Fever episodes in a holoendemic malaria area of Tanzania: parasitological and clinical findings and diagnostic aspects related to malaria

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Abstract
All episodes of acute illness, in children aged 0–9 years, were registered during 3 years in a health clinic in a village of about 500 inhabitants in a malaria holoendemic area on the Tanzanian coast. Of 668 clinical episodes, 39% were diagnosed as malaria. There was no death. Only 5% of the children with malaria episodes came to the clinic after more than 3 days of symptoms. All 11 severe anaemias occurred among these children. Fever was reported in 98%, vomiting in 15%, and diarrhoea in 8% of the malaria episodes. Intermittent fever was reported in 98% of the malaria patients with more than one day of fever, compared to 4% of those with other febrile illnesses. Parasite densities ≥ 10 000/μl were found in 48% of the malaria episodes. Density ≥ 400/μl were found in 96% of the malaria episodes and in only 8% of the other febrile illnesses. The 16 malaria episodes (4%) with densities below that level were all in children under one year of age. The ability of the rural medical aid or the doctor to differentiate malaria episodes from other febrile illnesses without microscopical examination was limited. Although very few malaria episodes were missed, substantial over-diagnosis resulted in specificity values of only 13% and 52% for their respective malaria diagnoses. It is concluded that intermittent fever was strongly associated with malaria, but a high accuracy of malaria diagnosis in febrile children requires microscopical examination. Any parasitaemia in children below one year of age, or a parasite density of ≥ 400/μl in all children aged 1–9 years, were highly indicative of clinical malaria episodes. Early treatment appeared to prevent mortality from malaria.

Introduction
About 110 million cases of clinical malaria occur worldwide every year, with 80% in sub-Saharan Africa. The mortality is high, up to 2 million (WHO, 1989). Most are small children and nearly all fatal cases occur in rural areas before the children reach hospital. This is probably mainly due to difficulties in identification and treatment of the clinical episodes of malaria in peripheral health clinics.

Drug resistance is an increasing problem (BJöRKMAN & PHILLIPS-HOWARD, 1990). Chloroquine is no longer reliable as presumptive treatment and restricted use of antimalarial drugs to reduce development of resistance is increasingly important. The treatment of malaria is further complicated by the higher costs and limited availability of alternative drugs to chloroquine.

Thus early and correct diagnosis is a key issue in the control of malaria mortality and morbidity, in which peripheral health clinics and village health workers play a major role. However, the diagnostic performance of health units without microscopical examination, a common situation in rural health centres, has been little studied. Furthermore, even with microscopy, the diagnosis of clinical malaria is complex in endemic areas with a high prevalence of asymptomatic parasitaemias. The ability of mothers to identify clinical malaria episodes at an early stage is also important and needs to be evaluated. Two studies, in Nigeria (MOLINEAUX & GRAMICCA, 1981) and Thailand (HONGIVATANA et al., 1985), have reported low recognition and understanding of malaria disease whereas, in another study from Kenya, women showed a high recognition rate of malaria symptomatology (SPENCER et al., 1987).

We report the results of a 3 years study embracing all episodes of acute illness in children up to 9 years of age attending a clinic in a holoendemic village situated on the Tanzanian coast.

Material and Methods
Study area
Nyamisati is situated in the Rufiji delta in the mangrove swamps surrounding the outflow of Rufiji river into the Indian Ocean. Malaria is holoendemic (spleen rate in children 2–9 years >75%) and perennial, with peak transmission towards the end of the rainy season (March to May) (Unpublished observations). There is no insecticide spraying in the area, and only very limited use of bednets. No malaria chemoprophylaxis was distributed in the village during the time of the study.

From 1986 to 1988 there was a research project in the village studying different aspects of malaria. The research team consisted of a physician, a nurse and 2 locally trained assistants. A newly opened health care clinic operated in conjunction with the research team. The clinic was primarily run by a rural medical aid (RMA) with 2 years training. The clinic was open all working days from 08:00 to 16:00. After working hours the research team was directly available for emergency cases. Medical care was free. Drugs were available only through the clinic, thus all consultations and treatments were properly recorded.

