1998

Age-Dependent Susceptibility to Severe Disease with Primary Exposure to Plasmodium falciparum

J. Kevin Baird
ALERTAsia Foundation, jkevinbaird@yahoo.com

Sofyan Masbar
Malaria Program, Naval Medical Research Institute, Rockville, Maryland

Hasan Basri
Malaria Program, Naval Medical Research Institute, Rockville, Maryland

Soekartono Tirtokusumo
Malaria Program, Naval Medical Research Institute, Rockville, Maryland

Budi Subianto
Malaria Program, Naval Medical Research Institute, Rockville, Maryland

See next page for additional authors

Age-Dependent Susceptibility to Severe Disease with Primary Exposure to *Plasmodium falciparum*

J. Kevin Baird, Sofyan Masbar, Hasan Basri, Soekartono Tirtokusumo, Budi Subianto, and Stephen L. Hoffman

Malaria Program, Naval Medical Research Institute, Rockville, Maryland; US Naval Medical Research Unit No. 2, Jakarta, and Provincial Health Service, DINAS Kesehatan, Abebura, Irian Jaya, Indonesia

This study investigated the incidence of severe disease following primary exposure to *Plasmodium falciparum* by nonimmune children and adults in Irian Jaya, Indonesia. Four months after arrival, the cross-sectional prevalence of *P. falciparum* was 72%, and the monthly cumulative incidence of clinical diagnoses of malaria was 81%. Delirium or unconsciousness prompted evacuation to the hospital. Records of emergency evacuation of persons with a clinical diagnosis of malaria revealed an incidence density among adults (>15 years) of 1.34 events/person-year in the third month, whereas the rate in children remained stable at ~0.25 events/person-year (relative risk = 4.51, 95% confidence interval [CI] = 1.94–11). Through the first 6 months of exposure, 23.2% of adults were evacuated to the hospital with a diagnosis of malaria compared with 8.6% of children (relative risk = 2.7, 95% CI = 1.9–3.8). In this population with relatively few infants or people of advanced age, the risk of severe disease following primary exposure to *P. falciparum* increased with age.

Severe disease caused by *Plasmodium falciparum* in areas of intense transmission occurs almost exclusively among children [1]. Where endemic transmission is low, most severe disease occurs in children, but adults are also susceptible [2]. Adults sometimes have higher attack rates due to occupational exposure to infective anopheline mosquitoes. Nonetheless, the prevailing view is that nonimmune adults and children suffer equally upon primary exposure to *P. falciparum.* Few studies have reported age-specific rates of severe disease during epidemic malaria among nonimmune persons. When age-specific rates of morbidity or mortality from epidemic falciparum malaria have been described, adults have been consistently reported at higher risk of severe disease [3–8].

During unrelated studies of malaria in areas of transmigration in Irian Jaya, Indonesia, we noticed adult newcomers being treated for severe malaria more often than children. We retrospectively analyzed the age-specific incidence of severe disease among transmigrants from Java, Sumatra, Lombok, or Sulawesi. There has been little risk of infection on Java for >30 years [9], and these transmigrants arrive with little or no acquired immunity [10]. The risk of infection in Sumatra, Lombok, and Sulawesi is far lower than in Irian Jaya but greater than in Java. We considered most infections in Irian Jaya to be due to primary exposures.

Materials and Methods

Study site. The village of Arso PIR IV in northeastern Irian Jaya opened in late June 1992. Groups of 200–300 transmigrants arrived from Java, Sumatra, Lombok, and Sulawesi. During the next 3 months, the population grew to its capacity of 1200 people. The village is located at the southeastern edge of an oil palm plantation, within a few kilometers of the border with Papua New Guinea. The northeastern coastal region of Irian Jaya is hyperen-

Received 15 October 1997; revised 12 January 1998.

American and Indonesian committees for the protection of human subjects in medical research reviewed and approved the work described in this report.

Financial support: Naval Medical Research and Development Command work unit numbers STOE6.3A-2406, STOF6.3A-2501, and STOF6.3-002AA010HFX. The views expressed in this report reflect those of the authors and do not purport to represent official policy or views of the US Navy or the Department of Defense.

