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CURATIVE THERAPY IN ADULT
RESIDENTS OF NORTHERN GHANA

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INCIDENCE OF SYMPTOMATIC AND ASYMPTOMATIC *PLASMODIUM FALCIPARUM* INFECTION FOLLOWING CURATIVE THERAPY IN ADULT RESIDENTS OF NORTHERN GHANA

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Abstract. Adult residents of holoendemic malaria regions in Africa have a naturally acquired immunity (NAI) to malaria that renders them more resistant to new infections, limits parasitemia, and reduces the frequency and severity of illness. Given such attributes, it is not clear how one might evaluate drug or vaccine efficacy in adults without serious confounding. To determine symptomatic and asymptomatic malaria attack rates in adults of northern Ghana, 197 men and women underwent curative therapy for any pre-existing malaria infections at the start of the high transmission (wet) season. They were monitored for first parasitemia and first clinical episode of infection by *Plasmodium falciparum* over a 20-week period (May–October 1996). The cumulative incidence of primary infection by *P. falciparum* was 0.98 and incidence density of infection was calculated to be 7.0 cases/person-year. Symptoms were reported by 19.5% of the individuals at the time of first recurrent parasitemia. Incidence of infection, parasite density, and the frequency of symptoms were comparable in males and females. The results suggest that NAI did not provide these adults with significant defense against rapid re-infection and suggest that this population-infection design could serve to demonstrate the efficacy of a drug or vaccine in preventing parasitemia.

INTRODUCTION

Malaria is one of the leading causes of morbidity and mortality in the tropics, affecting individuals of all ages, but primarily very young children and pregnant women.¹ Integrated approaches against both the parasites and vectors are required to control this disease with vaccines offering the best hope for sustained control in areas of intense transmission.^{2,3}

Malaria morbidity in adult Africans has long been considered of minor importance⁴ because adult residents of holoendemic areas have usually developed high levels of protective immunity as a result of their long and continuous exposure to malaria infections. The two forms of immunity described are 1) an anti-disease immunity that allows one to carry parasite loads without symptoms, and 2) an anti-parasite immunity that is responsible for a marked reduction of parasite densities after a certain age.^{5–7} Malaria slides from adults in highly endemic areas are usually positive regardless of the clinical context⁸ and adults are known to become rapidly re-infected with malaria parasites after treatment.⁹ Appropriate criteria for deciding when adults should receive treatment for malaria have never been agreed upon. It has been variably suggested that treatment should be based on parasite density threshold,¹⁰ febrile condition,^{11,12} symptom history,¹³ or an association between symptom history and parasitemia.^{14,15}

The present study was conducted to measure the incidence and features of symptomatic and asymptomatic infection by *Plasmodium falciparum* in malaria-immune adult Ghanaians who had been radically cured of all pre-existing *Plasmodium* infections. Effort was made to study newly incident infections in comparably sized cohorts of males and females 18–55 years old who were lifetime residents of the Kassena-Nankana district of northern Ghana. This study was conducted during the peak malaria transmission season to characterize malaria in the area and to provide the foundation

data needed for valid and efficient design of malaria vaccine and anti-malarial drug trials in the region.

SUBJECTS AND METHODS

Study site and population. The Kassena-Nankana district lies within the Guinea savanna woodlands between latitudes 10°30' and 11°00' north and between longitudes 10°00' and 10°30' west. It is located in the upper northeast region of Ghana at its border with Burkina Faso. The Kassena-Nankana district has an area of 1,675 km² and a population of 140,000 living in roughly 13,000 dispersed compounds. The main occupation is subsistence farming of predominantly millet and livestock. The Kassena-Nankana district has a mean monthly temperature range of 20–45°C and rainfall averages between 800 and 1,000 mm per year, occurring mainly between May and October. Malaria transmission by *Anopheles gambiae* and *Anopheles funestus* peaks at the close of wet season (during October and November). Malaria parasite prevalence among children < 5 years old in the Kassena-Nankana district was significantly greater in the wet season (May to October) than in the dry season (November to April).¹⁶ Malaria is the leading diagnosis of illness in the district hospital, accounting for 60% of all admissions and 41% of hospital deaths.¹⁷

