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# Clinical algorithm for treatment of *Plasmodium falciparum* malaria in children

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## Summary

**Background** Identification of children who need antimalarial treatment is difficult in settings where confirmatory laboratory testing is not available, as in much of sub-Saharan Africa. The current national policy in Malawi is to treat all children with fever, usually defined as the mother's report of fever in the child, for presumed malaria. To assess this policy and to find out whether a better clinical case definition could be devised, we studied acutely ill children presenting to two hospital outpatient departments in Malawi.

**Methods** The parent or guardian of each enrolled child (n=1124) was asked a standard series of questions about the symptoms and duration of the child's illness. Each child was examined, axillary and rectal temperatures and blood haemoglobin concentrations were measured, and a giemsa-stained thick smear was examined for malaria parasites. Logistic regression procedures were used to identify clinical predictors of parasitaemia.

**Findings** High temperature (37·7°C or above), nailbed pallor, enlarged spleen, and being seen at one of the clinics rather than the other were associated with an increased risk of malaria parasitaemia in univariate analyses. A revised malaria case definition of rectal temperature of 37·7°C or higher, splenomegaly, or nailbed pallor was 85% sensitive in identifying parasitaemic children and 41% specific; the corresponding sensitivity and specificity for the nationally recommended definition that equates mother's history of fever with malaria were 93% and 21%. The revised case definition had 89% sensitivity in identifying parasitaemic children with haemoglobin concentration below 80 g/L and 89% sensitivity in identifying children with parasite density greater than 10 000/μL, characteristics that indicate a clear need for antimalarial treatment.

**Interpretation** These results suggest that better clinical definitions are feasible, that splenomegaly and pallor are helpful in identifying children with malaria, and that much overtreatment of children without parasitaemia could be avoided.

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## Introduction

In malarious areas, health workers frequently have to decide whether or not to prescribe an antimalarial drug to an ill child. Under ideal conditions, a blood smear from each child with suspected malaria would be examined and children with parasitaemia would be treated. In Malawi and in most countries of sub-Saharan Africa where malaria is holoendemic or hyperendemic, microscopic diagnosis is rarely available and clinical signs and symptoms have to be used to identify the children who need treatment for malaria. The Ministry of Health of Malawi has promoted a policy of presumptive antimalarial treatment for all children with fever or with a history of recent fever, consistent with WHO recommendations.[1] This policy was designed to identify a high proportion of children with malaria parasitaemia and to be very sensitive, so that those at risk of developing severe malaria receive treatment. In practice, because fever is reported in

a high proportion of children brought to health facilities, application of this broad clinical definition for malaria results in the treatment of many children who do not have parasitaemia. Also, this approach may mean that children with febrile illness are not adequately assessed for other treatable causes. In a 1992 study from Malawi, a third of children who met this case definition for malaria also had clinical evidence of pneumonia.[2]

After efficacy studies showed that chloroquine was no longer effective therapy for malaria,[3] the Malawi Ministry of Health's recommended first-line treatment of acute uncomplicated malaria was changed from chloroquine to sulfadoxine-pyrimethamine (March, 1993). A specific case definition for malaria is even more important in Malawi than in countries where chloroquine is used because sulfadoxine-pyrimethamine is more expensive than chloroquine and has a higher rate of serious and fatal side-effects.[4,5] In addition, limitation of the use of sulfadoxine-pyrimethamine would, in theory, reduce the rate at which resistance to this drug develops.[6] Any replacement for sulfadoxine-pyrimethamine is likely to be even more expensive and may have more severe side-effects.

A more specific clinical algorithm would reduce unnecessary treatment, save money, and oblige health workers to examine children who do not need antimalarial treatment more thoroughly than is current practice. We examined the effect of the current national policy on prescribing for malaria and sought to devise a better clinical definition for malaria.

## Methods

The study was carried out at two hospital outpatient departments. Mangochi District Hospital, located on the southern shores of Lake Malawi at 250 m elevation, is a 250-bed public hospital where medical care is provided free of charge; Nkhoma Hospital, located in the central highlands at 1250 m elevation, is a 250-bed private mission hospital where a small fee (US$ 0·25) is charged for health-care services.

At each site, a systematic sample of children under 5 years old brought to the clinic because of an illness were eligible for enrolment. We invited every fourth child at Mangochi District Hospital and two of every three children at Nkhoma Hospital to participate. Patients were enrolled over 8 weeks during the high-transmission season for malaria in April and May, 1993.