Reprints or correspondence: Dr. J. Kevin Baird, NMRI Malaria Program, 12300 Washington Ave., Rockville, MD 20852.

The Journal of Infectious Diseases 1998;178:592–5

0022–1899/98/7802–0046$02.00

demic for falciparum and vivax malaria. Annual attack rates range from 100% to 500% [11].

Access to the site affected the ability to conduct medical evacuations. The road leading to Arso PIR IV was unpaved and accessible only by 4-wheel-drive vehicles. A paved highway connecting the district to the provincial capital, Jayapura, was 5 km away. The district health center, 8 km away, was staffed by a physician and 3 nurses, who served a population of ~25,000 people. A regional hospital at Abepura was 45 km away, and the provincial hospital in Jayapura was 60 km away. Evacuation to the hospital was reported to the village head whether initiated from the village or the regional clinic.

Study subjects. The subjects were residents of Arso PIR IV. The population was typical of transmigration settlements in the region. Most residents (64%) were members of young families with children from rural areas of Java. Families from elsewhere in Indonesia (25% from Sulawesi, Lombok, or Sumatra), and lifelong residents of Irian Jaya (11%) constituted the remainder.

Health care and medical evacuation. A health care worker operated a clinic in the village. He was a high school graduate with 2 years of training in providing primary care to people in isolated areas. Such workers are trained to diagnose and treat common infections or injuries, including uncomplicated malaria, and to recognize more serious illness for referral to a physician.

Medical evacuation to the hospital was almost always prompted by a patient's delirium or loss of consciousness. This process required transportation arrangement and a formal letter of referral from the village manager. In general, evacuation to the hospital represented a difficult and time-consuming task for the health care worker, the patient, and the managers of the village. Evacuation took place only when it appeared that a patient's life was in danger.

Evacuation records and incidence density calculation. The manager of Arso PIR IV, a career officer with the Department of Transmigration, maintained an office and residence in the village. That office maintained records of medical evacuation documenting the date of evacuation, age, sex, condition, clinical diagnosis, and treatment outcome. If any patients walked to the clinic and were later evacuated, they were reported to the administrative head within hours. We calculated crude incidence density of medical evacuation with a listed diagnosis of malaria. Evacuees were arbitrarily divided into child (<16 years) and adult groups, and the monthly incidence was calculated using the total population of the village during that month to estimate person-time at risk.

Risk of infection. Residents took chloroquine prophylaxis for the first 90 days. However, studies in the region demonstrated that chloroquine was no more effective than placebo [12]. Blood smears were collected from 98 to 347 residents (mean sample size = 178) by survey case detection (screening without regard to the presence of symptoms of malaria). Smears were stained with Giemsa reagents and read by expert microscopists. The cross-sectional surveys occurred during 1992 in early July, late July, late August, late September, and late October. The prevalence of blood smear-proven malaria was 2%, 24%, 9%, 58%, and 72%, respectively, and 90%–100% of infections were due to *P. falciparum.* The age-specific prevalence of *P. falciparum* was relatively uniform among age groups at each sample [13]. Records of treatment of clinical malaria kept by the health center showed the monthly number of treated cases represented 20%, 68%, 81%, 79%, and 62% of the population of the village, respectively.

Table 1. Malaria statistics in Arso PIR IV, Irian Jaya, Indonesia, 6 months after arrival.

Age group (years)	Population	Evacuations	Deaths	Evacuation rate (%)	Mortality rate (%)
<2	45	4	1	8.9	2.2
2–5	137	16	1	11.7	0.7
6–10	151	6	0	4.0	0
11–15	87	10	0	11.5	0
16–25	214	54	1	25.1	0.5
26–40	345	86	3	24.9	0.9
>40	80	8	2*	10.0	2.5
Total	1059	184	8	17.4	0.8

* These 2 patients were 41 and 45 years old.