Subject selection and consent. A representative sample population of adult men and non-pregnant women between the ages of 18 and 55 years was sought. The sample was randomly selected using the Navrongo Demographic Surveillance System, a longitudinal census of all district residents that is updated every three months.¹⁸ We tallied the total number of eligible adults (48,032) within the four geographic zones of the district and randomly selected 16 index compounds, with selections weighted by population size. Chiefs, elders, and potential subjects were then visited, the research work was explained and discussed, and opinions were sought before enrollment. Translation, narration, dis-

cussion, and communal consent were the essential elements of the informed consent process.

This research was approved by scientific and ethical review boards of the Ghanaian Ministry of Health and the U.S. Navy and was conducted in accordance with regulations governing the protection of human subjects in medical research.

Enrollment and screening. The screening process involved clinical history, vital signs, physical examination by a physician, collection of 1.0-ml venous blood for malaria smears, and hematology screening. Urine was collected from all women for β -human chorionic gonadotropin pregnancy testing. Laboratory screening involved microscopy of Giemsa-stained thick and thin blood smears, hemoglobin testing, and qualitative testing for glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. Remaining blood and plasma were archived for future laboratory work. Specific exclusion criteria were pregnancy, allergic reaction to antimalarial drugs, and illness or a condition requiring hospitalization.

Radical cure therapy of malaria. Just prior to the start of the rainy season (April 1996), radical cure therapy was used to achieve complete clearance of any patent, dormant, or incubating malaria infection from blood and liver. Volunteers were treated with oral quinine sulfate (650 mg three times a day for four days) followed by doxycycline, (100 mg twice a day for 10 days). Subjects testing normal for G-6-PD (NADP⁺ spot test; Sigma Chemical Co., St. Louis, MO) received primaquine (0.5 mg base/kg of body weight once a day for 14 days). Nineteen subjects who tested as deficient for G-6-PD received only quinine and doxycycline treatment. All doses were supervised and directly observed over the 18 days of radical curative or 14 days of curative therapy.

Surveillance and referral. Routine blood films were obtained on day 15 of the initial treatment and were repeated at two-week intervals for the duration of the study (20 weeks) by trained fieldworkers permanently residing in each of the 16 compound clusters. Fieldworkers visited subjects three times a week at their homes to inquire of their general health and check for fever by measuring axillary temperature. Each visit began with a direct question: "Have you been sick since the last visit?" If the answer was no, the interview ended. If the answer was yes, the subject was asked to describe his or her symptoms and these were recorded. If a subject complained of current illness to the fieldworker or had an axillary temperature $\geq 37.5^{\circ}\text{C}$, a non-routine blood film was obtained. Subjects were transported to the district hospital where the blood smear was examined by an expert malaria microscopist. Based upon presenting signs, symptoms, and microscopy results, physicians decided upon a treatment plan.

Study end points, treatment, and follow-up. The two primary outcome variables in this study were 1) time to the primary post-cure parasitemia and 2) time to the first episode of parasitemia associated with clinical symptoms. Blood slides were prepared as Giemsa-stained thick and thin smears examined by 1,000 \times light microscopy using oil immersion. Parasitemias were scored per microliter of blood by counting the number of asexual parasites per 200 white blood cells, assuming 8,000 white blood cells per microliter, and multiplying the parasite count by 40. A slide was con-

sidered negative if no parasites were observed within 100 high-power fields.

Our working diagnosis of clinical malaria was a patent asexual stage parasitemia accompanied by any one or more of the following symptoms: fever, headache, chills, myalgia, dizziness, nausea, and diarrhea. All symptomatic subjects with microscopy-confirmed malaria were promptly treated with chloroquine diphosphate (25 mg base/kg of body weight over a 48-hr period) and monitored for outcome. Chloroquine failures were treated with three tablets of Fansidar[®] (500 mg of sulfadoxine plus 25 mg of pyrimethamine; F. Hoffman-La Roche, Basel, Switzerland).

