

INDICATORS OF LIFE-THREATENING MALARIA IN AFRICAN CHILDREN

KEVIN MARSH, M.B., CH.B., DAYO FORSTER, PH.D., CATHERINE WARUIRU, M.B., CH.B.,
 ISIAH MWANGI, M.B., CH.B., MARIA WINSTANLEY, M.B., CH.B., VICTORIA MARSH, M.B., CH.B.,
 CHARLES NEWTON, M.D., PETER WINSTANLEY, M.D., PETER WARN, F.I.M.L.S., NORBERT PESHU, M.B., CH.B.,
 GEOFFREY PASVOL, M.D., AND ROBERT SNOW, PH.D.

Abstract Background. About 90 percent of the deaths from malaria are in African children, but criteria to guide the recognition and management of severe malaria have not been validated in them.

Methods. We conducted a prospective study of all children admitted to the pediatric ward of a Kenyan district hospital with a primary diagnosis of malaria. We calculated the frequency and mortality rate for each of the clinical and laboratory criteria in the current World Health Organization (WHO) definition of severe malaria, and then used logistic-regression analysis to identify the variables with the greatest prognostic value.

Results. We studied 1844 children (mean age, 26.4 months) with a primary diagnosis of malaria. Not included were 18 children who died on arrival and 4 who died of other causes. The mortality rate was 3.5 percent (95 percent confidence interval, 2.7 to 4.3 percent), and 84 percent of the deaths occurred within 24 hours of ad-

mission. Logistic-regression analysis identified four key prognostic indicators: impaired consciousness (relative risk, 3.3; 95 percent confidence interval, 1.6 to 7.0), respiratory distress (relative risk, 3.9; 95 percent confidence interval, 2.0 to 7.7), hypoglycemia (relative risk, 3.3; 95 percent confidence interval, 1.6 to 6.7), and jaundice (relative risk, 2.6; 95 percent confidence interval, 1.1 to 6.3). Of the 64 children who died, 54 were among those with impaired consciousness ($n=336$; case fatality rate, 11.9 percent) or respiratory distress ($n=251$; case fatality rate, 13.9 percent), or both. Hence, this simple bedside index identified 84.4 percent of the fatal cases, as compared with the 79.7 percent identified by the current WHO criteria.

Conclusions. In African children with malaria, the presence of impaired consciousness or respiratory distress can identify those at high risk for death. (N Engl J Med 1995;332:1399-404.)

MALARIA remains a major cause of childhood morbidity and mortality in the tropics. The World Health Organization (WHO) has worked to define standard criteria for the recognition and management of severe malarial disease.¹ However, although African children account for 90 percent of the mortality associated with *Plasmodium falciparum* worldwide,² there have been no comprehensive clinical descriptions of severe malaria in this group. Although there have been studies in other populations, there may be major differences in the clinical manifestations of malaria at different ages and under different levels of endemicity. We report here the results of a study of malaria in hospitalized Kenyan children. Our goal was to define the spectrum of severe disease and to assess the appropriateness of the current WHO criteria for severe and complicated malaria.¹

METHODS

Study Site

The study was carried out at Kilifi District Hospital, Kenya. A detailed description of the predominantly rural population served by this hospital has been published elsewhere.³ Approximately 120,000 outpatients are seen each year, and an average of 3000 children are admitted yearly to the 35-bed pediatric ward.

Data Collection

Since 1989 a research team from the Kenya Medical Research Institute (KEMRI) has been part of the pediatric inpatient service of

the hospital. All children are seen on admission by a KEMRI clinician, and summary data are recorded for entry in a cumulative data base. A blood sample is taken to determine the hemoglobin concentration and the white-cell count (Coulter counter, Coulter Electronics), and to allow a quantitative examination of a blood film for malarial parasites. Other studies — including measurements of plasma creatinine, electrolytes, glucose, lactate, and blood gases, as well as radiographic and microbiologic studies — are performed as clinically indicated.

We have used data on all children admitted between May 1989 and November 1991 with a primary diagnosis of malaria. This diagnosis was made only when a child had peripheral parasitemia and no other detectable cause for the clinical presentation, after a review of all the available data.