In late October 1992, when it became clear that the situation in Arso PIR IV constituted a public health emergency, vigorous efforts to contain the epidemic were undertaken by local authorities. Mass drug administration (chloroquine and primaquine) and bendiocarb fogging occurred over several weeks. These measures arrested the epidemic, that is, rates of febrile illness and medical evacuations promptly dropped.

Results

Table 1 shows the age-specific frequency of emergency medical evacuation to the hospital with a clinical diagnosis of malaria during the first 6 months of exposure to endemic falciparum malaria in Arso PIR IV. The highest rates of evacuation occurred among 16- to 25-year-olds (25.1%) and 26- to 40-year-olds (24.9%). Children aged 6–10 years had the lowest frequency of evacuation (4%). A total of 8 evacuated patients died. Most deaths occurred in adults (6/639, 0.94%), and only 2 (0.48%) of 420 children died, but this difference was not significant ($P = .34$). During the first 6 months of residence, 23.2% of adults (148/639) and 8.6% of children (36/420) were evacuated to the hospital with a clinical diagnosis of malaria ($P < .0001$; relative risk = 2.7, 95% confidence interval [CI] = 1.9–3.8).

Figure 1 shows the incidence of emergency medical evacuation with a clinical diagnosis of malaria among children and adults during the first 2 years in Arso PIR IV. The incidence of evacuation among adults increased sharply up to the third month of residence, with 1.37 events/person-year (relative risk = 4.51, 95% CI = 1.94–11). Evacuations of adults totaled 48 in that month. Another increase appeared among adults during months 14 and 15. In contrast, incidence in children reached 0.27 events/person-year (~7 evacuations/month) in the first month and never increased beyond 0.3 through the 24 months of observation.

Discussion

Adult transmigrants taking residence in the hyperendemic Arso region of northeastern Irian Jaya experienced a 4.5-fold

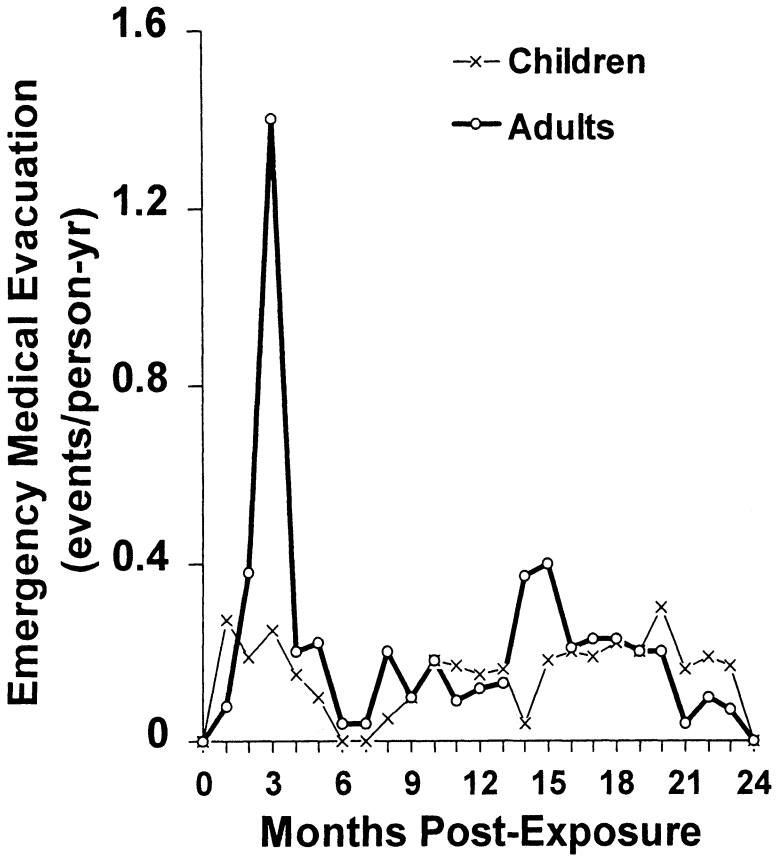

Figure 1. Incidence density of medical evacuation to hospital with malaria diagnosis among transmigrants from Java taking residence in Arso region of Irian Jaya, Indonesia.