Data handling and analysis. Cumulative incidence (CI), expressed as the risk of an outcome and/or probability of infection during the 20 weeks, and incidence density (ID), which estimates new infections per unit of person-time at risk, were used as quantitative tools in determining the frequency of newly incident *Plasmodium* infections in this cohort. Due to the pre-erythrocytic stage incubation period of the parasite, the first 10 days following curative therapy were excluded from analyses as risk-free person-time. To identify predictors of a positive blood slide, and to determine whether the use of specific complaints or combinations of complaints significantly increased the likelihood of correctly predicting a positive blood smear, we used logistic regression models that fitted parasite positivity against symptoms recorded. The multivariate interactions among reported symptoms and parasitemia were investigated by graphical modeling¹⁹ using the MIM 3.0 software.²⁰ The best fitting model was determined by means of a backwards elimination procedure and a less stringent cutoff value of $P < 0.1$ was applied to improve the likelihood of finding associations given a small sample size.

RESULTS

The study plan is chronologically depicted as a flow diagram in Figure 1. During the initial radical or curative therapy stage, 98.7% of the 16,758 drug doses were administered and witnessed with only one volunteer dropping out. The baseline characteristics of the enrolled study population that completed radical or curative treatment and contributed person-time and/or study endpoints are presented in Table 1. The mean age, weight, and hemoglobin concentration among females was significantly different from that of males; older age was possibly an artifact that arose from the necessity of restricting female enrollment to those not pregnant or nursing. Patent malaria infections were identified in 110 (55.8%) of 197 subjects at enrollment and *P. falciparum* accounted for 102 (92.7%) of the 110 malaria infections, with the remaining 7.3% due to infections by *P. malariae* (7) and *P. ovale* (1). Gametocytes were observed in 29.6% of these subjects. Glucose-6-phosphate dehydrogenase deficiency was detected in 19 (9.6%) of the 197 enrolled subjects (7.1% of the women versus 11.6% of the men; $P = 0.28$). Baseline malaria prevalence was significantly greater among males (58% versus 38%; $P = 0.01$). All subjects belonged to the two main ethnic groups (Kassim and Nankam), in near balanced numbers, and had lived their entire lives in the area.

Blood smear screening on day 15 following the start of radical or curative therapy demonstrated parasite clearance

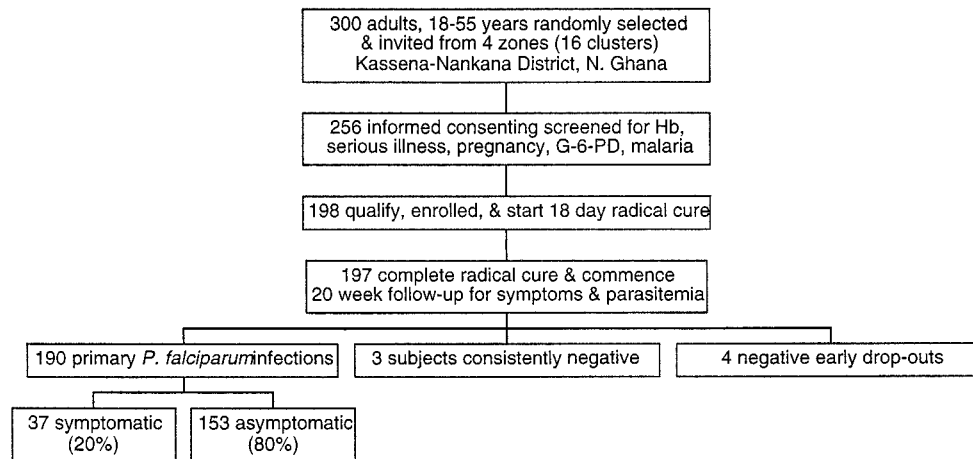


FIGURE 1. Study plan.