Clinical Assessment

All children were assessed according to the WHO criteria for severe and complicated malaria,¹ which consist of 10 defining clinical or laboratory criteria, supported by 5 additional, nondefining, criteria (Table 1). The state of the patients' consciousness was assessed with use of the Blantyre coma score,^{4,5} which is designed for use in young children and is based on verbal, motor, and gaze responses to stimulation. To distinguish between coma and transient postictal phenomena, children who had seizures were ascribed a definitive coma score one hour after the termination of the seizure, or after six hours if the seizure was terminated with anticonvulsant drugs. Prostration¹ was determined by observing whether a sitting position could be maintained without support from an attendant. Since pulmonary edema is undefined in the WHO criteria, we have substituted a more clinically useful criterion, which we have termed respiratory distress. Respiratory distress was defined as the presence of any of the following signs: alar flaring, chest recession (intercostal or subcostal), the use of accessory muscles of respiration, or abnormally deep (acidotic) breathing. The more restrictive criterion of severe respiratory distress was satisfied only by the children with documented recession or abnormally deep breathing. Other minor operational modifications of the WHO criteria are described in Table 1.

Clinical Assessment

Management

All children with evidence of neurologic involvement or with other acutely severe features such as respiratory distress were treated with parenteral quinine.⁶ Children able to take oral medication received chloroquine until January 1990; thereafter, they received pyrimethamine-sulfadoxine (Fansidar) plus chloroquine. Acetaminophen syrup or suppositories were used routinely as antipyretic agents. The

From the Kenya Medical Research Institute—Clinical Research Centre, Kilifi Unit, Kilifi, Kenya (K.M., D.F., C.W., I.M., M.W., V.M., C.N., P. Winstanley, P. Warn, N.P., G.P., R.S.); and the Nuffield Department of Clinical Medicine (K.M., D.F., P. Winstanley, P. Warn, G.P., R.S.) and the Department of Paediatrics (C.N.), Oxford University, John Radcliffe Hospital, Headington, Oxford, United Kingdom. Address reprint requests to Dr. Marsh at the KEMRI Unit, P.O. Box 230, Kilifi, Kenya.

Supported by the KEMRI—Oxford—Wellcome Trust Research Programme at Kilifi and by the special program of the United Nations Development Program, the World Bank, and the World Health Organization for research and training in tropical diseases. Dr. Marsh is a Wellcome Trust Senior Clinical Research Fellow. Dr. Newton holds a Wellcome Trust Advanced Training Fellowship. Dr. Snow is a Wellcome Trust Senior Fellow in Basic Science.

Table 1. Prevalence of Conditions Included in the WHO Criteria for Severe Malaria among Kenyan Children Admitted to the Hospital, and Associated Mortality.

CRITERION	PATIENTS WITH ADMISSION DATA AVAILABLE		MORTALITY	RELATIVE RISK (95% CI)*	χ^2	P VALUE
	no.	PREVALENCE no. (%)				
Defining						
Coma†	1844	185 (10.0)	31 (16.8)	12.6 (7.2–22.0)	71.4	<0.001
Severe malarial anemia‡	1816	320 (17.6)	15 (4.7)	1.4 (0.8–2.5)	1.1	0.290
Respiratory distress§	1833	251 (13.7)	35 (13.9)	9.4 (5.5–16.2)	62.9	<0.001
Hypoglycemia¶	698	92 (13.2)	20 (21.7)	5.4 (2.9–10.2)	24.9	<0.001
Circulatory collapse	1844	7 (0.4)	5 (71.4)	47.7 (7.8–293.5)	14.1	<0.001
Renal failure**	1844	2 (0.1)	0	—	—	—
Spontaneous bleeding	1843	2 (0.1)	0	—	—	—
Repeated convulsions††	1842	338 (18.3)	23 (6.8)	2.9 (1.7–4.9)	13.3	<0.001
Acidosis‡‡	110	70 (63.6)	15 (21.4)	2.1 (0.6–7.0)	1.6	0.207
Hemoglobinuria	1844	2 (0.1)	1 (50.0)	30.7 (1.8–504.6)	4.2	0.041
Supporting						
Impaired consciousness§§	1844	151 (8.2)	9 (6.0)	2.0 (0.9–4.1)	2.9	0.091
Jaundice	1806	84 (4.7)	10 (11.9)	4.6 (2.2–9.4)	12.9	<0.001
Prostration¶¶	1571	192 (12.2)	10 (5.2)	1.8 (0.9–3.6)	2.3	0.126
Hyperpyrexia	1816	192 (10.6)	3 (1.6)	0.5 (0.1–1.5)	2.1	0.143
Hyperparasitemia***	1839	163 (8.9)	7 (4.3)	1.4 (0.6–3.0)	0.5	0.480

*CI denotes confidence interval.