Study groups
The study included all children aged up to 9 years attending the clinic from 1986 to 1988. All clinical episodes, whatever their aetiology, were recorded. Further, during May–November 1987 the mothers of the children attending the clinic with fever as the dominant symptom were asked what they thought was the child's disease. The RMA and the research physician then made their preliminary clinical diagnosis. These tentative diagnoses were then correlated to the final one based on the results of microscopy of blood smears.

Four general surveys were made between 1986 and 1989 including all inhabitants of the village. The parasitaemias of the 'healthy' (asymptomatic) children, in the relevant age group, in these surveys were used as reference comparison data.

Clinical evaluations
Anamnestic data were recorded for children with episodes of any disease and physical and appropriate laboratory examinations were done by the RMA or the research physician. Symptoms of fever, vomiting and diarrhoea were specifically asked about. The duration and type of fever were recorded for children with fever episodes. All those with fever as the main symptom were examined by the research team. Temperatures were measured with a Phillips electronic thermometer. An axillary temperature above 37.5°C was considered as elevated (SCHMITT, 1984; TRAPE et al., 1985). Fever episodes lacking symptoms suggesting diseases of other origin, and with microscopically confirmed parasitaemia, were considered as clinical malaria episodes.
Laboratory examinations
Thick and thin blood films from fingerprick blood were made at the time of all clinical episodes and stained with Giemsa's stain. After identification of the species, parasite counts were estimated against leucocytes assuming 8000 white blood cells per µL. A blood film was considered negative if no parasite was detected in 100 oil-immersion microscope fields of the thick film at a magnification of ×1000. Microscopy was performed by the same individual (the research physician) throughout the study.

Statistical methods
χ² analysis was performed to test differences in distributions and Student's t test to evaluate differences between means. Mean parasite densities were calculated as geometric densities, i.e. among those with detectable parasites only.

Ethical considerations
Ethical approval for all the different components of the malaria research project was obtained from the ethical committee of the National Institute of Medical Research, Tanzania and the Karolinska Institute, Sweden. The studies were explained several times directly to the villagers and the village authorities during meetings, attended by both men and women but on different occasions for cultural-religious reasons.

Results
Clinical episodes
In all, 249 children attended the clinic with 668 episodes of illness; 395 were diagnosed as clinical malaria (=malaria episodes) and 273 received other diagnoses, mainly pneumonia, meningitis, scabies, conjunctivitis and otitis. All the cases diagnosed as clinical malaria had positive blood slides. There was only one fatality, an infant who died from pneumonia.

The duration of fever in children with clinical malaria or other diagnoses is summarized in Table 1 and the number of days with fever before reaching the clinic is shown in Table 2. Ten children with high parasitaemias diagnosed as malaria did not complain of fever but came because of general weakness. Two had pica syndrome. All had had symptoms for more than 4 d, and most reported fever some time earlier.

The types of fever in relation to malaria are summarized in Tables 1 and 3. In children under 5 years old who reported fever, elevated temperature was recorded in 61% of the malaria episodes and 97% of other diseases (P<0.001). In 5–9 years old children, the temperature was elevated in 60% of malaria cases and 71% of others. Of the children with clinical malaria and fever for more than one day, 98% reported intermittent fever.

Severe manifestations of malaria were uncommon. No cerebral symptoms were observed in malaria patients during the study period although 10 mothers reported convulsions in connection with high fever in their children. Eleven small children had haemoglobin values under 70 g/litre, 3 having less than 50 g/litre. All had come to the clinic more than one day after the onset of fever. The haemoglobin level for the other children with malaria was 95 g/litre in the 0–4 years age group and 98 g/litre in the 5–9 years age group. The occurrence of less severe symptoms such as vomiting and diarrhoea is shown in Table 3. The difference in frequency of vomiting in children with clinical malaria compared with other diagnoses was significant in the under 5 years age group (P<0.05) but not in older children (P=0.1).

Plasmodium falciparum accounted for 97% of the malaria episodes and P. malariae for 3%. The geometric mean parasite densities in clinical malaria cases, children with febrile illness of other aetiology and asymptomatic children are shown in Table 4. The densities in malaria episodes were more than 10-fold higher than those in other febrile illnesses. Even the 'healthy' asymptomatic children had higher parasite densities than children with other febrile illness (P<0.05 for the age group 0–2 years).

