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Clinical predictors of malaria in Gambian children with fever or a history of fever

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Abstract

Diagnosis of malaria in children is difficult without laboratory support because the symptoms and signs of malaria overlap with those of other febrile illnesses such as pneumonia. Nevertheless, in many parts of Africa diagnosis of malaria must be made without laboratory investigation. Therefore, a scoring system has been developed to assist peripheral health care workers in making this diagnosis. Four hundred and seven Gambian children aged 6 months to 9 years who presented to a rural clinic with fever or a recent history of fever were investigated. A diagnosis of malaria was made in 159 children who had a fever of 38°C or more and malaria parasitaemia of 5000 parasites/μL or more. Symptoms and signs in children with malaria were compared with those in children with other febrile illnesses to identify features which predicted malaria. Symptoms and signs were incorporated into various logistic regression models to test which were best independent predictors of malaria and these regression models were used to construct simple scoring systems which predicted malaria. A nine terms model predicted clinical malaria with a sensitivity of 89% and a specificity of 61%, values comparable to those obtained by an experienced paediatrician without laboratory support. The ability of peripheral health care workers to diagnose malaria using this approach is now being investigated in a prospective study.

Keywords: malaria, *Plasmodium falciparum*, diagnosis, predictor models, children, The Gambia

Introduction

In areas of high endemicity, diagnosis of clinical malaria can be difficult even when laboratory support is available because a high proportion of the population is parasitaemic. Malaria parasites are more likely to be the cause of a patient's illness when they are present at a high rather than a low density (TRAPE *et al.*, 1985; BAUDON *et al.*, 1986; EJEZIE & EZEDINACHI, 1992) and an elegant model has been devised (ARMSTRONG SCHELLENBERG *et al.*, 1994; SMITH *et al.*, 1994) which allows definition of the parasite density which gives the optimum separation between clinical cases of malaria and asymptomatic infections in a specific community. Thresholds are influenced by the level of malaria endemicity and they are age-dependent (ROGIER *et al.*, 1996).

Unfortunately, in many parts of the developing world, malaria must be diagnosed and treated without the benefit of any laboratory support. Fever, a cardinal symptom of malaria, is often equated with malaria and treatment given accordingly. However, when this practice is followed, a large number of patients may be inappropriately treated with an antimalarial drug, especially outside peak malaria transmission seasons (OLIVAR *et al.*, 1991; SOWUNMI & AKINDELE, 1993). For this reason attempts have been made to develop guidelines which can improve the diagnosis of malaria by evaluating symptoms and signs. Such attempts have met with mixed success. One of the first such studies was an investigation of children in the Republic of the Congo by TRAPE *et al.* (1985) which showed that the degree of fever was a useful predictor of malaria, as were the absence of otitis, tonsillitis or clinical signs of pneumonia. In a study in Mali, ROUGEMONT *et al.* (1991) showed that high fever of short duration was more likely to be associated with malaria than with other illnesses. In The Philippines, GOMES *et al.* (1994) investigated whether the nature of a patient's fever could help to discriminate between malaria and other febrile conditions. In that community, a history of rigors and sweating was a strong predictor of malaria, especially in children. Similarly, in Tanzania, ROOTH & BJÖRKMAN (1992) found that a history of intermittent fever was strongly associated with a diagnosis of malaria. Other studies have investigated whether consideration of symptoms and signs other than fever can help in the diagnosis of malaria. In Zimbabwe, BASSETT *et al.* (1991) were unable to identify any useful additional predictor and studies undertaken in Malawi (REDD *et al.*, 1992) and The Gambia (O'DEMPSEY *et al.*, 1993) showed a considerable overlap in the symptoms and signs of malaria and pneumonia. However, in the latter study, anaemia and splenomegaly showed some specificity for a diagnosis of malaria. In Papua New Guinea, splenomegaly, a normal stool and the absence of a cough were found to be positive predictors of malaria in children (GENTON *et al.*, 1994). In the most recent study, undertaken in Malawi (REDD *et al.*, 1996), a combination of rectal temperature of 37·7°C or higher, splenomegaly and nail pallor was almost as sensitive as a conventional diagnosis based on a history of fever, but twice as specific.

To explore further the potential of symptoms and simple clinical signs to improve the clinical diagnosis of malaria we undertook a further study in Gambian children in which we used a different approach, devising a 'malaria score' that can be used to indicate the probability of an individual patient having malaria.

