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Malaria morbidity and mortality in children under three years of age on the coast of Benin, West Africa

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Abstract

Malaria morbidity and mortality were measured in a population of 1500 children under 3 years of age from April to December 1989. During monthly home visits, an average of 26 children in 1000 had fever, of whom 15 had parasitaemia. Children less than 6 months old had significantly fewer fever episodes, whether associated with parasitaemia or not. Overall, prevalence of fever with parasitaemia rose steadily from April to August, then decreased but reached a second peak in November. Peaks coincided with the 2 rainy seasons in April to June and September to October. Comparison with a control group demonstrated that children with parasitaemia exceeding 1000 infected red blood cells per microlitre of blood had fever significantly more often than children with lower levels of parasitaemia. The average number of fever episodes per child per year was 2·4, and 33% of these were estimated to be caused by malaria. All cause mortality was 26/1000/year and the malaria mortality rate was 8/1000/year. Malaria deaths were most frequent in the second year of life.

Introduction

Malaria is generally recognized as a major threat to health in Benin. Health staff are trained to give presumptive treatment for malaria whenever fever is detected. Paediatricians recommended chemoprophylaxis with chloroquine for the very young. Mothers are aware of the malaria problem and treat their children with chloroquine both curatively and prophylactically. Chloroquine is readily available at every market. Although drug resistance has begun to emerge in the cities, it is still less of a problem in rural areas (Chippaux *et al.*, 1989).

The Pahou primary health care (PHC) project was started in 1983 for the purpose of health systems research, i.e. to compare various ways of organizing and managing PHC. Epidemiological activity in this context provided demographic information and served to measure morbidity and mortality among children as a basis for planning and targetting health interventions.

Cross-sectional studies in 1987 showed a very high prevalence (of the order of 12%) of fever unaccompanied by other symptoms such as cough or diarrhoea. Extrapolation of these results suggested an average of 6 episodes per child per year. Among the causes of death of children aged 4 to 35 months, who died in 1986 and 1987, fever, whether or not accompanied by convulsions, ranked first, accounting for 48% of deaths.

Since all these reports were based on interview data, the possibility could not be excluded that both interviewers and persons interviewed had been jumping to conclusions about the nature or cause of a disease, given the general awareness that malaria is the number one health problem in the country.

It thus seemed appropriate to document more objectively the magnitude of the malaria problem among young children in the project area. An extra component was therefore incorporated in a longitudinal study already in progress, to measure body temperature and to collect blood samples from selected children to verify the presence of malaria parasites.

Materials and Methods

Study area

The study area was situated on the Atlantic coast of south Benin in West Africa and covered 18 villages consisting of 138 hamlets. A village typically consisted of a nucleus or 'central hamlet' with a number of small hamlets spread around it. The median number of inhabitants per village was 550 (range 300–2000). The total population was 13 000. Compounds were numbered within villages. Each household in the area had a unique 4 digit number and each member a sequential number within the household. The dominating ethnic groups were Fon (55%) and Aizo (25%). Subsistence farming, horticulture for the nearby city, fishing and small trade were the main economic activities.The overall average temperature was 25°C but daily variation may exceed 10°C in this coastal area. Average relative humidity through the year ranged from 70 to 90%. Annual rainfall was of the order of 1200 mm. There are four seasons: a long dry season from December to March, a long rainy season from April to July, a short dry season in August and September, and a short rainy season from October to November.

Three ecological zones were distinguished from south to north. The coastal strip extends from east to west along the beach and is delimited to the north by a lagoon. The marshlands, also parallel to the coast, are delimited by the same lagoon on the south and by a second lagoon on the north. Crossing this second lagoon, one enters the northern plateau with laterite soil rather than sand.

Follow-up

All children under 3 years of age living in the project area, approximately 1500, were visited monthly from April 1989 to December 1989. The proportion of children absent, even after repeated visits, was 5% or less each month.

Newborn children were enrolled on the first visit of the field-worker following birth. Children who reached the age of 36 months were no longer followed. Children who migrated in or out of the study area were similarly enrolled or considered lost to follow-up.