in all subjects. The first infections thereafter were identified during week 3 of post-cure follow-up. The cumulative incidence of primary *P. falciparum* infection over the 20 weeks following cure are plotted for males and females in Figure 2. Both sexes demonstrated the most profound increase in new infections during weeks 5–10, when the CI increased from 0.22 to 0.81 in males and 0.21 to 0.77 in females. Three subjects remained consistently aparasitemic to the 20-week endpoint. Four others dropped out of the study (negative) at various earlier time points. The collective 20-week CI for *P. falciparum* infection in adults was 0.98. The respective 20-week wet season IDs for infection in males and females was 7.2 and 6.7 (relative risk [RR] = 1.07, 95% confidence interval = 0.70–1.24) infections/person-year. The CI of illness coincident with parasitemia during this period was 0.42 among males and 0.49 among females (Figure 2). Analysis by location (Figure 3) found the acquisition of primary infection to be most rapid in the western compounds and slowest in the south (mean time to infection: west = 7.2 weeks versus south = 8.7 weeks; $P = 0.03$). Mean times to the first episode of confirmed symptomatic malaria were similar among the four locations studied.

Table 2 shows the characteristics of these primary infections in male and female subjects. There were no statistically significant differences between sexes for either CI, ID, the frequency of symptomatic primary infections, or the geometric mean (GM) density of parasitemias. Irrespective of sex, adults experienced a 20-week wet season ID of 7.0 (95% confidence interval = 5.1–6.8) new *P. falciparum* in-

fections per person-year of exposure. There were four females (4.7%) and three males (3.6%) who did not develop a detectable parasitemia during their 8–20-week participation. All were G-6-PD normal. One of these subjects was infected with *P. falciparum* at enrollment, two others with *P. malariae*, and six of the seven made voluntary clinic visits for diagnosis and treatment of illness during the study period. Analysis by age, which divided the population into two near equal groups, < 40 years old ($n = 100$) and ≥ 40 years old ($n = 97$), revealed that mean times to parasitemia and symptomatic parasitemia in the older age group were both significantly delayed ($P < 0.01$) relative to those in the younger group (Figure 4). As a result, wet season ID in the older group was 5.8 infections/person-year compared with 7.1 in the younger group ($P = 0.17$). Parasite densities at infection and at the time of symptoms were similar in the two groups.

There were 190 primary, post-cure infections by *P. falciparum* during the 20 weeks following cure. Symptoms and physical complaints characterized the first appearance of parasites in 37 (19.5%) of these 190 infections. Comparable proportions of males and females were symptomatic at this first parasitemia (males: 22 of 109 = 20.2%; females: 15 of 81 = 18.5%). Fever was present in eight (21.6%) of the 37 primary infections that presented with clinical illness, but was not associated with the level of parasitemia. Among individuals with asymptomatic primary parasitemias who were not treated, asexual stage parasites were variably present in subsequent follow-up slides. Parasitemia was detected in 65% of 566 follow-up slides from 113 representative

TABLE 1
Baseline characteristics of the Ghanaian study population*

Characteristic	Males	Females	<i>P</i>
No. of subjects (%)	112 (56.8)	85 (43.1)	–
Mean age (years) (95% CI)	35.4 (33.3–37.5)	43.3 (41.3–45.2)	<0.01
Mean weight (kg) (95% CI)	57.4 (56.0–58.8)	50.3 (49.0–51.6)	<0.01
Mean Hb level (g/dl) (95% CI)	12.1 (11.8–12.4)	10.8 (10.3–11.2)	<0.01
No. <i>Plasmodium falciparum</i> positive (%)	64 (57.1)	33 (38.8)	0.01
GM parasitemia/ μ l (95% CI)	135 (103–177)	98 (78–123)	0.07
No. febrile (%)	2 (1.0)	1 (0.5)	–

* CI = confidence interval; Hb = hemoglobin; GM = geometric mean.