Materials and Methods

Study area

The study was undertaken in the town of Farafenni and the surrounding villages in The Gambia, on the north bank of the River Gambia about 100 km from the coast, between September 1993 and March 1994. This period included high and low malaria transmission seasons, but only data collected in the malaria transmission season are presented in this paper as only 10 cases of malaria were detected during the dry season period of surveillance, making determination of predictors impractical. The study area is flat Sudan savannah with some mangrove swamps and marshy flatland close to the river. The flatland is often flooded, providing suitable breeding sites for *Anopheles gambiae* s.s. and *An. melas*, the main malaria vectors in the area (BRYAN, 1979). The climate is typical of the sub-Sahel with a short period of rain (July–October) and a dry season covering the remainder of the year. In 1993, the rainfall recorded in the study area was 946mm.

Farafenni town has a government health centre staffed by a team of doctors and trained nurses, 2 private clinics and a number of pharmacies. The health centre

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has facilities for in-patient care and is the main referral centre for an area which serves a population of about 30000 people.

Study population

The study population comprised children aged 6 months–9 years who attended the Farafenni health centre or a clinic operated by the UK Medical Research Council (MRC) at its Farafenni field station. Screening of children was carried out at each clinic every morning by 2 trained clinic assistants. A clinic assistant obtained a history from the mother or carer of each child brought to the clinic. If a history of fever was given, the axillary temperature was measured with a digital clinical thermometer. A child was eligible for recruitment to the study if there was fever (body temperature ≥37·5°C), or a history of fever during the preceding 3 d and no other obvious cause for the fever such as an abscess. Children with a severe, acute illness requiring in-patient treatment or those with a chronic disease were excluded.

If consent to join the study was given, a finger-prick blood sample was collected for parasitological and haematological examination. The study clinician (B.O.O.), who did not know the laboratory results, interviewed the mother about her child's illness and conducted a clinical examination according to a set protocol. A prescription was then given based on his clinical diagnosis. The child was then seen by an experienced nurse who had previously checked the results of the blood film examination and the packed cell volume (PCV). Adjustments to the child's treatment were made according to the laboratory results necessary: for example, chloroquine was given if a blood film contained malaria parasites but malaria had not been diagnosed by the paediatrician. Children who had clinical features of malaria and a positive blood film were treated with chloroquine (25 mg/kg over 3 d). Children with an acute respiratory infection were given co-trimoxazole or penicillin. Children who required admission or parenteral treatment were referred to the health centre. Children were asked to report back to the clinic one month after presentation if they remained well but to return earlier if satisfactory progress was not made after the initial treatment.

Laboratory methods

The PCV was determined using blood collected directly into capillary tubes. Thick blood films were stained with Giemsa's stain and 100 high power fields (HPF) were examined before a film was considered negative. If more than one parasite per HPF was present, the number per HPF was recorded and the number per μL was calculated assuming that one parasite per HPF was equivalent to 500 per μL (GREENWOOD & ARMSTRONG, 1991).

Statistical methods

Study children were categorized according to clinical and laboratory findings as cases of malaria or of another diagnosis. A case of malaria was defined as an illness characterized by an observed axillary temperature of 38·0°C or more and *Plasmodium falciparum* parasitaemia ≥5000 per μL. This cut-off level was chosen on the basis of previous analyses which indicated that parasitaemia of this level is the fever threshold in Gambian children (ARMSTRONG SCHELLENBERG *et al.*, 1994). The sensitivity and specificity of each symptom and sign in predicting a diagnosis of malaria as defined above was calculated, together with a χ^2 statistic. This information was reviewed by 3 physicians and 2 statisticians who selected the most promising symptoms and signs for use in the next stage of the analysis. Logistic regression was used to model the probability of malaria in terms of these variables. Each selected symptom or sign was defined in such a way that it was a positive predictor of malaria and hence had a positive coefficient in the regression model. Backward elimination was used to achieve a subset of symptoms and signs which were independent predictors of malaria ($P<0·05$). A 'malaria score' was calculated from this subset in 3 ways: (i) a simple count of symptoms and signs present in each child, (ii)the sum of the rounded (to integers) regression coefficient for the symptoms and signs present, and (iii)the sum of the exact regression coefficients for the symptoms and signs present, with the sum rounded to integers. The third method, although not practical for use in the field, was used as a standard against which to compare the other scoring methods. Additionally, reduced logistic regression models were derived by eliminating the weakest predictor of malaria at each stage. Six terms and 4 terms models were compared with the full model.