Morbidity

Rectal temperature was measured during each monthly visit by means of an ordinary mercury thermometer for at least one minute. At the beginning of the study it was verified that field-workers read the temperature correctly, and during the study this was regularly checked in the field. Whenever a child with fever (>37·9°C) was detected, a technician took a blood sample on the same day, prepared a thick and a thin blood film on the same slide, and filled a heparinated capillary tube with blood for determination of the packed cell volume (PCV).

For every child with fever a control from another household, who had been visited the same day, was selected without symptoms, with the same date of birth (±3 months), and living in the same ecological zone. The same procedures were followed for control children as for children with fever.

Duration of fever episodes

In a sub-sample of approximately 850 children comprising nearly equal numbers from the 3 ecological zones, the mother or guardian was asked if the child had been ill in the past 7 d. If such was the case, the interviewer asked how many days ago the illness had begun and for how many days it had lasted. The field-worker then ascertained the dates of onset and termination of the episode. If the child was ill on the day of the interview, a card was given to the mother on which squares indicated the days. The field-worker marked with a cross the days the child had been ill and the mother was asked to mark each following day with a cross if the child continued to be ill, or a circle if the child was better again. The field-worker retrieved the card towards the end of the month. Analysis of this information was restricted to those episodes which had begun during the 7 d immediately before the interview. The mother was interviewed at 94% of visits, the father or the grandmother at 3% and an aunt or a neighbour at another 3%.

Mortality

If a child had died, a medical doctor interviewed the parents to determine the cause of death using a check-list of signs and symptoms. The village health worker was also interviewed if he had seen the child during the terminal illness. Classification of causes of deaths was based on standardized criteria. In particular, malaria was recorded if the terminal illness was of short duration and characterized by high fever in the absence of an evident explanation such as signs of a respiratory infection. Convulsions were reported in 50% of these cases, vomiting in 30% and signs of severe anaemia in 20%.

Laboratory methods

Blood samples were taken to the laboratory at the end of the day and kept in a refrigerator until processing on market day, when no data collection took place. Slides were stained with a rapid Giemsa method and examined by one of 2 observers using a ×100 oil immersion objective and ×10 eyepieces.

The level of parasitaemia was determined from the thin blood film by dividing the number of infected red blood cells (IRBC) in 75 fields by the total number of red blood cells examined, which, from previous data, was estimated to be 280 per field (Chippaux *et al.*, in press). Multiplication of the proportion of IRBC and the total number of red blood cells per µl yielded the estimated number of parasites per µl. The number of red blood cells per µl was estimated from the PCV by means of a linear regression equation based on data collected in 3 clinics in areas adjacent to the study area (Chippaux *et al.*, in press). Detection of a single infected red blood cell in a thin film would result in an estimate exceeding 100 IRBC/µl. Thus a negative thin film indicated that fewer than 100 IRBC were present per µl of blood. Thick blood films were used to check for gametocytes in the blood and this information was dealt with separately. All parasites detected were *Plasmodium falciparum*, the dominant species in this area.

Statistical analysis

Odds ratios relating risk of fever to level of parasitaemia were estimated by maximum likelihood methods for matched case-control studies (Breslow & Day, 1980) by means of the program MULTLR (Campos-Filho & Franco, 1989). The program automatically disregards cases for which the matched control is missing. Attributable risks were computed for each category of parasitaemia as $(r\text{-}1)/r$, where r is the odds ratio. The average of these category-specific estimates, weighted according to the proportion of cases in each category, is the population attributable risk (Breslow & Day, 1980).

Likelihood ratio test statistics for heterogeneity or trend in the morbidity rates were derived from the comparison of hierarchic logistic models which described prevalence as a function of the independent categorical variables age, sex, ecological zone, or month of the year. The numbers of cases in different months were regarded as independent of each other even though the same children were seen each month. This seemed to be justified as only a few children had multiple episodes. Results of univariate analyses are presented, but it was verified by multi-variate analyses that significant effects were independent of each other.