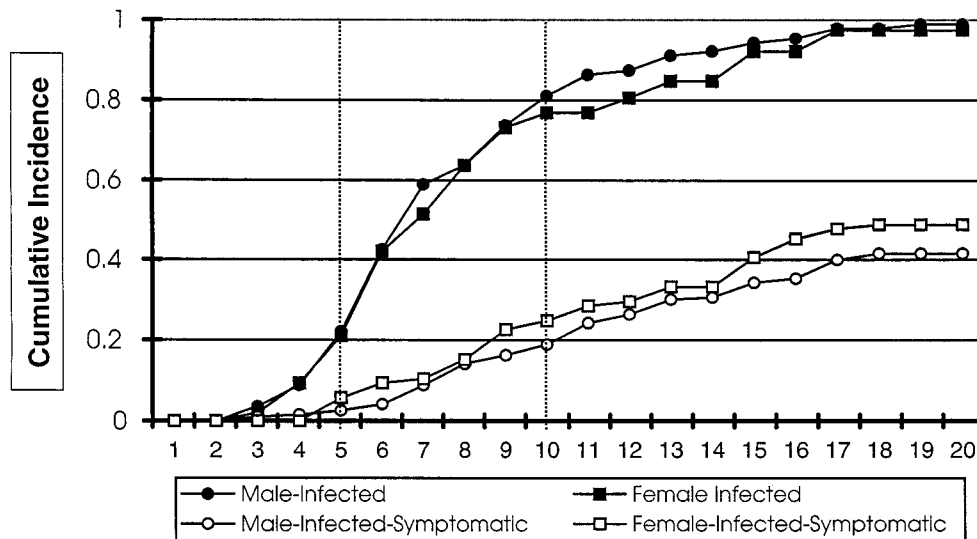


FIGURE 2. Cumulative incidence after radical cure of primary *Plasmodium falciparum* infections and of *P. falciparum* infections with symptoms in adult males and females in the wet season (May–December 1996) in northern Ghana.

subjects and usually not detected over more than three consecutive examination dates. During the course of study time applied to the 153 infected-asymptomatic volunteers, there were 242 occasions, judged to be clinical malaria on the basis of signs and symptoms that prompted blood smear examination. Asexual stage parasites of *P. falciparum* were present at 62 of these 242 occasions and those of *P. malariae* were present in one case. Asexual stages of *P. falciparum* were thus associated with 99 of 279 cases of malaria-like illness in these previously cured adults. The frequencies of specific complaints/symptoms associated with these infections are plotted against those of 180 other cases where parasites were undetected (Figure 5). The frequency of dizziness, chills, and headache were significantly greater among those with a confirmed parasitemia.

Stepwise logistic regression that was applied to the data revealed dizziness and myalgia as potential ($P < 0.1$) predictors of a positive blood slide, while diarrhea was unrelated. The multivariate dependencies among parasitemia and reported symptoms were further investigated using graphical

modeling. This approach showed dizziness and myalgia to be directly linked to parasitemia, with diarrhea independent of all other variables. The other reported symptoms (chills, nausea, headaches, and fever) were independent of the parasitemia given a presentation of dizziness and/or myalgia. Patients who reported chills or nausea were likely to also report dizziness or myalgia, but rarely both. Headache and fever were independent of the other symptoms given the presence of chills.

Table 3 shows the range and GM densities of primary post-cure *P. falciparum* parasitemias that were measured in symptomatic and asymptomatic cases. Relatively low-density parasitemias characterized more than 85% of the infections and were associated with physical complaints. The density of asymptomatic parasitemias at first appearance of infection was no different than the density of parasitemia later associated with the first occasion of clinical illness following curative treatment. There were no significant differences between sexes, or between symptomatic and asymptomatic cases in the frequency of high parasitemias or in the GM densities of parasitemias.

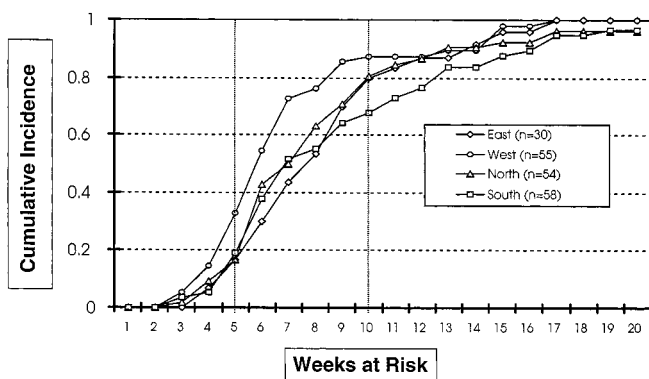


FIGURE 3. Cumulative incidence after radical cure of primary *Plasmodium falciparum* infections by location in the Kassena-Nankana District of northern Ghana during the wet season (May–December 1996).

