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Adult Javanese migrants to Indonesian Papua at high risk of severe disease caused by malaria

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SUMMARY

Migrants from Java arrive in hyperendemic Papua, Indonesia lacking exposure to endemic malaria. We evaluated records of evacuation to hospital with a diagnosis of severe malaria from a transmigration village in northeastern Papua. During the first 30 months, 198 residents with severe disease were evacuated (7·5 evacuations/100 person-years). During this period the risk of evacuation for adults (>15 years of age) was 2·8. (95% CI = 2·1–3·8; $P < 0·0001$) relative to children, despite apparently equal exposure to risk of infection. Relative risk (RR) for adults was greatest during the first 6 months (RR > 16; 95% CI ⩾ 2·0–129; $P = 0·0009$), and diminished during the second 6 months (RR = 9·4; 95% CI = 2·7–32·8; $P < 0·0001$) and the third 6 months (RR = 3·7; 95% CI = 1·7–7·9; $P = 0·0004$). During the next two 6-month intervals, the RR for adults was 1·6 and 1·5 (95% CI range 0·8–2·6; $P < 0·18$). Adults lacking chronic exposure were far more likely to progress to severe disease compared to children during initial exposure, but not after chronic exposure to infection.

INTRODUCTION

Adults having lifelong exposure to holoendemic malaria caused by *Plasmodium falciparum* rarely suffer serious disease despite apparently continuous infection [1–3]. In contrast, infants and young children with malaria in these areas suffer relatively high rates of life-threatening disease, manifest as severe anaemia, respiratory distress, lactic acidosis and cerebral malaria [4–6]. Very young children in holoendemic Sub-Saharan Africa account for most of the 1–2 million deaths caused by malaria each year [7]. Nonetheless, severe malaria is not exclusively a disease of children; endemic and epidemic malaria in Asia and the Americas afflict residents of all ages, as do infections among travellers [8–10]. Susceptibility to severe disease among otherwise healthy non-immune people is widely considered uniform across age groups [11, 12]. This view stems largely from the widely held notion that protection from severe disease arises as the cumulative product of heavy exposure to infection through childhood [13–15].

Intrinsic differences between the immune systems of children and adults, distinct from the extrinsic factor of cumulative exposure to infection, may also impact the immune response to *P. falciparum*. These differences may be strictly developmental [16, 17] or established by exposure to non-*P. falciparum* antigens experienced through the normal course of life [18]. Intrinsic age-related changes to the immune system

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may be the basis of profoundly distinct immune responses to repeated infection by *P. falciparum*, and thus significantly affect the clinical course and consequence of infection. The relative susceptibility of children in heavily endemic areas may be driven primarily by intrinsic factors rather than by insufficient exposure to infection. We previously conducted epidemiological studies of Javanese migrants to hyperendemic Indonesian Papua that supported this view [19, 20]. Defining the cellular and molecular basis of age-dependent clinical immunity may guide approaches to inducing adult-like protection from *P. falciparum* in children [21, 22].

Discerning intrinsic age-related differences in susceptibility to primary infection by *P. falciparum* requires access to human populations abruptly exposed to high risk of infection. Most published reports of malaria epidemics fail to communicate sufficient detail to estimate age-specific risks of severe disease. Among the few that do, a pattern of exaggerated adult susceptibility emerges [23, 24]. Studies of non-immune travellers with malaria reveal a similar pattern [25–28]. This laboratory conducted a retrospective analysis of age-related risk of severe disease caused by malaria among non-immune Javanese migrants to Papua [29]. The risk of emergency evacuation to hospital with a clinical diagnosis of malaria among adults was 2·7 (95% CI = 1·9–3·8) relative to children during the first 6 months of exposure. This report describes a similar study in another migration settlement in the same region.

MATERIALS AND METHODS

Study design

In this retrospective cohort study, records of emergency evacuation from a remote village to tertiary health care facilities with a provisional diagnosis of malaria were reviewed for the period when the village first opened in September 1997 to February 2000. The analysis focused on the risk of evacuation for malaria among adults (age >15 years) relative to children (age $\leqslant 15$ years). Monthly estimates of age-specific risk were derived from the reported number of evacuations divided by estimated monthly total population at risk derived from concurrent annual census data.