χ^2 test statistics for heterogeneity or trend in the mortality rates were based on Poisson assumptions (Breslow & Day, 1987). Comparison of proportions was made by means of the conventional χ^2 test. Variation of mean packed cell volumes between subgroups was evaluated by analysis of variance.

The point prevalence rate of fever was considered as the proportion of child-days during which a child had fever. Multiplication by the number of days in a month yielded the number of fever days per child per month. Subsequent division by the median duration of one episode gave the number of episodes per child occurring that month. Summation of the results per month gave the number of episodes per child per year, estimating the number of episodes in the three months during which no observations were made from the monthly average number of episodes during the remaining nine months.

Cumulative rainfall figures per month were provided by a meteorological station 5 km from the centre of the project area.

Results

Relationship of fever and parasitaemia

Children with fever (cases) were compared to asymptomatic controls. For 21 cases a matching control could not be found on the same day that the case had been detected. Thin blood films were positive for 58% of cases and 41% of controls. However, 92 cases (28%) had parasitaemia levels exceeding 1000 IRBC/µl of blood, compared with 16 controls (5%). Taking children with a negative thin blood film as reference, odds ratios increased as the level of parasitaemia increased (Table 1). The risk of having a fever for a child with more than 20 000 IRBC/µl was 43 times greater than for a child with a negative smear. The odds ratio was significantly elevated for levels exceeding 1000 IRBC/µl; below this level the excess risk was small and statistically insignificant. This was also true when finer subdivisions were used, in particular when parasitaemia levels were categorized as 100–500, 500–1000, 1000–1500, 1500–2000 etc. Only 24% of cases with parasitaemias of 100 to 1000 IRBC/µl could be considered to be caused by malaria, while this percentage was 84 or higher among cases with parasitaemia levels exceeding 1000 IRBC/µl. The level of 1000 IRBC/µl was considered a pathogenic threshold above which fever could be assumed to have been caused by malaria, while below it such a diagnosis would be less probable. Consequently, data have been presented for fever associated with any parasitaemia and separately for fever with severe parasitaemia (>1000 IRBC/µl).

Rainfall

The first rain fell in late March (Fig. 1) and rainfall increased steadily until June followed by a sharp drop in July and August, the short dry season. A second peak occurred in October, the short rainy season, and virtually no rain fell in November and December.

Malaria morbidity

Overall prevalence of fever varied between 20 and 38 per thousand per month (Fig. 2). The point prevalence of fever cases with parasitaemia increased steadily from 12 per thousand in April to 19 per thousand in August. This rise coincided with the increasing rainfall but continued for 2 months after the rains had practically stopped. Prevalence then decreased but rose to a second peak in November, 2 months after the beginning of the short rainy season. The prevalence of cases with parasitaemia levels >1000 IRBC/µl rarely exceeded 10 cases per thousand; it was highest in July and August. The proportion of infected cases who had parasitaemia >1000 IRBC/µl was 81% in August but only 25% in May and June. Statistical tests detected no significant difference between the monthly prevalence rates of fever (χ^2=14·4, 8 degrees of freedom [df]) or of fever and parasitaemia (χ^2=10·5, 8 df). Prevalence of fever with severe parasitaemia (i.e. >1000 IRBC/µl) showed significant month-to-month variation (χ^2=23·4, 8 df).

Children younger than 6 months had fever, whether or not associated with parasitaemia, significantly less often than children aged 7–35 months (Table 2). Prevalence of fever associated with severe parasitaemia increased with age from birth to the second year of life. There was no significant difference in prevalence of fever or fever associated with (severe) parasitaemia between boys and girls.

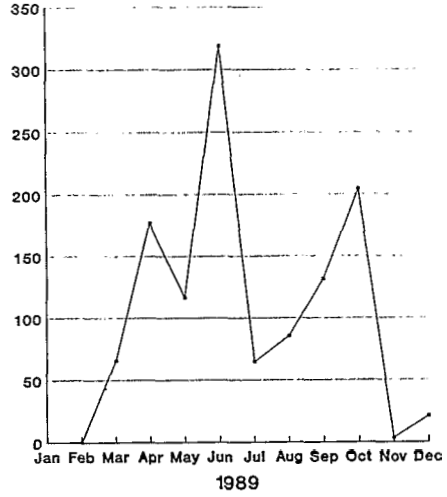

Fig. 1. Cumulative rainfall (mm) per month during one year on the coast of Benin, West Africa.