DISCUSSION

The results of this study show that wet season malaria transmission in the Kassena-Nankana district of northern Ghana is intense and that the incidence of infection and clinical illness associated with malaria in adults is virtually identical in males and females. Despite a natural immunity derived from a lifetime of intense exposure, our results demonstrate that adults become rapidly re-infected and parasitemic following effective radical cure treatment. Neither genetic resistance nor long-acquired immunity appears to be sufficiently strong or widely present in this population to completely inhibit parasitemia. Rapid re-infection and patency among treated malaria-immune adults was recognized more than a decade ago in western Kenya.⁹ This general susceptibility and rapid appearance of low-density blood stage infections

TABLE 2

Characteristics of first infections with *Plasmodium falciparum* after radical cure in adult male and female study subjects during the wet season (May–December 1996) in northern Ghana*

Characteristic	Males	Females	P
Person-weeks at risk	777	629	–
No. with primary <i>P. falciparum</i> infections/total subjects (%)	109/112 (97.3)	81/85 (95.3)	0.45
No. symptomatic at first positive slide/total positive subjects (%)	22/109 (20.2)	15/81 (18.5)	0.77
Cumulative incidence/20 weeks of the wet season	0.99	0.97	–
Incidence density/person-year	7.3	6.7	0.56
GM parasitemia/ μ l—first appearance—Asymptomatic (95% CI)	129 (96–169)	162 (118–223)	0.27
GM parasitemia/ μ l—first appearance—Symptomatic (95% CI)	451 (171–1,190)	347 (131–921)	0.72

* GM = geometric mean; CI = confidence interval.

may result from the ineffectiveness of anti-sporozoite and anti-liver stage immunity or to an asexual blood stage effect coupled with a pre-erythrocytic stage immunity that reduces but does not completely eliminate all infected hepatocytes.^{2,9}

In spite of comparable malaria attack rates measured in adult males and females, the relatively small size and ecological uniformity of the Kassena-Nakana district study area, and seasonal climatic conditions that impinge evenly, thereby smoothing over ecologic and hydrologic differences, our analysis identified a significant difference between locations in the mean time to infection. This difference may relate to the geographic concentration of well-established irrigation systems in the western compounds. If this was not due to chance, it is likely that even more highly significant differences between locations will exist in the Kassena-Nakana district during dry season conditions. This observation may be supported by location analysis of data from recent studies conducted during the wet and dry season using infant cohorts. Drug and vaccine efficacy trials might be intentionally focused within particular areas of the Kassena-Nakana district to achieve rapid endpoints and tight confidence intervals.

Contrary to expectations, the ID of primary parasitemia in this adult cohort was virtually identical to that of a loca-

tion-matched cohort of infants (6–24 months old) who were treated and followed through 20 weeks of wet season in the following year (Adult ID = 7.03 infections/person-year versus Infant ID = 7.06 infections/person-year; RR = 0.99, 95% confidence interval = 0.82–1.19).²¹ The cumulative incidence profiles of adult and infant cohorts indicate the same rapid increase and plateau effect. Among infants, the most rapid increase in incidence occurred between five and 10 weeks with a plateau reached at week 10 that incremented only slightly more by the 20-week endpoint. In an analogous manner, new infections among adults increased most steeply from weeks 5 (male CI = 0.22, female CI = 0.21) to 10 (male CI = 0.81, female CI = 0.77). Among infants, only 18 new infections occurred in weeks 11–20, leaving 2.3% of the wet season cohort parasite-free. In a similar manner, the adult CI was 0.88 in week 13 and only 18 additional subjects (9.5% of the infected cohort) developed patent infections during the ensuing seven weeks of study.