Comparisons were made between the 3 scoring methods by calculating sensitivity and specificity for each algorithm with different cut-off points. These were plotted on receiver–operator characteristic (ROC) curves, although tables focused on algorithms with high sensitivities and specificities were found to be more useful for the purposes of assessing the algorithms. Further analysis was undertaken to examine the effect of age on sensitivity and specificity. Children were subdivided into 3 age groups (6–11 months, 1–4 years and 5–9 years) and a Mantel–Haenszel odds ratio was calculated to investigate whether age was a confounding factor. Test were also performed to examine whether there were significant interactions with age.

The above procedure was then repeated in order to model high parasitaemia (≥5000 per μL) in terms of symptoms and signs. For this set of models axillary temperature was included as a potential predictor.

Results

Study children

Four hundred and seven children aged 6 months–9 years who presented to clinics in Farafenni with a febrile illness during the malaria transmission season were studied; 159 children who had an axillary temperature of 38·0°C or more and *P. falciparum* parasitaemia at a density of 5000 per μL or more were diagnosed as clinical cases of malaria and the remaining 248 children were considered as cases of other febrile illnesses, mainly acute lower respiratory tract infections. The main clinical characteristics of children in the 2 groups are shown in Table 1. Children with malaria were older than children with other febrile illnesses and they had a higher temperature and a lower mean PCV.

Table 1. Clinical features of children diagnosed as cases of malaria and those with other febrile illnesses

	Malaria	Other diagnoses
No. of children	159	248
Sex (male:female)	88:71	129:119
Age (months)[a]	40·6±25·4	28·8±23·6
Duration of illness (d)[a]	3·5±2·7	3·9±4·3
Temperature (°C)[a]	39·4±0·7	38·4±1·1
Parasitaemia		
Rate (%)	100	34
Density (per μL)[b]	41304 (5000–300000)	16 (0–250000)[c]
Packed cell volume (%)[a]	29·6±5·7	31·4±5·4

[a]Mean±SD.
[b]Geometic mean (range in parentheses).
[c]One child with a very high parasite density was not counted as a case of malaria as he was afebrile and did not have a history of recent fever.

Derivation of algorithms

A total of 16 symptoms and 32 clinical signs was investigated as possible predictors of clinical malaria. (Details of these are available on request from the authors.) Four symptoms and 12 clinical signs were selected as

the most promising predictors of malaria based on their predictive values on univariate analysis and on clinical judgement (Table 2). Table 3 shows the full model for predicting malaria and 2 reduced models each derived using logistic regression.

Table 2. Individual predictors for a diagnosis of clinical malaria in Gambian children

	Prediction of malaria		Relative risk of malaria[c]
	Sensitivity[a]	Specificity[b]	
Symptoms			
Reduced feeding	72	49	1·76
Sleepiness	82	34	1·79
Shivering	72	47	1·69
Absence of cough	65	60	1·88
Signs			
Appears to be very sick	11	96	1·66**
Hot on palpation	99	20	11·63
Abnormally sleepy	16	91	1·40*
Cough not heard	87	46	2·57
Pallor			
Conjunctiva	33	84	1·67
Tongue	32	84	1·63
Palm	43	79	1·80
Absence of rash	95	17	2·70
Increased respiratory rate	67	57	1·85
Palpable liver	19	93	1·81
Enlarged spleen	14	94	1·69**
Normal chest examination	96	17	3·96

[a]Those with malaria showing symptom or sign.
[b]Those without malaria not showing symptom or sign.
[c]Risk of malaria in those with symptom or sign/risk in those without symptom or sign. All values are significant, with $P<0·001$ in all cases except those marked with one or two asterisks (*), indicating $P<0·05$ and $P<0·01$, respectively.

The sensitivities and specificities of different scores, selected as giving sensitivities and specificities greater than 30%, and of 3 scoring methods for each model, are shown in Table 4. The range of sensitivities and specificities of different scores using the full model is shown in the Figure. Table 4 shows also the area under the ROC curve for each model, which indicated that, although the full model was best, there was little difference in predictive power over the whole range of scores between the 3 models. However, the full model is preferable because there was less fluctuation in sensitivity and specificity at different cut-off scores compared with the other 2, making it more robust. Similarly, there was little difference between the 3 methods of scoring, indicating little loss of precision by using the standard scoring system. Using the full model and cut-off scores of 6 and 8 respectively, methods (i) and (ii) both gave sensitivities close to 90% and specificities over 60%. The performance of these 2 algorithms did not differ significantly in the different age groups, and there was no evidence that age was a confounding variable.