Table 1. Association of fever and malaria parasitaemia

Level of parasitaemia[a]	Cases of fever	Healthy controls[b]	Odds ratio[c]	95% confidence interval	AR[d]
≤100	136	177	1·00	–	
101–1000	97	108	1·32	0·89–1·95	24
1001–5000	41	12	6·30	2·25–15·03	84
5001–20000	21	3	12·06	2·93–49·69	92
>20000	30	1	43·27	5·42–345·25	98

[a]Information on parasitaemia was missing for 13 cases and 16 controls; expressed as number of infected red blood cells per µl of blood.
[b]Individually matched to cases for age, zone and day of visit.
[c]Computed by conditional logistic regression.
[d]Attributable risk (per cent) for each level of exposure.

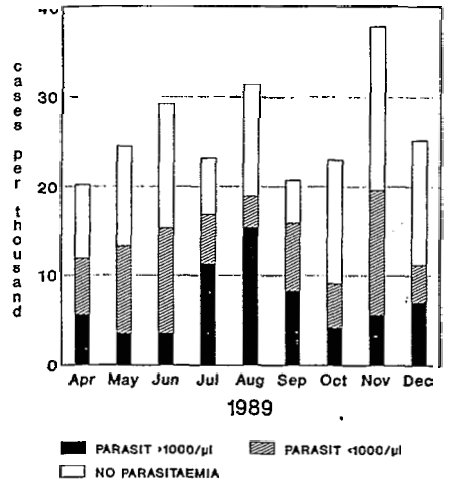

Fig. 2. Point prevalence of fever per month subdivided according to the associated parasitaemia level; Pahou, Benin, 1989.

Table 3. Packed cell volume (per cent) by level of parasitaemia for children with fever and individually matched controls[a]

Level of parasitaemia[b]	Cases of fever Mean	s.d.	Healthy controls[c] Mean	s.d.
≤100	36·6	4·5	36·5	4·2
101-1000	34·9	5·0	36·3	5·3
1001-5000	32·2	5·5	35·7	6·0
5001-20000	32·2	4·7	35·0	5·0
>20000	33·7	4·5	33·0	[d]
Total	34·9	5·0	36·4	4·7

[a]Numbers of observations in each category are given in Table 1; s.d.=standard deviation.
[b]Number of infected red blood cells per µl of blood.
[c]Matched for age, ecological zone and day of visit.
[d]Only one observation.

Fifteen thick blood films contained gametocytes; 4 of these films were from controls. Four of the 11 cases with gametocytes had negative thin films. Twenty-seven children had fever on 2 occasions, and 2 children had fever on 3 occasions.

Fever episodes had a median duration of 4 d. The average number of fever episodes per child per year was estimated as 2·4. Based on the distribution of parasitaemia levels among the controls, the population attributable risk, i.e. the proportion of all fever episodes caused by malaria, was estimated to be 33%.

Parasitaemia in afebrile children

The proportion of control children with a positive thin blood film varied from month to month between 32 and 53%. Thus seasonal variation was only slight and could not be distinguished from a purely random fluctuation. The proportion of infected controls was 29% among the 35 children below 6 months of age, compared to 43% among older children; it was 46% for boys and 36% for girls. These differences were not statistically significant. There was no difference between ecological zones.