Study site

The village of Arso XIV (Wulukubun) in northeastern Indonesian Papua (formerly known as Irian Jaya) served as the study site. Malaria caused by *P. falciparum* and *P. vivax* is hyper- to holoendemic and transmitted by all three established species of the *Anopheles punctulatus* complex: *An. punctulatus*, *An. koliensis* and *An. farauti*. Exposure to biting anophelines occurs in and around homes between dusk and dawn [30, 31]. Attack rates for malaria in the Arso region have typically ranged between 0·5 and 4 infections/person-year [32–35]. Cross-sectional studies in similar villages revealed relatively uniform prevalence of parasitemia across age groups during the first year of exposure [20]. In a recent study in a similar setting we followed 243 migrants to their first infection by *P. falciparum* or *P. vivax* and found no difference in the attack rates between adults and children [36]. We know of no age-related risk factor for exposure to infection in this setting.

Table 1. *Annual census reports for Arso XIV*

Year	Children (<16 years)	Adults (>15 years)
1998	346	156
1999	571	840
2000	623	840

Study population

Residents of Arso XIV came predominantly from Java (83% of residents), where the risk of malaria has been less than 1 infection per 10000 person-years for most areas since the mid-1960s [37, 38]. Melanesian Papuan people native to the area constituted most of the remainder (16% of residents). Age-specific census data for Arso XIV reported in January of each year were available for 1998, 1999 and 2000. The total numbers of residents on these dates were 502, 1411 and 1463. Table 1 lists the available census data and the relative numbers of children ($\leqslant 15$ years old) and adults (>15 years old).

Emergency evacuation

A government nurse delivered health care through a permanent health post located in the centre of the village. Serious ailments required referral to a regional clinic or hospitals 15 and 35 km distant. In general, only perceived life-threatening clinical conditions prompted medical evacuation of patients. For malaria, a routine illness in the new settlement, only severe disease marked by delirium or unconsciousness would prompt evacuation. The referral required the

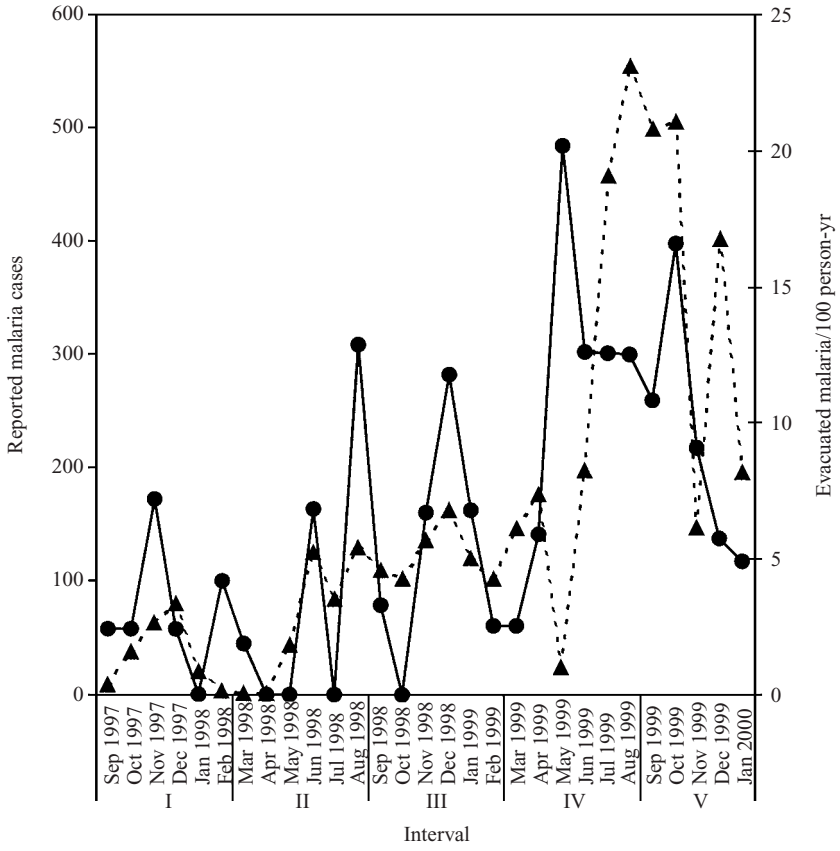

Fig. 1. Monthly number of malaria treatments recorded in the health post at Arso XIV (▲, dotted line) and the monthly incidence of emergency evacuations with a clinical diagnosis of malaria recorded at the village administrative centre (●, solid line). Roman numerals at foot of graph delineate intervals of 6 months used to estimate relative risk (Table 2).