Nine children with malaria had parasitaemias in excess of 200 000 parasites/µL. All came to be seen within 3 d after the onset of fever. Twenty-three children with >100 000 parasites/µL came to the clinic 1–7 after onset of symptoms. The frequencies of the different levels of parasitaemias in malaria and non-malaria patients are shown in Table 5. The malaria episodes with fewer than 400 parasites/µL all represented the first clinical episodes of 16 children below one year of age.

Diagnosis of febrile illness
Between May and November 1987 we studied the preliminary diagnostic abilities of the mothers, the RMA and the research physician for all children brought to the clinic with fever as the only or main symptom. The final diagnosis was based on the results of microscopy of blood smears. Of the 164 fever cases, 118 were classified as malaria episodes, 10 as influenza, 2 as common cold, 3 as probably tooth eruptions and the other 31 as fever episodes with unspecified diagnosis. Nine additional children came to the clinic with breathlessness as primary symptom in addition to fever. They were not considered as primarily 'fever patients' by the mothers and were all diagnosed by the RMA and doctor as pneumonias.

Only 2 mothers mentioned malaria as a possible diagnosis and the blood films from those children were negative.

The correlation between the preliminary diagnoses made by the RMA and the research physician after amnestic recordings and physical examination and the

Table 1. Reported fever in children 0–9 years old with malaria episodes and clinical episodes of other origin

<table>
<thead>
<tr>
<th>Number of Episodess</th>
<th>Number of Other clinical episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria episodes</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>395</td>
</tr>
<tr>
<td>Reporting continuing fever</td>
<td>273</td>
</tr>
<tr>
<td>1 d</td>
<td>83 (21%)</td>
</tr>
<tr>
<td>2–3 d</td>
<td>287 (75%)</td>
</tr>
<tr>
<td>Continuous ≤4 d</td>
<td>10 (3%)</td>
</tr>
<tr>
<td>Continuous ≥5 d</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

*The 10 children without reported continuing fever attended the clinic with general weakness and had been febrile earlier.

Table 2. Days of fever in children 0–9 years before attending the clinic with episodes of malaria

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>No. of children</th>
<th>No. of episodes</th>
<th>Mean duration (d)</th>
<th>≤1 d</th>
<th>Duration of fever 2–3 d</th>
<th>≥4 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2</td>
<td>270</td>
<td>2–0</td>
<td>204 (76%)</td>
<td></td>
<td>36 (80%)</td>
<td></td>
</tr>
<tr>
<td>2–3</td>
<td>45</td>
<td>2–5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–5</td>
<td>80</td>
<td>2–3</td>
<td>52 (65%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–9</td>
<td>395</td>
<td>2–1</td>
<td>292 (74%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Intermittent fever, diarrhoea, and vomiting were reported in children with malaria episodes and other febrile illnesses. Table 4 presents the mean parasite densities by age in children with malaria episodes and other febrile illnesses compared to asymptomatic children from four surveys. Results are expressed as numbers of parasites/μL (including positive blood films only), with 95% confidence intervals in parentheses.

Table 4. Mean parasite densities by age in children with malaria episodes and other febrile illnesses compared to asymptomatic children from four surveys

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Malaria episodes</th>
<th>Other febrile illnesses</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>9570 (8318, 11015)</td>
<td>10070 (8876, 18113)</td>
<td></td>
</tr>
<tr>
<td>3-4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6. Accuracy of clinical diagnosis of febrile episodes by a rural medical aid and by a physician

<table>
<thead>
<tr>
<th>Clinical diagnosis made by</th>
<th>Rural medical aid</th>
<th>Medical doctor</th>
</tr>
</thead>
<tbody>
<tr>
<td>True status</td>
<td>Malaria</td>
<td>Not malaria</td>
</tr>
<tr>
<td>Malaria</td>
<td>118</td>
<td>114</td>
</tr>
<tr>
<td>Not malaria</td>
<td>46</td>
<td>40</td>
</tr>
<tr>
<td>Total</td>
<td>164</td>
<td>154</td>
</tr>
<tr>
<td>Sensitivity (malaria diagnosis)</td>
<td>97%</td>
<td>99%</td>
</tr>
<tr>
<td>Specificity (malaria diagnosis)</td>
<td>13%</td>
<td>52%</td>
</tr>
<tr>
<td>Predictive value (malaria diagnosis)</td>
<td>74%</td>
<td>84%</td>
</tr>
<tr>
<td>Predictive value (not malaria diagnosis)</td>
<td>60%</td>
<td>96%</td>
</tr>
</tbody>
</table>