Table 2. Malaria morbidity in a dynamic population of 1500 children visited monthly; Pahou, Benin, April to December 1989

	No. of visits	Fever[a] No.	Rate[e]	Fever[a] and parasitaemia[b] >100/µl No.	Rate[e]	>1000/µl No.	Rate[e]
Age (months)[d]							
0–5	2485	39	15·7[e]	24	9·7	7	2·8[f]
6–11	2381	72	30·2	36	15·1	14	5·9
12–23	3853	110	28·5	62	16·1	36	9·3
24–35	4191	114	27·2	66	15·7	35	8·4
Ecological zone							
Plateau	2325	65	28·0	35	15·1	23	9·9
Marshland	6055	146	24·1	86	14·2	38	6·3
Coastal strip	4530	126	27·8	68	15·0	31	6·8
Sex							
Male	6254	168	26·9	93	14·9	39	6·2
Female	6656	169	25·4	96	14·4	53	8·0
Total	12910	337	26·1	189	14·6	92	7·1

[a]Fever is defined as a rectal temperature>37·9°C.
[b]Information on parasitaemia was missing for 13 cases.
[c]Rate per thousand visits.
[d]Age could not be determined for two children.
[e]χ^2 for heterogeneity of rates: 14·9, 3 degrees of freedom, $P<0·005$.
[f]χ^2 for trend with age: 8·2, 1 degree of freedom, $P<0·01$.

Malaria and anaemia

Packed cell volume was lower in children with fever than in their matched controls. A break-down by level of parasitaemia (Table 3) revealed that cases and controls had similar PCVs in the absence of parasitaemia. When parasites were present, sick children had lower PCVs than healthy children for the same level of parasitaemia. A two-way analysis of variance controlling for level of parasitaemia showed that this effect was statistically significant (t=1·98, $P<0·05$).

Malaria mortality

There were 29 deaths during the study period among children less than 3 years of age, an annual

Table 4. Childhood mortality from all causes and from malaria in Pahou, Benin. Monthly follow-up April to December 1989

	Child-months	All causes Cases	All causes Rate[a]	Malaria Cases	Malaria Rate[a]
Age (months)					
0–5	2539	11	52·0[b]	1	4·7
6–11	2491	4	19·3	2	9·6
12–23	4026	8	23·8	5	14·9
24–35	4355	6	16·5	1	2·8
Ecological zone					
Plateau	2424	8	39·6	4	19·8
Marshland	6335	15	28·4	3	5·7
Coastal strip	4652	6	15·5	2	5·2
Sex					
Male	6497	16	29·6	7	8·8
Female	6913	13	22·6	2	3·5
Total	13410	29	26·0	9	8·1

[a]Rate per thousand children per year.
[b]χ^2 for trend 4·49, 1 degree of freedom, $P<0·05$.

death rate of 26·0 per 1000 (95% confidence interval 17·4–36·3). Nine were early neonatal deaths (within 7 d of birth). Nine deaths were probably due to malaria, i.e. 45% of non-neonatal deaths. The annual cause-specific death rate was 8·0 per 1000 (95% confidence interval 3·7–14·2). Malaria deaths were equally distributed over the months April to September but none was observed in October, November, or December. All-cause mortality decreased with age (Table 4) but malaria deaths occurred most frequently in the second year of life. Mortality within ecological zones was higher as distance from the sea increased. Rates were higher for boys than for girls. None of these risk differentials, with the exception of the decreasing trend with age, attained statistical significance due to the small number of cases.

Discussion

The purpose of the present study was descriptive: to measure morbidity and mortality from malaria in the child-population for which the Pahou PHC project was responsible. All 1500 children were visited monthly in their homes, thus avoiding any bias related to the (non-)utilization of medical care. The results demonstrated that malaria morbidity was present throughout the 9 months of observation from the beginning of the long rainy season to the first months of the long dry season. Febrile children with parasitaemia >1000 IRBC/µl could be found during every month of the study (Fig. 2) even though there was a clear peak in July and August. This peak followed the peak rainfall in June.

Observation could not be continued through the remaining months of the dry season due to logistical and financial constraints. Nevertheless, it seems likely that malaria transmission continued through the dry season and this is consistent with what is known of the vector populations. Studies in neighbouring areas have shown sympatry of *Anopheles gambiae s.s.* and *A. melas*. The former is more prevalent in the rainy seasons, when stagnant water gathers in the marshlands and the salinity of the lagoons diminishes. Although a less effective vector (BRYAN, 1983), the latter is sufficiently abundant to maintain malaria transmission during the dry season.