We assumed that adult life-long residents of Navrongo, in contrast to their young children, would manifest a lower or delayed incidence of patent re-infection, lighter parasitemias at the time of re-infection, and mild or negligible illness. We found lighter parasitemias and decreased clinical manifestations in adults, but a near identical rate of re-infection following radical cure. A lower attack rate in adults might have been observed had both cohorts been studied simultaneously, but was not apparent in our comparison of wet season IDs for adults during 1996 and for infants during 1997. Heightened transmission impacting upon adults, or reduced trans-

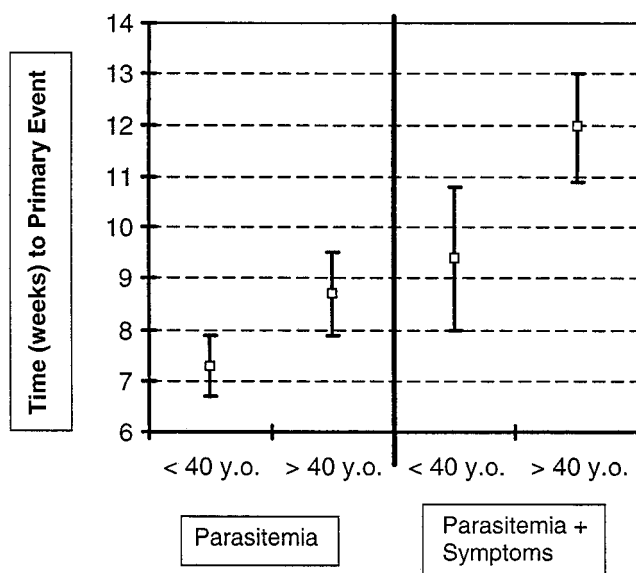


FIGURE 4. Mean time to primary infection by *Plasmodium falciparum* and primary symptomatic infection by age group in adult Ghanaians. Error bars indicate 95% confidence intervals.

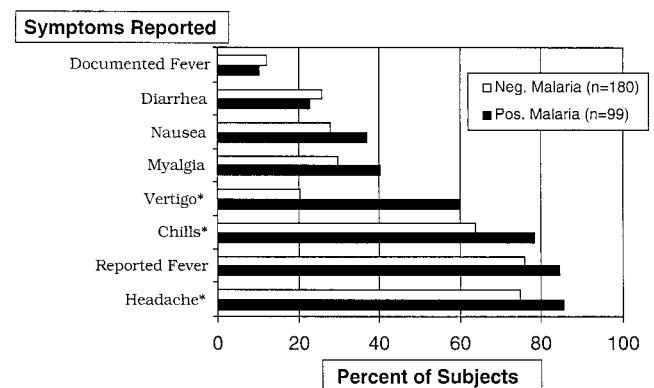


FIGURE 5. Comparative physical complaints/symptoms reported by adult Ghanaians with positive or negative malaria blood smears. * Indicates a statistically significant difference between groups.

TABLE 3
Range and geometric mean densities of first *Plasmodium falciparum* infections after radical cure in adult Ghanaians

Parasitemia range (/ μ l blood)	Asymptomatic		Symptomatic	
	Males	Females	Males*	Females†
<2,000	82	64	40	46
2,000–9,999	3	1	3	5
10,000–19,999	2	0	2	0
>20,000	0	1	2	1
Combined	87	66	47	52
GM parasitemia (range)	129 (40–12,560)	162 (40–31,640)	199 (40–97,680)	200 (40–22,000)

* Males: 22 symptomatic at first positive slide; 25 of 87 others (initially asymptomatic-positive) later became symptomatic-positive.

† Females: 15 symptomatic at first positive slide; 37 of 66 others (initially asymptomatic-positive) later became symptomatic-positive.

mission experienced by the infant cohort may have obscured real differences attributable to age-dependent immunity.

