventions should be initiated in the perinatal period.

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