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Malaria attacks in children exposed to high transmission: who is protected?

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Abstract

In persons naturally exposed to high transmission, how significant, in terms of immune protection, is the occurrence or non-occurrence of a malaria attack during a given observation period? This question was studied in a West African village where *Plasmodium falciparum* malaria is holoendemic with intense and perennial transmission. A cohort of 94 children aged 4 months–14 years from Dielmo village, Sénégal, was studied over 4 months, June–September 1990. 41 children had no malaria attack and 53 children suffered between one and 6 attacks. The average number of attacks was 1·80, 2·25, 1·87, 0·29 and 0·07, respectively, in children aged 4–11 months, 1–2, 3–6, 7–10 and 11–14 years. The transmission level was 75 infective bites per person. Analysis of the distribution of the number of attacks in individual children suggested that all children within the same age group had either the same, or a very similar, level of protection. This suggests that the acquisition of clinical protection in areas where malaria is highly endemic involves a progressive and homogeneous decrease of the probability of having a malaria attack (attacks occur less frequently as age increases, in all children), rather than the acquisition of complete protection by an increasing number of children. The differences between the number of clinical attacks observed in young children and their presumed exposure suggest that protective mechanisms become effective from the first reinfection onwards, and are independent of the cumulative exposure to a great variety of antigens.

Introduction

In areas where malaria is highly endemic, epidemiological studies have consistently shown that mortality and morbidity due to malaria occur mainly among infants and young children. In older children and adults, acquired immunity is usually sufficient to prevent the development of symptoms during infections. The precise mechanisms of this protection are still unclear and a common method of investigation is the comparison of the results of immunological tests on persons considered to be either protected or unprotected. In order to constitute these 2 sample groups within a population living in an endemic area, 2 different criteria could be used: either the person's age (older children and adults are presumed to be protected), or the clinical data obtained from prospective surveillance (persons who have an attack during the observation period are presumed unprotected). Both methods present specific problems in the interpretation of the results. With the first method non-specific factors related to age may interfere with the results (BAIRD *et al.*, 1991); with the second, it is necessary to determine the significance, in terms of protection, of the occurrence or non-occurrence of a malaria attack during a given observation period. We have studied this latter problem, using preliminary observations carried out over a 4-month period in a group of Sénégalese children.

Material and Methods

As part of a research project into the development of malaria immunity, the entire population of Dielmo village in Sénégal (population 255) has been the object of a longitudinal study since 1990, consisting of close monitoring of numerous epidemiological, clinical and immunological factors. Malaria transmission in this village is intense and perennial (115 infective bites per person per year in 1990) and the parasite rate is over 85% in children over 1 year of age throughout the year (TRAPE *et al.*, 1991).

In order to identify all malaria attacks, routine medical examinations were carried out from 1 June to 30 September 1990 (maximum transmission period) by a medical team operating day and night in the village. Households were visited daily. The systematic observations included thick blood film examinations twice a week and temperature readings every 2 d. Supplementary thick smears, medical examinations, and further tests were made when fever or other symptoms were present.

For this study, we took into account the results of 94 children aged between 4 months and 14 years who had spent at least 75% of their life in Dielmo. We considered as *Plasmodium falciparum* attacks 120 episodes of fever (temperature ≥38·5°C) associated with sharp increases in parasitaemia (Trape *et al.*, paper in preparation). During 110 of the attacks (92%) the parasite/leucocyte ratio exceeded 2, a criterion previously proposed for diagnosing clinical malaria among children living in holoendemic areas (TRAPE *et al.*, 1985). With the exception of 29 brief attacks which were diagnosed retrospectively, all attacks were immediately treated using a 3 d regimen of quinine+quinidine+cinchonine (Quinimax®, 25 mg/kg/d) (DELORON *et al.*, 1989). No severe attack was observed. The absence of chemoprophylaxis and/or self treatment was controlled by systematic determination of antimalarial drugs in the urine once a month, and during the course of all fever cases, using the modified Saker-Solomons test (MOUNT *et al.*, 1989). *P. falciparum* was present in 85% of the thick blood films taken in the absence of fever. Trophozoites were observed in all except one child during the study.