Children were selected for the study after their routine assessment by a medical assistant; the study did not interfere with routine clinic practice. After informed consent was obtained from the child's mother or guardian, information was collected on the child's age and sex, reasons why he or she had been brought to the clinic, duration of illness, whether the child had fever or cough, and the duration of these symptoms. Weight, height, and rectal and axillary temperatures were measured. Physical examination by one of three experienced clinical officers included an assessment of the nailbeds for pallor and an assessment of the spleen for enlargement. A blood sample obtained by fingerprick was used to measure haemoglobin and to prepare a giemsa-stained thick blood film. Stained blood smears were examined by experienced microscopists, and 50 high-power fields were examined before a slide was judged to be without parasites. For slides that had *Plasmodium falciparum* parasites, leucocytes and malaria trophozoites were counted; parasite densities were calculated assuming a leucocyte density of 6000/μL. Haemoglobin concentration was measured by spectrophotometry (HemoCue system, Mission Viejo, California, USA). The clinical examiner did not know the results of laboratory tests until after the physical examination findings had been recorded. Final diagnoses, treatment, and whether the child required admission to hospital were all decided after laboratory results were available.

| Risk factor | % of parasitaemic children with risk factor | Odds ratio (95% CI) | |
|---|---|---|---|
| | | Univariate analyses | Multiple logistic regression |
| Examined at Nkhoma hospital | 60 | 3·75 (2·9–4·85) | 4·07 (3·03–5·46) |
| Splenomegaly | 48 | 3·33 (2·54–4·36) | 3·52 (2·58–4·79) |
| Nailbed pallor | 42 | 1·85 (1·43–2·39) | 1·93 (1·43–2·61) |
| History of fever | 93 | 3·37 (2·32–4·88) | 1·86 (1·21–2·86) |
| Rectal temperature (per °C) | · · | 1·59 (1·41–1·79) | 1·41 (1·24–1·62) |
| Chills | 22 | 1·89 (1·37–2·63) | * |
| Axillary temperature (per °C) | · · | 1·54 (1·37–1·72) | * |
| Complaint of fever | 74 | 1·43 (1·11–1·86) | * |
| Age (per month) | · · | 1·02 (1·01–1·03) | * |

*Not included in final model.

Table 1: **Univariate analyses and multivariate logistic regression models for clinical findings predictive of *P falciparum* parasitaemia**

Univariate logistic regression was used to examine individual clinical findings for association with malaria parasitaemia. Variables associated with parasitaemia in univariate analyses were included in stepwise multivariate logistic regression procedures designed to create a model with the fewest clinical indicators possible. Terms were entered into the model and remained in only if they were statistically associated with *P falciparum* parasitaemia ($p<0·05$). Both forward selection and backward elimination methods were used. Based on the results of the multivariate logistic regression, the sensitivity and specificity of a revised case definition were compared with those of the case definition recommended in the national policy, that ill children with fever or history of fever should be presumed to have malaria. In addition, the sensitivities of these clinical definitions to identify children with parasitaemia and haemoglobin concentration below 80 g/L and to identify children with malaria parasitaemia density greater than 10 000/μL were compared.

The study protocol was approved by the Malawi National Research Review Committee.

## Results

During the 8-week study period, 1124 children under 5 years old were enrolled—592 (53%) from Mangochi and 532 (47%) from Nkhoma. The median age was 13 months (range <1–60 months), and 588 (53% of those with recorded sex) were boys. Mothers reported fever as part of the illness in 983 (88%) children, although only 406 (37%) children had rectal temperature of 38°C or higher. 672 (60%) children had *P falciparum* parasitaemia, with a geometric mean density of 4034 parasites/μL; 76% of children at Nkhoma were parasitaemic compared with 45% at Mangochi.

In univariate analyses (table 1), history of fever reported by the mother, examination at Nkhoma Hospital, having a complaint of fever, rectal and axillary temperatures as continuous variables, enlarged spleen, and pallor of the nailbeds were all associated with malaria parasitaemia. The strongest association with malaria parasitaemia was examination at Nkhoma Hospital; this finding accords with the difference in percentage with parasitaemia between the hospitals. The second strongest association was a history of fever reported by the mother.