higher risk of clinically diagnosed severe malaria relative to their children. Records of microscopic confirmation of malaria were not recovered, but the sharp increase in severe illness among adults corresponded with similarly increasing prevalence of smear-confirmed *P. falciparum* malaria in cross-sectional surveys. Conversely, the incidence of medical evacuation and prevalence of symptoms fell immediately after intervention with drugs and insecticide. In the 10 years of work with new transmigrants in Irian Jaya, we have rarely encountered fever without parasitemia, and this epidemic was not exceptional. While there are other causes of febrile illness in Irian Jaya, none has been shown to be associated with epidemics of febrile disease among newcomers from nonendemic areas. Taken together, these observations implicate *P. falciparum* as the cause of severe disease in the evacuated residents of Arso PIR IV.

The case-fatality rate among evacuated patients was lower than expected. Most studies show that 10%–20% of patients hospitalized with cerebral malaria die. Only 4.4% of subjects evacuated from Arso PIR IV died at the hospital (8/184 evacuations). This may be related to protective effects exerted by self-administered suppressive chloroquine therapy and prophylaxis. Alternatively, the health care worker may have been ordering the evacuation of patients with less than severe malaria. Finally, relatively low density and less-threatening parasitemias may evoke more alarming symptoms in persons with primary compared with chronic exposure.

Differential exposure to biting anophelines does not help explain the apparent susceptibility to severe disease among adults. In contrast to forest-dwelling vectors such as *Anopheles dirus,* the *Anopheles punctulatus* complex vectors in the Arso region prefer open, sunlit habitats, and they feed almost exclusively within the bounds of transmigration villages at times when all ages are present and exposed [13]. Mosquito bed-nets were used by most households and tended to be used by both children and adults. We did not identify a potentially confounding factor that could explain the high rate of severe disease among adult transmigrants. Moveover, prevalence tended to be uniform among newcomers, suggesting uniform exposure to infection and relatively equal risk of emergency evacuation across age groups.

Published reports tended to corroborate our findings. Greenberg and Lobel [3] reported 66 deaths among 1111 American travelers who acquired falciparum malaria abroad and were treated in US hospitals between 1959 and 1987. The case-fatality rates among subjects <20, 20–39, 40–70, and >70 years were 0.4%, 2.2%, 5.8%, and 30.3%, respectively. The very high case-fatality ate in Americans >70 years old almost certainly reflects some increased risk of death due to underlying diseases of the aged, but 5- and 15-fold higher risks of death among younger adults was nonetheless striking. Soni and Gouws [4] reported a 14.6% case-fatality rate among 103 severe malaria patients aged >12 years admitted to the hospital

in seasonally hypoendemic KwaZulu/Natal from 1984 to 1991. None of the 32 children hospitalized during that time died ($P < .02$). Data from an epidemic of malaria in Vanuatu between 1975 and 1985 showed that small children were least susceptible to cerebral malaria [5]. Among 5820 cases of malaria in one district (Port-Vila) between 1983 and 1985, only 2 cases of cerebral malaria occurred among children <4 years of age, whereas 44 cases occurred among residents >15 years old. Among 3991 infections and 173 deaths, the case-fatality rate for German travelers >60 years old was 15.9%, whereas the case-fatality rate in younger age groups of Germans was 1.0%–3.9% (ages not specified) [6]. During an epidemic of malaria in the highlands of Kenya, deaths among adults outnumbered those in children 2 to 1 [7].

Over 100,000 people died during the malaria epidemic of 1934–1935 in Ceylon (Sri Lanka). Gill [8] published data from Kurunegala, a town with "exceptionally complete statistical data." Overall mortality in children <10 years of age was 11.0% versus 22.9% among those >10 years of age. The relative risk of death for older people was 2.08-fold higher (95% confidence limits = 1.89–2.28). In a comprehensive search of the literature, we found no data showing parity between younger and older groups in rates of morbidity or mortality among nonimmune populations.

