Seroconversion to Circumsporozoite Antigen of *Plasmodium falciparum* Demonstrates a High Risk of Malaria Transmission in Travelers to East Africa

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Circumsporozoite (CS) antibodies have been shown to be reliable indicators of malaria transmission in endemic areas. Their prevalence in travelers can indicate the degree of exposure to plasmodial infection. Two hundred sixty-two short-term travelers to Kenya were recruited to a prospective study to determine the incidence of CS antibody conversion. All travelers were receiving malaria chemoprophylaxis. Serum samples were drawn before departure and 4–6 weeks after their return to Germany. Sera from 310 volunteers who did not leave Germany served as controls. Serum specimens from 13 (4.96%) of the 262 travelers were found to be positive after return. None of the travelers developed symptoms of clinical malaria or antibodies against the blood stages of *Plasmodium falciparum*. All 310 control samples tested negative. These data demonstrate a considerable risk of malaria transmission for short-term travelers to East Africa.

In people exposed to *Plasmodium falciparum* transmission, some of the anti-sporozoite antibodies in their sera are directed against a main surface protein, the circumsporozoite protein (CS protein). Therefore, the detection of significant antibody titer to CS protein in a person indicates previous inoculation with sporozoites, but not necessarily the development of disease.

In persons living in areas of endemicity, prevalence and levels of CS antibodies have been shown to correlate with the entomological inoculation rate and to serve as an indicator of transmission [1–4]. The sensitivity and specificity of an available ELISA system have been evaluated in nonimmune patients after one episode of clinical malaria [5]. Whereas the sensitivity was found to be rather low (55.8% during a period of 8–90 days after onset of symptoms), its specificity was assessed at 100%.

Risk estimates for malaria incidence in unprotected travelers to West and East Africa have been 2%–3% per month [6]. A study involving 222 patients presenting after return from sub-Saharan Africa demonstrated a surprisingly high prevalence of CS antibodies among individual travelers: 48.8% were found to be positive, whereas this was true for only 5.6% of package tourists [7]. However, no pre-travel sera were available from these patients to verify seroconversion.

To estimate the actual infection pressure among short-term travelers to East Africa, we investigated the incidence of seroconversion of CS antibodies in a representative group of tourists.

**Materials and Methods**

**Patients.** Altogether, 289 travelers were recruited to this study from our travel clinic during a period of 3 months. Inclusion criteria were as follows: residency in Germany for >10 years, planned journey to Kenya for at least 7 days and not exceeding 6 weeks, no history of previous malaria, intake of sufficient malaria chemoprophylaxis during and 4 weeks after their journey, and informed consent. Only tourists traveling to East Africa for a hotel stay at the coast were recruited. Serum specimens were drawn from each participant before departure and within 4–6 weeks after return. Malaria was excluded in all participants by thin and thick blood smears as well as by a negative immunofluorescence antibody test (IFAT). Negative controls consisted of 310 volunteers who had never been to malarious areas.

**Methods.** Antibodies against the immunodominant epitope of the *P. falciparum* CS protein, the highly conserved tandem repeat of amino acids (NANP) were determined by a (NANP)40-ELISA (Sclavo Dignostici, Siena, Italy) as previously described [8]. By use of calibration sera with defined international extinction units (IEU), the cutoff value for measurement of CS antibodies was defined as 6.25 IEU [8].

All sera were also examined by an IFAT to determine levels of antibody to merozoites of *P. falciparum* derived from continuous culture. Titers of 1:64 and higher were considered positive [9–11].

Statistical analysis was done with *χ*² test by use of Epi Info version 6.0 software (CDC, Atlanta).

**Results**

Of the 289 recruited travelers, 262 (90.7%) could be followed up after their return to Germany. For these 262 remaining travelers (117 male, 145 female; average age, 35.5 years; range, 2–82 years), the average duration of travel was 17.1 days (range, 7–42 days). All travelers took antimalarials for chemoprophylaxis (mefloquine, 93%; chloroquine plus proguanil, 7%); 204 (77.9%) reported full compliance with chemoprophylaxis, and 175 (66.8%) used additional measures of exposure prophylaxis.
All serum samples drawn before departure were CS antibody-negative. After the travelers’ return from East Africa, 13 (4.96%) of the 262 serum specimens investigated were found to be positive, while 249 (95.04%) remained negative. Testing for merozoite antibodies by IFAT yielded negative results in all specimens.

Travelers with positive and negative reactions in the CS ELISA did not differ significantly by sex ($P = .495$), age ($P = .645$), destination ($P = .704$), duration of their journey ($P = .91$), travel circumstances ($P = .31$), or type of or compliance with malaria chemoprophylaxis ($P = .24$) or exposure prophylaxis to mosquito bites ($P = .83$). All 310 volunteers who had not traveled to malaria-endemic areas had negative results by CS ELISA as well as by IFAT for merozoite antibodies.

Discussion

Of 262 investigated travelers, 4.96% developed a serological response to CS antigen of *P. falciparum* during their journey to East Africa. This proportion is not as high as the rate of positive reactions to CS antigen (21.2%) that was found previously among 222 travelers after their return from sub-Saharan Africa [7]. This difference is probably due to the different inclusion criteria in the present study (only short-term travelers with hotel stays along the coast). Considering the previously demonstrated low sensitivity of the ELISA used in this investigation [3–5], at least one-third of all infected persons may have been undetected by this test. On the other hand, no specimen of the malaria-negative control group tested positive for CS antibodies. A high specificity concerning the diagnosis of plasmodial infection can be assumed, since similar results were demonstrated previously [3, 5]. Therefore, the actual infection pressure appears to be considerably higher than the rate of positive antibody responses to CS antigen measured.

None of the travelers with CS antibodies in this study developed clinically apparent malaria or merozoite antibodies. Although it is not known exactly what proportion of persons who seroconverted would have developed clinical malaria without chemoprophylaxis, these data emphasize the importance of adequate prophylactic measures when traveling to areas with a high malaria incidence.

Testing for CS antibodies in nonimmune travelers might become a method for determining the efficacy of malaria prevention measures. By screening of symptomatic and asymptomatic travelers, more reliable data regarding the risk of malaria transmission in travelers, and, therefore, the true necessity of malaria chemoprophylaxis in various endemic areas, could be obtained.

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References