Stepwise multiple logistic regression modelling was used to identify clinical findings that could be used, in combination, to predict which children had *P falciparum* parasitaemia. Forward selection and backward elimination procedures generated the same model, indicating the robustness of the modelling procedure. The relation of parasitaemia to clinical signs did not differ significantly between the two hospitals; additionally, no other second-order interaction terms were associated with a child's having malaria parasitaemia. Examination at Nkhoma

| Case definition | To identify children with any *P falciparum* parasitaemia | | To identify children with parasitaemia and haemoglobin <80 g/L* | To identify children with parasite density >10 000/μL blood* |
|---|---|---|---|---|
| | Sensitivity | Specificity | Sensitivity | Sensitivity |
| National policy (any history of fever) | 93% (624/672) | 21% (93/452) | 97% (286/296) | 95% (272/285) |
| Rectal temperature ≥37·7°C or nailbed pallor or splenomegaly | 85% (570/672) | 41% (184/452) | 89% (262/296) | 89% (254/285) |

*Specificities not calculated because non-anaemic, parasitaemic children and children with parasite densities under 10 000/μL may need antimalarial treatment.

Table 2: **Sensitivities and specificities of various case definitions for malaria**

Hospital, increasing rectal temperature as a continuous variable, splenomegaly, and nailbed pallor remained associated with parasitaemia after elimination of non-associated factors (table 1). The Hosmer-Lemeshow statistic indicated a non-significant lack of fit ($\chi^2$=9·902 with 8 degrees of freedom, p=0·271). Increasing axillary temperature was only slightly less valuable as an indicator than was rectal temperature; the overall $\chi^2$ value for the model fell from 260·2 to 253·2 when axillary temperature was substituted for rectal temperature.

Because health workers require a dichotomous variable to identify children with "high" temperatures, we sought a threshold value to select children who need treatment for malaria. The mean rectal temperature for children with malaria parasitaemia was 38·1°C and the mean for children without parasitaemia was 37·5°C; the midpoint between these two values was 37·8°C. We next evaluated discrete rectal temperature thresholds (every 0·1°C from 37·0°C to 38·8°C) as predictors of a child's having malaria parasitaemia. We used the $\chi^2$ test to identify the temperature giving the maximum discrimination between parasitaemic and non-parasitaemic children. A rectal temperature threshold of 37·7°C gave the highest $\chi^2$ value (58·1). The maximum $\chi^2$ value was achieved at this temperature threshold at both Mangochi District Hospital ($\chi^2$=40·6) and at Nkhoma Hospital ($\chi^2$=7·9). The $\chi^2$ method gave a nearly identical result to the midpoint between the means of parasitaemic and non-parasitaemic children, but it was a slightly more sensitive threshold. For these reasons, high rectal temperature was defined as 37·7°C or higher in subsequent analyses. The maximum $\chi^2$ value for axillary temperature was at 37·4°C.

From these results, the signs that were included in our revised case definition to identify children with malaria parasitaemia were rectal temperature of 37·7°C or above, splenomegaly, or nailbed pallor. History of fever, although associated in the final multivariate logistic regression model, was excluded from this definition, because its inclusion would have meant identifying nearly all children as having malaria parasitaemia. In the composite model the addition of mother's history of fever contributed little, increasing the model $\chi^2$ value from 252·1 to 260·2. According to the final model, a child with splenomegaly, rectal temperature of 37·7°C or higher, nailbed pallor, and history of fever would have a 95% likelihood of having parasitaemia; a similar child with splenomegaly, rectal temperature of 37·7°C or higher, and nailbed pallor, but without a history of fever would have a 92% likelihood of having parasitaemia.

The revised malaria definition would have correctly identified 85% of children with parasitaemia as having malaria and 41% of those without parasitaemia as not having malaria (table 2). The current national policy would have correctly classified 93% of children with malaria parasitaemia but only 21% of children without parasitaemia (table 2). The revised definition identified 89% of children who were parasitaemic and had haemoglobin concentrations of 80 g/dL or lower and 89% of children with parasite densities greater than 10 000/μL.

If the revised definition had been used, 102 children with parasitaemia (15%) would have been erroneously classified as not having parasitaemia, 54 more than were misclassified by the national policy case definition. Children with parasitaemia who would not have been identified by the revised definition had a median age of 18 months, a median haemoglobin concentration of 95 g/L (compared with 81 g/L for children whom the case definition identified, p<0·001), and a geometric mean density of 1536 trophozoites/μL (compared with 4798/μL for children identified, p<0·001).