When high parasitaemia was modelled in terms of the 16 symptoms and signs (Table 3), axillary temperature was included as a possible predictor. Body temperature was, however, a very poor predictor of high parasitaemia when adjusted for other predictors. This was probably due to the narrow range of axillary temperature found among children included in the study, all of whom had either observed fever or a history of fever.

Physician's diagnosis

The physician diagnosed correctly 86% of cases of malaria and 61% of cases of other febrile illnesses on clinical grounds without the results of blood film examination.

Table 3. The full model and two reduced models for predicting malaria for each of the two case definitions used

	Coefficients of logistic regression models					
	Full model[a] (Nine terms)		Reduced model 1[a] (Six terms)		Reduced model 2[a] (Four terms)	
Predictors	A	B	A	B	A	B
Sleepy	0·56	–	–	–	–	–
Reduced feeding	0·77	0·81	0·94	0·82	1·01	–
Absence of cough	1·00	1·03	1·00	0·89	1·04	0·83
Shivering	0·56	0·97	–	1·07	–	1·24
Feels hot	3·45	–	3·48	–	–	–
Cough not heard	1·33	1·21	1·20	1·13	1·22	1·10
Pallor of palm	0·89	0·89	0·98	1·00	–	1·03
Absence of rash	1·50	1·52	–	0·94	–	–
Increased respiratory rate	1·12	0·75	1·01	–	1·26	–
Abnormal spleen	–	1·08	–	–	–	–

[a]A=parasitaemia ≥5000/μL and temperature ≥38°C; B=parasitaemia ≥5000/μL only.

Table 4. The sensitivities and specificities of different cut-off scores using three models

	Full model (Nine terms)			Reduced model 1 (Six terms)			Reduced model 2 (Four terms)		
Scoring method	Cut-off score[a]	Sensitivity (%)	Specificity (%)	Cut-off score[a]	Sensitivity (%)	Specificity (%)	Cut-off score[a]	Sensitivity (%)	Specificity (%)
No. of symptoms and signs present	5	97	36	3	98	31	2	98	29
	6	89	61	4	80	67	3	67	69
	7	61	80	5	45	91	4	27	95
Sum of rounded regression coefficients	7	97	40	5	97	39	–	–	–
	8	88	64	6	79	68	–	–	–
	9	61	82	7	45	91	–	–	–
Sum of exact regression coefficients (rounded)	7	100	32	5	99	35	2	98	29
	8	93	52	6	90	50	3	67	69
	9	76	75	7	74	71	4	37	89
	10	43	92	8	45	92	–	–	–
Area under ROC[b] curve		0·83			0·81			0·75	

[a]Score ≥ the value given.
[b]Receiver–operator characteristic.

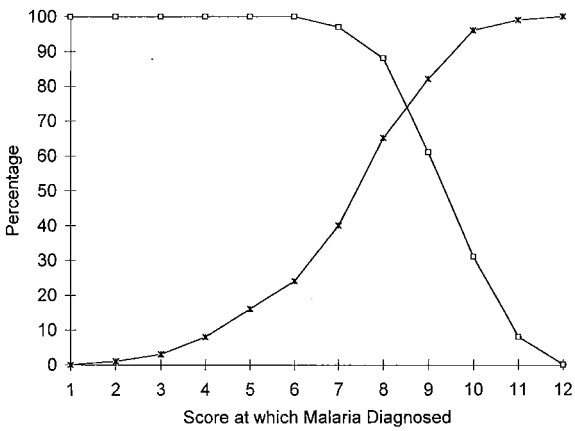

Figure. Sensitivity (□) and specificity (✱) of different scores in malaria diagnosis using the nine-term model with weighting of the detection of a hot body on clinical examination.