†Patient is unable to localize a painful stimulus. (Because this criterion cannot be applied to children under eight months old, this definition was modified to include younger children who made no motor responses to painful stimuli [four children].)

‡Hemoglobin <5 g per deciliter, with parasitemia (>10,000 parasites per cubic millimeter).

§The original WHO criterion was pulmonary edema (not defined).

¶Blood glucose <40 mg per deciliter (2.2 mmol per liter).

||Clinical shock. (The original WHO criterion was systolic pressure <50 mm Hg and cold, clammy skin.)

**Urine output <12 ml per kilogram per 24 hours and plasma creatinine >3.0 mg per deciliter (265 μ mol per liter). (Creatinine was measured in 254 patients.)

††Three or more in 24 hours.

‡‡Plasma bicarbonate <15 mmol per liter.

§§Patient has depressed level of consciousness but can localize a painful stimulus (see the Methods section).

¶¶Patient is not in a coma but cannot sit. (Denominator includes only children seven months old or older.)

|||Temperature >40°C.

***Parasite count >500,000 per cubic millimeter. (The original WHO criterion was variable, depending on epidemiologic setting.)

blood glucose concentrations of children with disturbed consciousness were measured frequently (every one to four hours) at the bedside. Comatose children had nasogastric tubes inserted and their stomach contents aspirated. Convulsions were controlled with either intramuscular paraldehyde or intravenous diazepam. Phenytoin — if necessary, with the addition of phenobarbital — was used as the standard treatment of children with uncontrolled seizures. All children with evidence of neurologic involvement underwent lumbar puncture to exclude a diagnosis of meningitis; because we have seen raised intracranial pressure in children with cerebral malaria,⁷ lumbar puncture was delayed until the patient had regained consciousness to the point of being able to localize a painful stimulus; meanwhile, the child was treated presumptively with benzyl penicillin and chloramphenicol, the standard regimen in Kenya for childhood meningitis. This treatment was discontinued once the possibility of meningitis had been excluded. Blood transfusions for severe anemia (defined as hemoglobin concentrations <5 g per deciliter) were restricted to children with respiratory distress.^{8,9} An exception was made for children with hyperparasitemia (>20 percent) and low hemoglobin concentrations, in whom transfusion was sometimes initiated to compensate for the anticipated rapid loss of red cells over the subsequent 24 hours.

Statistical Analysis

Analysis was carried out with the use of SPSS PC+ and EGRET. Initially, frequency distributions of all variables were produced to allow us to observe the spread and decide on suitable grouping categories. In general, groups for continuous variables were chosen on the basis of accepted clinical cut-off points (e.g., hypoglycemia: a glucose concentration of less than 40 mg per deciliter [2.2 mmol per liter]; severe anemia: a hemoglobin concentration of less than 5 g per deciliter).

With the use of EGRET, univariate logistic-regression models were

fitted for all variables, with death as the outcome variable, and adjustment for age. Relative risks of dying were estimated as odds ratios with 95 percent confidence intervals.

A relatively generous cut-off point was chosen in deciding which variables were important enough to merit inclusion in a multivariate model that would best explain the risk of death. All variables with a P value of 0.10 or less were included in the first fit of the multivariate model. Each variable in turn was then removed from the model, and its effect on overall deviance and the associated P value observed. All variables that had a significant overall effect on the model (P<0.05) were then retained for inclusion in a minimal effects model, the one that best explained outcome. Age was again retained in the minimal-effects model. All possible two-way interactions were added to the model in turn to test significance.

RESULTS

Between May 1989 and November 1991, 7538 children were admitted to Kilifi District Hospital. *P. falciparum* was detected in the peripheral-blood films of 3014 children (40 percent), of whom 1866 had a primary diagnosis of malaria. The mean age of children admitted with a primary diagnosis of malaria was 26 months, and 86 percent were under 4 years of age. There was no predominance of either sex at any age. Eighty-six children died (case fatality rate, 4.6 percent; 95 percent confidence interval, 3.7 to 5.6). Eighteen children arrived in a mori-

bund state and died during initial attempts at resuscitation and before the admission procedure could be completed. An additional four children died later, not primarily because of malaria, although this had been the original reason for admission to the hospital. The case fatality rate in the 64 children with a primary diagnosis of malaria who completed the admission procedure (1844 children) was thus 3.5 percent (95 percent confidence interval, 2.7 to 4.3 percent), with 84 percent of the deaths occurring within 24 hours of admission. The rest of the analysis presented in this paper is based on data from these 1844 children. The incidence of severe malaria among patients admitted to the hospital declined markedly after the age of four years, and there were only two deaths attributable to malaria in children over four years of age.