Results

During the 4 months surveillance period, 41 children had no *P. falciparum* attack, and 53 children suffered between one and 6 attacks. The maximum average number of attacks was among children aged 1–2 years, and it decreased with increasing age (Table 1: $P<0·0001$; ANOVA, with square root transformation). This decrease was particularly obvious in children older than 6 years: the average number of attacks was 6 times higher in children aged 3–6 years than in those aged 7–10 years.

Table 1. Age distribution of falciparum malaria attacks, Dielmo, Sénégal, 1 June–30 September 1990

Age group[a]	No. of children	No. of attacks	Mean no. of attacks per child
4–11 months	5	9	1·80
1–2 years	20	45	2·25
3–6 years	31	58	1·87
7–10 years	24	7	0·29
11–14 years	14	1	0·07
Total	94	120	1·28

[a]Age at inclusion.

To determine whether the children who had no attack during the observation period could be considered to be better protected than the other children, we compared the observed distribution of children having had 0, 1, 2,

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3, 4 or more attacks with the expected Poisson distribution, which would reflect a similar probability for all children of suffering an attack. Table 2 shows that the observed and expected numbers did not differ significantly when children aged 4 months–6 years and 7–14 years were considered separately. In contrast, when all children were considered together, the observed and expected figures were significantly different ($P<0{\cdot}001$; χ^2 test).

Table 2. Observed and expected distribution of children according to age and the number of falciparum malaria attacks in individual children over a four-month period

No. of attacks	Age group 4/12–6 years Observed	Expected	7–14 years Observed	Expected	Total Observed	Expected
0	11	7·6	30	30·7	41	26·2
1	11	15·1	8	6·5	19	33·5
2	12	15·1	0	0·7	12	21·4
3	14	10·1	0	0·1	14	9·1
<	8	8·1	0	0	8	3·8
Total	56	56	38	38	94	94

Discussion

These observations are compatible with the assumption that all children within the same age group were equally protected/susceptible. At a given age, all children in this survey had either the same level of protection (whether or not they suffered a malaria attack during the observation period), or a level of protection so similar that an observation period of 4 months, with this number of children, was insufficient to demonstrate differences between them. This suggests that the acquisition of clinical protection in areas where malaria is highly endemic involves a progressive and homogeneous decrease of the individual probability of having a malaria attack (attacks occur less frequently as age increases, in all children), rather than the acquisition of complete protection by an increasing number of children. I f we had chosen to class children without malaria attacks in the protected group, and those children with malaria attacks in the unprotected group, 20% (11/56) of children aged between 4 months and 6 years would have been counted as protected, whereas the probability of their suffering an attack should be considered to be equal to that of other children in the same age group. Conversely, 21% (8/38) of children aged 7 to 14 years would have been counted among the unprotected children, whereas their level of protection should also be considered to be equal to that of other children in the same age group.

Can the youngest children in this survey be considered as unprotected? The transmission level of malaria in Dielmo, during the 4 months observation period, was estimated by night-time mosquito collection and dissection to be 75 infective bites per person (KONATE, 1991). The differences between the number of clinical attacks observed in young children and their presumed exposure seems to be much too high to be explained only by the fact that children were less exposed than adults to mosquito bites (PORT *et al.*, 1980), or by the failure of some infected mosquitoes to transmit sporozoites (ROSENBERG *et al.*, 1990). Therefore, even in young children, it is probable that only a small proportion of infections was accompanied by clinical symptoms. After the first year, maternal antibodies no longer play a protective role, which suggests that other protective mechanisms come effectively into play from the first reinfection onwards, and that these are independent of the cumulative exposure to a great variety of malarial antigens.

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