Discussion

When fever or a history of fever is used as the sole criterion for a diagnosis of malaria, over-diagnosis is frequently substantial, especially during periods of low malaria transmission (OLIVAR *et al.*, 1991; SOWUNMI & AKINDELE, 1993). When nearly all malaria parasites were sensitive to chloroquine, a cheap and safe drug, this was of little importance and it was reasonable to treat with this drug all patients with any suspicion of malaria. However, this is no longer the case and it is becoming increasingly necessary, even in tropical Africa, to choose a more expensive drug for the first line of treatment for malaria. In such circumstances, accurate diagnosis becomes increasingly important.

A diagnosis of malaria can be made with complete confidence only if it is supported by a parasitological diagnosis. Thus, as drug resistance spreads, it is becoming increasingly important that those required to diagnose and treat malaria at peripheral health centres should be provided with microscopy or, possibly, antigen detection tests. However, it is probable that the majority of the health care providers responsible for the treatment of malaria in Africa will have to rely upon their clinical skills for the foreseeable future. Are there any symptoms or simple clinical signs that can help them to differentiate malaria from other febrile illnesses? Previous studies in Africa have indicated that the height of fever and the presence of pallor and/or of splenomegaly do improve the specificity of diagnosis, with only a moderate effect on sensitivity (ROUGEMENT *et al.*, 1991; O'DEMPSEY *et al.*, 1993; REDD *et al.*, 1996). Our study has confirmed that pallor is a useful predictor of malaria and that other useful discriminators between malaria and other febrile conditions are reduced feeding, shivering, absence of a cough, absence of a rash, and raised respiratory rate. One problem in all studies of this kind is that there is no absolute criterion for a clinical diagnosis of malaria against which possible predictors can be assessed. In our study we used, as the definitive diagnosis of malaria, the combination of a history suggestive of malaria, a temperature of 38°C or higher, and observed parasitaemia of 5000/μL or more, the fever threshold defined previously for the study population (ARMSTRONG SCHELLENBERG *et al.*, 1994)

In the absence of laboratory support, the experienced clinician makes an assessment of the probability that an individual patient has malaria on the basis of the presence or absence of a variety of symptoms and signs. To help those with less experience to follow a similar course we have devised an approach to the diagnosis of malaria that can be used by a peripheral health care worker. To derive the model we used logistic regression analysis, which is preferable to classical discriminant analysis as it is optimal for a wider range of probability distributions (HAND, 1992). Logistic regression was used to define 9 positive predictors of malaria which were then used to devise a malaria score that could be applied to individual patients. As the number of these signs and symptoms present increased, so did the probability that an indvidual child had malaria. In our study population, we chose a score of 6 or more signs and symptoms to indicate malaria. Weighting the score in favour of 'feels hot', which had the highest regression coefficient, and use of a cut-off score of 8 did not alter substantially the specificity or the sensitivity of the algorithm. If a field worker had applied the 9 terms algorithm to the symptoms and signs identified in this study he or she could have obtained a sensitivity in the diagnosis of malaria that was similar to that achieved by an experienced paediatrician without laboratory support, with the same specificity. The score had a much higher specificity for the diagnosis of malaria than the WHO/UNICEF Sick Child Evaluation chart, which had a sensitivity of 97% but a specificity of only 40%. Although the study population ranged from 6 months to 9 years, the ability of the algorithm to predict clinical malaria did not differ significantly between age groups in this range.

How might this approach to the diagnosis of malaria be used in practice? Scoring would allow a peripheral health care worker to assess the probability that an individual patient had malaria on a scale varying from very unlikely to highly likely. This could be useful in determining treatment priorities when resources are scarce. For example, scarce second-line drugs could be reserved for patients with scores above a defined cut-off, whilst patients with lower scores might be given first-line drugs, even when it is known that these are not likely to be optimally effective. We think that this approach to the diagnosis of malaria might also be useful in the evaluation of malaria control programmes. Use of a score above a defined level associated with parasitaemia above a defined level might prove a more accurate end point for intervention trials than fever plus parasitaemia, the end point used most frequently at present. Whilst some of the components used to develop our malaria score, for example pallor, are likely to apply to all malaria endemic communities, others, especially symptoms that are influenced by language, are likely to be area-specific, so the components used to develop a malaria score may need to be varied from area to area.

A weakness of the present study is that the same data set was used both to devise the model and to evaluate it, thus underestimating the rate of misclassification. However, this is unlikely to have been a serious source of error as the sample size relative to the number of variables included in the model was large (HAND, 1992). A further prospective study is in progress in a different part of The Gambia to evaluate the ability of field staff to use the scoring system effectively.

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