written permission of the civil authorities and thereby created an administrative record of emergency evacuations. The record of evacuation included date, name, age, gender, address, and clinical diagnosis. This office also maintained records of complete censuses reported in January of each year. In April 2000 we visited Arso XIV and obtained these records.

Statistical analysis

Incidence of evacuation to the clinic or hospital with a recorded diagnosis of malaria constituted the primary outcome of interest and served as the indicator of severe disease. Age-specific person-time at risk was estimated for each month on the basis of census data reported in January of 1998, 1999 and 2000. We divided the population between children ($\leqslant$15 years) and adults ($>$15 years) and extrapolated a monthly estimate of each by extrapolating between the January census data assuming a steady rate of change in population over the year. Table 1 lists the available census data. The estimated respective totals of children or adults for each month divided by 12 gave person-years at risk for that month. The monthly number of child or adult evacuations divided by person-years at risk gave the incidence of evacuation in events per person-year. We multiplied this estimate by 100 to yield events per 100 person-years. The risk of evacuated malaria among adults relative to children was calculated. We divided the 30-month period of observation into five chronological periods of 6 months each (designated I–V). The sum of monthly evacuations and person-time at risk over the interval was used to calculate relative risk and 95% confidence interval (CI) using Epi-Info 2000 (version 1.0, Centers for Disease Control, Atlanta, GA, USA).

RESULTS

Malaria risk

Figure 1 illustrates the number of clinical cases of malaria recorded by the village nurse in the Arso XIV health post. During interval I this number climbed to as many as 80 cases/month, but fell to zero early during interval II. Malaria peaked again to 126 cases/month

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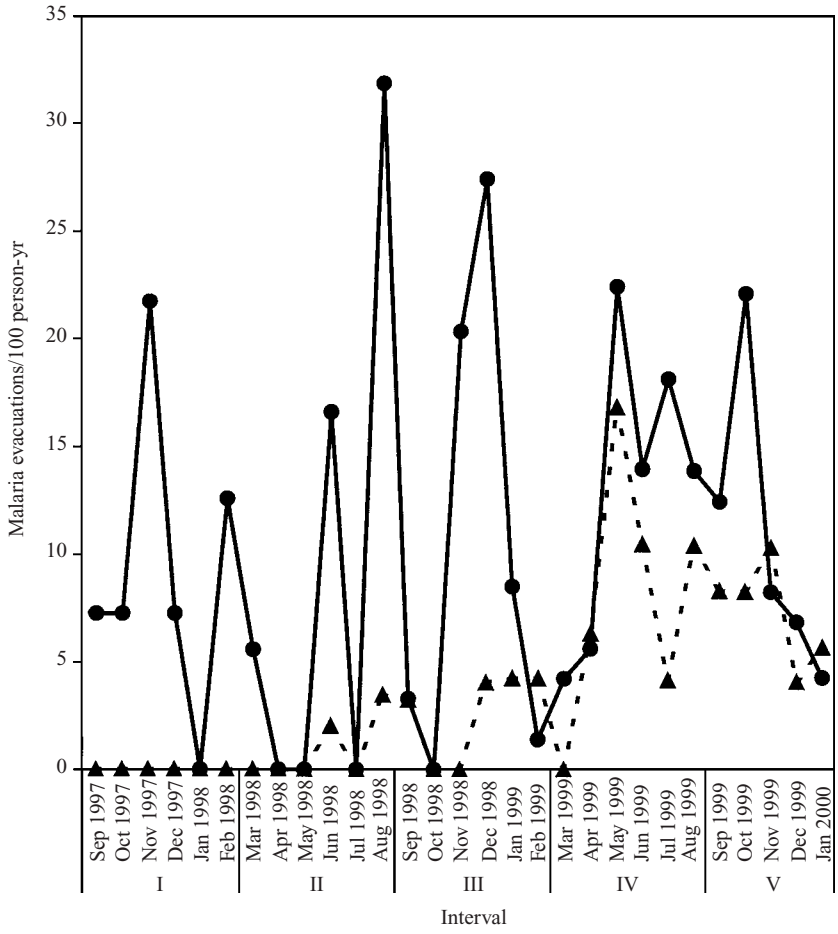