## Discussion

In this study we devised a clinical case definition for malaria that health workers could use to distinguish between children needing antimalarial treatment and those not needing such treatment. Studies attempting to develop an improved clinical case definition for malaria have been complicated by multiple definitions of fever and by the difficulty of identifying which children benefit from antimalarial therapy. History of fever is a non-specific finding, present in almost all children sick enough to be brought to clinic. Measured raised temperature alone is a more specific indicator of parasitaemia than history of fever, but is still inadequate because of poor sensitivity. Identification of children who need treatment for malaria requires distinction of malaria parasitaemia causing disease from parasitaemia that is not causing disease in a child ill from some other cause. The more insidious process that occurs with chronic and recurrent infection leading to severe anaemia may be a more important health consequence of malaria in Africa than acute febrile attacks.[7,8] Because the clinical consequences of malaria infection depend greatly on the clinical immunity of the patient, it is difficult to be certain that any specific malaria infection in an African child is or is not causing a health problem. Even with this uncertainty, infections of higher density are more likely to be associated with an acute febrile illness,[9–12] and, for anaemic children, effective antimalarial therapy treats malaria-associated anaemia.[3]

In our study, we defined malaria as malaria parasitaemia, even though some cases of parasitaemia might have been infections that would have resolved without complications or the need for treatment. In defining malaria as parasitaemia, we began with the assumption that children who do not have malaria parasitaemia do not need treatment for malaria. The logistic regression procedures identified three clinical signs—high rectal temperature, splenomegaly, or pallor of the nailbeds—that could be used in a clinical case definition to identify children with parasitaemia. Use of

this definition would have doubled the proportion of non-parasitaemic children who were correctly classified over that from the current definition. Use of this would therefore limit antimalarial treatment to children most likely to benefit. Some children with parasitaemia would not have been identified by the revised case definition, although it identified nearly 90% of children in greatest need of treatment for malaria, those with anaemia and those with higher-density infections. An assessment of antimalarial therapy for children not meeting the case definition is needed to evaluate the consequences of this misclassification. Such a trial would be analogous to a study that showed that children with mild acute respiratory infection did not require antimicrobial therapy.[13]

The proposed, new case definition requires health workers to measure temperature and examine for splenomegaly and nailbed pallor. Although inclusion of these three signs in any physical examination of an ill child might seem to be obvious, adequate performance should not be assumed. Surveys of health facilities in Cote d'Ivoire[14] and Angola[15] showed that body temperature was measured in only 68% and 2%, respectively, of children who were brought to clinic because of fever. Similarly, training to identify children with splenomegaly, although included in current curricula for health workers in Malawi, will require additional emphasis;[16] inter-observer variability and insensitivity have been particular drawbacks.[17] Standardisation and training of health workers to assess children for nailbed pallor may be the most difficult part of the case definition to implement; previous efforts that have used pallor to diagnose anaemia have had mixed results.[18–22] The severity of anaemia among young African children is greater than in the populations where clinical signs of anaemia have been equivocal: thus, severe anaemia in Africa may be easier to identify than previous studies suggest. Overdiagnosis of pallor or splenomegaly would tend to lower the specificity of the definition and reduce the proportion of non-parasitaemic children correctly classified. Use of an axillary temperature threshold rather than the rectal temperature threshold would affect the definition very little, so facilities that generally use axillary temperature measurement need not change their practice.

The epidemiology of malaria in Malawi, characterised by a long transmission season and rates of 10 to 50 infectious bites per person annually (Malawi Ministry of Health, unpublished) is similar to that in much of sub-Saharan Africa. Although these characteristics of malaria in Malawi should make our results applicable elsewhere, this study took place at only two sites during a single high-transmission season; results might be different during times of the year when transmission is less intense or in other populations. Even if similar sensitivity and specificity were found, the lower prevalence of malaria during the low-transmission season would lower the positive predictive value for this (and any other) case definition—children meeting the proposed case definition during the dry season would be less likely to have malaria than during the high-transmission wet season.

The associations we found between high temperature, splenomegaly, and *P falciparum* parasitaemia are supported by several previous investigations.[8,10] Previous case definition studies, however, whether evaluations of existing malaria definitions and or attempts to develop new case definitions, have produced less consistent results, mostly because of differences in methods and objectives. A study carried out in Niger found that febrile children with parasitaemia were more likely to have a high fever, illness lasting less than 3 days, and no other clinically evident cause of fever than were febrile children without parasitaemia.[12] The Niger study identified clinical signs that distinguished parasitaemic from non-parasitaemic febrile children. Children without fever were assumed not to need treatment for malaria. Bassett et al,[23] in Zimbabwe, were unable to identify any signs that would improve the clinical diagnosis of malaria;[23] however, their study included only children who were clinically suspected of having malaria. Definitions that require parasite density,[24,25] as measured by microscopic examination of a blood film, are impracticable in most health centres and hospitals in Africa.