Discussion

Prompt and early treatment of a malaria episode is essential to prevent severe illness and death. In Nyamisati, despite easy access to medical care, only 21% of the children sick with malaria were brought to the clinic on the first day of illness. In Togo, altogether only 20% of all suspected malaria cases were brought to the clinic, and of those only 17% came on the first day of disease. Home treatment with antimalarial drugs was more common in Togo (DEMING et al., 1989). Fever of different aetiology is common in young children, and is not considered by the villagers as dangerous in itself. It is therefore easily understandable that mothers wait a couple of days to see if the child gets well.

No fatality from malaria occurred in our study. This suggests that, when the majority of children are treated within 2-3 d, the high mortality often due to malaria in such areas is prevented. Early treatment also probably prevented severe anaemia, which was seen only in children who came to the clinic more than 4 d after onset of illness. Whether early treatment also prevented cerebral complications is more uncertain as cerebral malaria was not seen in the village and seldom seen in the District Hospital (ROOTH, 1984). Perhaps cerebral malaria is uncommon in highly endemic areas.

In more than 95% of the malaria episodes, fever was reported as the main symptom. However, raised temperature was recorded in only 60% of cases. In 78%, fever was reported to be intermittent compared to only 2% in cases of other illness. Of the patients with malaria episodes of more than one day's duration, 98% reported intermittent fever. Many children were thus probably brought to the clinic in a non-febrile phase of an intermittent fever. When mothers report intermittent fever, this does not necessarily mean a cyclic fever with regular intervals but, rather, irregular fever. They often talk about 'night fever' and 'fever up and down'. The fever in P. falciparum episodes is frequently erratic. It can even be continuous at the beginning of the illness, becoming paroxysmal in the second or even the third recurrence (HARINASUTA & BUNNAG, 1988; KWATKOWSKI & GREENWOOD, 1989).

Many viral infections (e.g., influenza and measles) show fever as main symptom on the first day of illness before more specific catarrhal symptoms develop. Conversely, clinical malaria can present with a range of symptoms normally associated with other infections. Symptoms like vomiting and diarrhoea, seen almost as often in malaria episodes as in other febrile diseases, thus have no diagnostic value. Similar findings were reported in a study in Zimbabwe (BASSET et al., 1991).

We consider that a parasite density in excess of 400 parasites per μL is a valid cut-off level for diagnosing clinical malaria in 1-9 years old children with fever as the main symptom. Using this criterion, only 8% of febrile cases of other aetiology would be falsely diagnosed as having malaria and given unnecessary treatment. In infancy, the first clinical malaria episode often occurs at
low parasite density; here the cut-off point is the level of patency. Previously, 5000 parasites/µl has been suggested as a cut-off point for treatment (TRAPE et al., 1985). In Nyamisati, this would have resulted in missed diagnosis and treatment of one-third of the clinical malaria episodes.

The possibility of having both malaria and another febrile infection must be considered. Recently, however, we showed that at least 2 viral infections, measles and influenza episodes. Diagnosis and treatment of one-third of the clinical malaria episodes.

However, even an experienced physician identified only half of the febrile episodes not related to malaria infection without microscopic examination. In rural areas in sub-Saharan Africa, identification and treatment of most malaria episodes is made at village level without microscopic examination. Many febrile episodes are then falsely diagnosed as malaria, resulting in unnecessary treatment with antimalarial drugs. This may be reduced if a specific fever history is obtained from the mothers. However, microscopic examination should be promoted as much as possible in different health care settings for optimal diagnosis of clinical episodes of malaria.

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References


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Announcement

The Tropical Health and Education Trust

Fellows of the Society have always been actively involved in many tropical countries in establishing and developing medical schools and other training institutions. But some of these schools, particularly in poorer African countries, face severe hardships. Students have no books, there is no foreign exchange for journals, equipment lacks spares, research cannot be supported and external aid is directed towards primary health care.

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