Fig. 2. Monthly incidence of emergency evacuation with a clinical diagnosis of malaria recorded at the village administrative centre for children (▲, dotted line) and adults (●, solid line) in Arso XIV. Roman numerals at foot of graph delineate intervals of 6 months used to estimate relative risk (Table 2).

in this interval. During interval III malaria peaked to 163 cases/month. Late during interval IV the number of recorded malaria cases in the village increased sharply to a high of 554 cases. This prompted intervention by the health authorities (mass drug administration using chloroquine and primaquine and spraying of residual insecticides in homes). The recording of routine malaria cases by the nurse did not appear consistent and were not applied to estimates of risk of medical evacuation.

Evacuated malaria

Microscopic confirmation of clinical diagnoses of malaria was not available at the village health post. However, review of the records at the secondary and tertiary health-care clinics and hospital that received the evacuated patients allowed review of diagnoses and outcomes among 69 of the 198 evacuations logged. Malaria microscopy results were recovered from 28 of these cases and all were positive. Among the 69 cases reviewed, death was recorded as the outcome for 6 (9% case fatality rate). Among the dead, only one patient was less than 30 years of age; an 18-year-old woman in her 36th week of pregnancy. The odds ratio for death in this sample of 69 patients was 10·0 (95% CI = 1·01–242; $P = 0{\cdot}026$) for those over 30 ($n = 26$) compared to patients under 30 ($n = 43$).

Figure 1 also illustrates the monthly incidence of evacuation with a clinical diagnosis of malaria. Incidence of evacuation generally followed the pattern of recorded malaria treatments in the village. The peak monthly incidence of malaria evacuation occurred in May 1999 with 20/100 person-years. A total of 198 people were evacuated to the clinic or hospital during the 30 months of observation. The estimated total person-time at risk during this period was 2637 person-years. The overall incidence of evacuation was 198 events per 2637 person-years (7·5/100 person-years).

Figure 2 illustrates age-specific monthly incidence of evacuated malaria. The incidence of evacuation

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Table 2. *Interval-specific risk for emergency evacuation in adults relative to children*

	Person-years		Evacuations				
Interval	Children	Adults	Children	Adults	Relative risk	95% CI	*P* value*
I	172	85	0	8	16·2	2·0–129	0·0009
II	281	139	3	14	9·4	2·7–32·8	<0·0001
III	365	275	9	25	3·7	1·7–7·9	0·0004
IV	286	429	23	56	1·6	1·0–2·6	0·051
V	246	359	18	39	1·5	0·8–2·6	0·179
Total	1350	1287	53	142	2·8	2·1–3·8	<0·0001

* Two-tailed.

for adults exceeded that for children at virtually all monthly points. Overall, 142 adults and 53 children were evacuated over the 30-month period, with estimated person-time at risk being 1287 and 1350 person-years, respectively. The 30-month risk of evacuation in adults relative to children was 2·8 (95% CI = 2·0–3·9; $P < 0·0001$). Table 2 summarizes interval specific risk of evacuation among adults relative to children. During the first interval eight adults and no children were evacuated. The incidence of evacuation for adults was 9·4/100 person-years and for children was <0·58/100 person-years (RR > 16, 95% CI > 2–129; $P < 0·0001$). During the second interval, 14 adults and 3 children were evacuated to hospital or clinic (RR = 9·4, 95% CI = 2·7–32·8; $P < 0·0001$). During the third interval, 25 adults and 9 children were evacuated to hospital or clinic (RR = 3·7, 95% CI = 1·7–7·9; $P < 0·001$). The remaining two intervals each showed a risk of 1·6 and 1·5 for adults relative to children (marginally significant at $P = 0·05$, and insignificant at $P = 0·18$, see Table 2).