Our results show that children who have malaria parasitaemia can be identified by health workers who can recognise high body temperature, splenomegaly, and nailbed pallor. Reliance on universal or near-universal treatment, such as occurs when the mother's report of fever in the child is used to decide on treatment,[26] is unnecessary and leads to treatment of many children who do not have parasitaemia. Although the wider availability of microscopy would greatly improve malaria treatment practices in African hospitals and clinics, better dignosis of malaria cannot wait until microscopy is available.

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# Long-term diabetogenic effect of single pregnancy in women with previous gestational diabetes mellitus

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## Summary

**Background** Pregnancy is associated with marked insulin resistance that seems to have little, if any, impact on the long-term risk of non-insulin-dependent diabetes mellitus (NIDDM) in the general population. The aim of this study was to test whether pregnancy would alter the risk of NIDDM among women with a high prevalence of pancreatic β-cell dysfunction, as indicated by a history of gestational diabetes mellitus.

**Methods** The cohort consisted of 666 Latino women with gestational diabetes attending a high-risk family planning clinic. They were followed up for up to 7·5 years, during which time they were weighed and underwent an oral glucose-tolerance test annually. The effect of an additional pregnancy, and of other risk factors for diabetes, was examined.

**Findings** 87 (13%) of the women completed an additional pregnancy. 80 of those women did not have NIDDM immediately after the additional pregnancy and their subsequent annual incidence rate of NIDDM was 30·9% (95% CI 12·7–49·1), more than 2·5 times the annual incidence rate of NIDDM in the cohort overall (11·9%; 95% CI 10·0–13·8). Proportional hazards regression analysis using the presence or absence of an additional pregnancy as a time-dependent variable confirmed that an additional pregnancy increased the rate ratio of NIDDM to 3·34 (95% CI 1·80–6·19), compared with women without an additional pregnancy after adjustment for other potential diabetes risk factors during the index pregnancy (antepartum oral glucose tolerance, highest fasting glucose, gestational age at diagnosis of gestational diabetes) and during follow-up (postpartum body mass index [BMI], and glucose tolerance, weight change, breast feeding, and months of contraceptive use). Weight gain also was independently associated with an increased risk of NIDDM; the rate ratio was 1·95 (95% CI 1·63–2·33) for each 10 lb (4·5 kg) gained during follow-up after adjustment for the additional pregnancy and the other potential risk factors.

**Interpretation** The study showed that a single pregnancy, independent of the well-known effect of weight gain, accelerated the development of NIDDM in a group of women with a high prevalence of pancreatic β-cell dysfunction. This finding implies that episodes of insulin resistance may contribute to the decline in β-cell function that leads to NIDDM in many high-risk individuals.

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*See Commentary page 208*

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## Introduction

Pregnancy has long been known to be "diabetogenic" in the sense that the progressive metabolic changes of gestation lead to marked insulin resistance,[1–3] compensatory hyperinsulinaemia,[2,3] and a slight worsening of glucose tolerance by the third trimester.[4,5] However, most studies indicate that the short-term metabolic alterations of pregnancy have little,[6–9] if any,[7,10] effect in increasing the risk of diabetes in non-pregnant individuals. In a review of the topic published in 1978, West[7] concluded that "present evidence does suggest that the effect of pregnancy [on the risk of non-insulin-dependent diabetes mellitus (NIDDM)] is probably negligible or trivial in many societies". More recently, Manson et al[10] reported that there was no independent relation between parity and the risk of NIDDM in a survey of more than 113 000 American nurses of varied ethnicity, while Kritz-Silverstein et al[9] reported a weak association between parity and the risk of NIDDM in a cohort of 1186 white women in the US. In the latter study, the association was independent of obesity, but it seemed to be limited to women who had had more than five pregnancies.

The fact that parity has little, if any, impact on the risk of NIDDM in the general population is consistent with the concept that most women have sufficient pancreatic β-cell reserve to tolerate repeated episodes of insulin resistance without developing diabetes. By contrast, most