Interestingly, in contrast to the near equal incidence density seen in adults and children, we observed among adults that the > 40-year-old age group had a lower ID of re-infection compared with those < 40 years old, suggesting an effective age-dependent, naturally-acquired immunity. Under identical conditions of risk, an anti-parasite immunity capable of barring certain genotypes and suppressing parasitemia to sub-clinical levels in adults would be expected to prevent or delay the patency of primary infections relative to those sustained by infants.

As expected, adults experienced parasite densities and febrile episodes that were considerably reduced from those recorded in the infant cohorts.²¹ It was interesting to note that many of the infected Ghanaian adults in the present study experienced episodes of illness that corresponded with, and may have arisen from, their *P. falciparum* infections. We concede that the exclusive role of the parasitemias as a cause of their illness cannot be ascertained with certainty since the same signs and symptoms were reported frequently by these same individuals in the absence of parasites. However, the 37 occasions of illness that corresponded precisely with the first appearance of parasites following radical cure are most probably the true result of infection. Literature on the subject of adult malaria implies that adults with lifelong exposure to malaria do not become ill when they become re-infected with malaria parasites.^{4,12} Our data suggest that this may not be the case when parasites have been completely cleared. Interesting recent consideration has been given to the impact of liver schizonticidal therapy upon protective immunity elicited by immunization of mice with radiation-attenuated sporozoites,²² and to the potential loss of pre-munition in clinically immune adults who have undergone such curative therapy to eliminate their “benign” chronic malaria infections.²³

None of the adult patients became severely ill, but they reported physical complaints that limited their capacity to function normally, prompting them to interrupt their usual routine and seek medical care. Most of the symptoms observed were rather nonspecific. However, there were significant differences between parasitemic and non-parasitemic patients that may not have been due entirely to chance. Although we did not undertake or power this investigation to test a specific hypothesis of adult clinical predictors of parasitemia, we found dizziness and myalgia to be the best multivariate predictors of parasitemia. This pattern was confirmed when multivariate interactions between different

symptoms and parasitemia were investigated. Parasitemia was directly linked only to dizziness and myalgia, which in turn were likely to occur in combination with chills or nausea. This is in contrast to other studies that did not find symptom reports useful in diagnosing clinical malaria.⁸ Our preliminary findings suggest that adults presenting with dizziness or myalgia in association with chills and headache are likely to be parasitemic. We believe that this graphical approach to the identification of key physical complaints and symptoms associated with parasitemias should be tested more rigorously.

The incidence data herein reported for adult males and females provides the necessary foundation for rational design of trials to evaluate drug or vaccine effects. Although African infants and pregnant women will certainly be the target population for vaccination when an effective product becomes deliverable, adults and school children will probably be the earliest recipients, in whom safety, tolerance, and infection-blocking qualities can be readily assessed. In this regard, it was important to demonstrate near universal susceptibility to re-infection and its rapid manifestation as patent parasitemias in adult Ghanaian males and females. Additionally important in planning such studies is our documentation of radical cure compliance and dropout rates, the proportion of radically cured subjects who dropped out prior to yielding an endpoint, and the frequency and nature of illness that developed coincident with re-infection. Applying our findings of an 80% attack rate within 12 weeks to a prospective 12-week trial of a drug/vaccine with predicted 75% protective efficacy (PE), and an 80% probability (power) of having the lower 95% confidence limit for that PE \geq 70%, we would require a population of 1,004 adults. With these variables kept the same, but with the lower 95% confidence limit relaxed to \geq 60% for the PE, we would need only to enroll 151 subjects.

In conclusion, this study has shown that Ghanaian adults of the northern Kassena-Nakana district experience a seasonal ID of infection by *P. falciparum* that was comparable with that of infants living in the same communities. Within the 20-week wet season, virtually all adults had manifested a patent primary infection and many reported illness that coincided with parasitemia. Adults experienced predominantly low-density infections, characterized by mild clinical illness. Dizziness, myalgia, chills, fever, and headache were the most commonly reported symptoms that prompted health clinic visits seeking medical care. This study provides the foundation for designing efficient, practical clinical trials and

preventive strategies against malaria in this holoendemic region.

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