DISCUSSION

An analysis of records of emergency evacuation with a clinical diagnosis of malaria revealed Javanese adults abruptly exposed to endemic malaria in northeastern Papua, Indonesia were at much greater risk of severe disease compared to children. These findings corroborated essentially similar outcomes in a different village in the same region [29]. This pattern accords with age-related susceptibility among non-immune people in the setting of epidemic malaria [23, 24] or travellers [25–28]. We considered intrinsic age-related differences in the immune systems of children and adults the most likely explanation for the apparent susceptibility of adults to onset of severe disease caused by primary exposure to *P. falciparum*.

Age-related differences in risk of infection represent an unlikely alternative explanation. We rejected this explanation in light of well-characterized patterns of risk of infection in the region. Arso XIV, like Arso PIR IV [29], was an agrarian community of cleared fields surrounded by dense forest. The anopheline vectors of the region prefer the open, sun-lit habitats created by these settlements, where virtually all feeding and breeding by these mosquitoes occurs [30, 31]. These vectors avoid the forest, and most residents do not wander into it, especially during the first year when they must establish sustenance and cash crops within the cleared area of the village. Cross-sectional studies in essentially identical settings revealed relatively uniform prevalence of infection across age groups during the first year of residence [22]. A recent longitudinal study of Javanese migrants in a nearby settlement revealed virtually identical incidence density of infection by both *P. falciparum* and *P. vivax* among adults and children during their first year in the region [36]. The children and adults settling into rural areas of northeastern Papua such as Arso XIV apparently experience equal exposure to risk of infection.

Other potentially confounding factors were considered as the basis of the observed differences in susceptibility between children and adults. Although the same individual served as the health post nurse during the entire study period, her relative inexperience in this setting during the early months may have resulted in a relatively low clinical threshold for evacuation. However, we doubt such a tendency would explain the apparently higher risk among adults. A presumably greater sensitivity to the health of children should have created a bias in the opposite direction, i.e. higher risk of evacuation for children. Another potential confounder may have been greater likelihood of early treatment among children. The

typically stoic adults may have been more likely to defer treatment compared to children, but the available evidence suggests essentially equally frequent consumption of antimalarials. We found no basis to attribute the extraordinarily high risk among adults to these potential confounding factors.

Studies of non-immune people exposed to *P. falciparum* in other settings also suggest adults being significantly more susceptible to severe disease. Among travellers with falciparum malaria hospitalized and treated in North America or Europe, higher age has consistently emerged as a significant risk factor for severe disease and death [25–28]. Higher hospitalization and death rates among adults in the setting of epidemic malaria have been reported [23, 24]. However, risk of severe disease among adults in populations with chronic exposure to relatively low risk of malaria, e.g. along the Thai–Burma border [39] or in urban areas of Sub-Saharan Africa [40], tends to be appreciably lower compared to young children. We believe the age-dependent exacerbation of risk of severe disease may appear only in adults and children who are not chronically exposed to infection by *P. falciparum*. Indeed, exacerbated risk of severe disease among adults rapidly waned (Table 2 and reference [29]) among the Javanese migrants transitioning from acute to chronic exposure.

Severe, life-threatening malaria caused by *P. falciparum* has been linked to the release of pro-inflammatory cytokines, especially tumour necrosis factor (TNF) [40–43]. The basis of adult susceptibility to severe disease caused by primary infection with *P. falciparum* may lie in the production of inordinately high levels of pro-inflammatory cytokines like TNF. Clinical studies correlated TNF levels with disease severity in European adults [44, 45]. Studies in a variety of animal models utilizing primary exposure to infectious agents or endotoxin demonstrated an often sharply greater susceptibility to severe disease among mature *vs.* immature animals [46, 47].

In summary, this study supports the hypothesis that intrinsic age-related differences between the immune systems of children and adults may drive distinct innate immune responses and clinical outcomes. The adult immune response to first infection apparently renders them more likely to progress to severe disease in the absence of prompt diagnosis and effective treatment. Non-immune adults may mount a potentially harmful immune response driven by innate or cross-reactive acquired immune effectors. This effect largely vanished with continued exposure to infection.

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