It is to be expected that in the dry season the proportion of fever cases due to malaria would be smaller than in the rainy season. Our inability to observe prevalence rates in January to March may therefore result in an upward bias of the population attributable risk, which was estimated at 33%. To approximate the magnitude of this bias, we hypothesized that, given our observation of no significant variation of fever rates over months, the prevalence of fever in January–March was the average of the 9 preceding months and that the distribution of cases and controls over parasitaemia levels was similar to the month of October, when prevalence of parasitaemia was lowest. Adding these hypothetical data to Table 1 resulted in a lowering of the population attributable risk by 8 percentage points. This provided a lower limit to our estimate.

To avoid under-reporting, field-workers received a small bonus for every case of fever they detected to compensate for the extra work involved. However, the technician measured body temperature a second time and could refuse to take a blood sample if the child had no fever. The second measurement, which might be hours after the first depending on the distance to be covered, was below 38·0°C for 33 cases who were nevertheless clearly ill. Often the mother had given aspirin or chloroquine or had bathed the child to bring body temperature down. Also, a natural variation of body temperature is to be expected as part of the disease process. It was verified that the distribution of such cases over categories of age, sex and ecological zone was no different from that in the total series.

An estimated malaria mortality rate of 8 per thousand per year compares well with reports from The Gambia (GREENWOOD *et al.*, 1987). The marked seasonality in malaria mortality which these authors reported was not observed in south Benin, however. As in The Gambia, malaria mortality in the present study was higher in the second year or life.

A so-called pathogenic or pyrogenic threshold of 1000 IRBC/µl in the present data distinguished those for whom malaria was the most likely cause of their fever from those for whom the cause probably had another origin. This value seems very low in comparison with other reports. TRAPE *et al.* (1985) suggested 5000 IRBC/µl, BAUDON *et al.* (1986) 10 000 IRBC/µl, and BENASSENI *et al.* (1987) 15 000 IRBC/µl. CHIPPAUX *et al.* (in press) estimated in Benin a threshold of 6000 for children under 3 years of age. One factor which may have caused these differences is that both BENASSENI *et al.* (1987) and BAUDON *et al.* (1986) recruited their controls from among patients attending an outpatient clinic. Observations in Benin suggest that patients, although afebrile, have higher levels of parasitaemia than healthy subjects visited at home. Thus the recruitment of 'hospital controls' would result in an inflated estimation of the pyrogenic threshold. It has been suggested that this threshold will vary according to the degree of immunity of the population studied (CHIPPAUX *et al.*, in press), and this is related both to host factors such as age and to transmission characteristics of the disease in a given locality. Lastly, different methods of determining parasitaemia levels may result in systematic differences which, however, do not invalidate the comparison of cases and controls as long as the same method is used for both groups.

The finding that PCV was lower in children with fever than in those without, for the same level of parasitaemia, might simply be due to cases having higher parasitaemia levels than controls within the same category. This does not seem to be the case, for a finer categorization of parasitaemia levels did not eliminate the difference, which remained of borderline significance ($P<0·06$). As fever is a consequence of the haemolysis of infected red blood cells, this finding is not surprising.

The present findings suggest that an effective malaria control programme can reduce fever episodes by 33% and mortality by 30 or 40%. Current PHC interventions in the study area include treatment with chloroquine by village health workers, chemoprophylaxis in pregnant women with 25 mg pyrimethamine per week, and partial chemoprophylaxis in children up to one year of age with 25 mg pyrimethamine per month following the recommendation by MORLEY (1977). The coverage of this latter programme is limited, however.

Possible future interventions to reduce the malaria burden include the introduction of impregnated bednets or impregnated curtains and more rigorous chemoprophylaxis. The population is already using bednets, so that the addition of impregnation would be a small and feasible step. People are also familiar with the concept of chemoprophylaxis and an intervention of this type would probably be well accepted. The success of such an intervention would depend on the capacity to distribute chemoprophylactic drugs systematically to individual children in ways that are at the same time practical, effective and cheap.

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