The studies in nonimmune transmigrants, when taken together with the published reports of acute exposure to falciparum malaria, show that children may be less likely than adults to suffer severe disease following primary exposure. One possible explanation is intrinsic age-related differences in immune function leading to differences in the balance between protective and harmful host immune responses to *P. falciparum* [14]. Clark [15] reported that adult rats (185 g) were twice as sensitive to the harmful effects of tumor necrosis factor α–inducing endotoxin as younger rats (65 g). This pattern correlated with the intrinsic susceptibility of the animals to death caused by *Plasmodium berghei.* A similar age-dependent sensitivity to factors in *P. falciparum* infection that induce tumor necrosis factor-α among humans may help explain the findings described in this report. The finding of adult susceptibility to severe disease with primary exposure to *P. falciparum* may have a direct bearing on issues of prevention, clinical management, and vaccine development. Longitudinal prospective studies designed to examine this phenomenon are needed.

Acknowledgments

We thank the many officials within the Ministry of Health and the Department of Transmigration, Republic of Indonesia, in both Jakarta and Jayapura, for their valuable assistance in gathering the data presented here. We are especially indebted to P. Albert and P. Petrus of the Department of Transmigration in Arso PIR IV who have labored to aid NAMRU-2 teams in the region for >10 years.

References

1. Binka FN, Maude G, Gyapong M, Ross D, Smith P. Risk factors for child mortality in northern Ghana: a case-control study. Int J Epidemiol **1995**; 24:127–35.
2. Luxemberger C, Ricci F, Nosten F, Raimond D, Bathet S, White NJ. The epidemiology of severe malaria in an area of low transmission in Thailand. Trans R Soc Trop Med Hyg **1996**;91:256–62.
3. Greenberg AE, Lobel HO. Mortality from *Plasmodium falciparum* malaria in travelers from the United States, 1959 to 1987. Ann Intern Med **1990**; 113:326–7.
4. Soni PN, Gouws E. Severe and complicated malaria in Natal/KwaZulu. S Afr Med J **1996**;86:653–6.
5. Bastien P. Particulares epidemiologiques des acces pernicieux a *Plasmodium falciparum* dan un contexe d'epidemie palustre. Vanuatu, 1975–1985. Med Trop **1987**;47:125–31.
6. Buck RA, Eichenlaub D. Prognostiche faktoren der malaria tropica—ergebnisse einer evaluationsstudie in der Bundesrepublik Deutschland 1963–1988. Gesundheitswesen **1994**;56:29–32.
7. Some ES. Effects and control of highland malaria epidemic in Uasin Gishu District, Kenya. East Afr Med J **1994**;71:2–8.
8. Gill CA. Some points in the epidemiology of malaria arising out of the study of the malaria epidemic in Ceylon in 1934–35. Trans R Soc Trop Med Hyg **1936**;29:429–80.
9. Baird JK, Sismadi P, Masbar S, et al. A focus of endemic malaria in central Java. Am J Trop Med Hyg **1996**;54:98–104.
10. Baird JK, Jones TR, Danudirgo EW, et al. Age-depedent acquired protection against *Plasmodium falciparum* in people having two years exposure to hyperendemic malaria. Am J Trop Med Hyg **1991**;45:65–76.
11. Jones TR, Baird JK, Bangs MJ, et al. Malaria vaccine study site in Irian Jaya, Indonesia: *Plasmodium falciparum* incidence measurements and epidemiologic considerations in sample size estimation. Am J Trop Med Hyg **1994**;50:210–8.
12. Fryauff DJ, Baird JK, Basri H, et al. Randomised placebo-controlled trial of primaquine for prophylaxis of falciparum and vivax malaria. Lancet **1995**;346:1190–3.
13. Baird JK, Purnomo, Basri H, et al. Age specific prevalence of *Plasmodium falciparum* among six populations with limited histories of exposure to endemic malaria. Am J Trop Med Hyg **1993**;49:707–19.
14. Baird JK. Host age as a determinant of naturally acquired immunity to *Plasmodium falciparum.* Parasitol Today **1995**;11:105–11.
15. Clark IA. Correlation between susceptibility to malaria and babesia parasites and to endotoxicity. Trans Roy Soc Trop Med Hyg **1983**;76:4–7.