Clinical and Prognostic Features of the Group as a Whole

The prevalence of clinical features that either define or are associated with severe disease in the WHO criteria is shown in Table 1. To assess the prognostic importance of clinical findings on admission, we first performed a univariate analysis, stratified by age, using the variables listed in Table 1. These variables, with the exception of those that were too rare (shock, renal failure, spontaneous bleeding, and hemoglobinuria) were modeled with the use of logistic-regression analysis.

We also excluded acidosis, since our sample was small and biased toward very ill children, as a result of our not having the ability to perform routine measurements during the whole study period, since we did not have a working pH and blood gas machine during the study. The full model could only be fitted with data on the 673 children whose venous blood glucose concentrations were determined on admission and for whom no data were missing. The model was therefore refitted without blood glucose as a variable, allowing the inclusion of 1776 patients (96 percent) with a primary diagnosis of malaria. The minimal-effect models with and without blood glucose values are shown in Table 2. This approach identified four variables as key prognostic indicators in inpatients with malaria: impaired consciousness, respiratory distress, jaundice, and hypoglycemia. These were used to construct simple prognostic indexes, which are compared with the WHO criteria for severe malaria in Table 3.

Specific Clinical Subgroups

Impaired Consciousness

The definitions of impaired consciousness and cerebral malaria are controversial.⁹ We have limited the term cerebral malaria to children who satisfy the strict WHO criteria of being in a deep coma, unable to make a localizing response. We used the term impaired consciousness for those with a Blantyre coma score of 4 or less to allow comparison with other recent studies of cerebral malaria.^{4,5}

Three hundred thirty-six children had coma or impaired consciousness on admission, with a mortality rate of 11.9 percent. One hundred eighty-five of these children were profoundly comatose and satisfied the stricter WHO definition of cerebral malaria, with a mortality rate of 16.8 percent. These groups form a continuum; the conditions of an additional 23 children deteriorated enough to satisfy the stricter definition at some point after admission. For some purposes it may be desirable to widen the definition of neurologic involvement even further to include children who are prostrate.¹ They present a characteristic picture: al-

though fully conscious, they are hypotonic and unable to sit up. There were 192 such children, and the mortality rate was 5.2 percent. Many had other features of severe disease, particularly jaundice or hypoglycemia; such children need to be identified to receive more intensive treatment.

Factors strongly related to mortality in children presenting with neurologic involvement included respiratory distress (relative risk, 3.7; 95 percent confidence interval, 1.7 to 8.0; $P < 0.001$); hypoglycemia (relative risk, 3.6; 95 percent confidence interval, 1.5 to 7.8; $P = 0.001$); and deep coma (relative risk, 4.8; 95 percent confidence interval, 1.6 to 13.9; $P = 0.008$). Severe anemia (hemoglobin concentration, < 5 g per deciliter) and jaundice were not significantly related to mortality.

Respiratory Distress

Two hundred fifty-one children were reported by the admitting clinician to be in some degree of respiratory distress; 35 of these children (13.9 percent) subsequently died. The more precise category of severe respiratory distress proved more useful in identifying high-risk children: of 133 children so described, 33 (24.8 percent) died. Of the 133 children with severe respiratory distress, 63 also had impaired consciousness, and this group had a mortality rate of 31.7 percent, as compared with 18.6 percent in the remaining children. Children with respiratory distress were significantly younger (mean age, 19 months) than children with impaired consciousness (mean age, 35 months); children with both conditions were of an intermediate age (26 months). No level of respiratory rate (even when adjusted for age) proved as useful as either respiratory distress or severe respiratory distress as a prognostic indicator. Similarly, the presence of auscultatory findings (crackles or wheezing) had no relation to the outcomes either in the group of all patients admitted with malaria as a whole or in the children with respiratory distress.

Plasma bicarbonate was not measured routinely throughout the study period; however, data were available on 38 of the children with severe

Table 3. Comparison of Alternative Prognostic Criteria for Severe Malaria.

CRITERIA*	MORTALITY IF CRITERIA SATISFIED	MORTALITY IF CRITERIA NOT SATISFIED	DEATHS PREDICTED
	no. of deaths/total no. (%)		%
1. WHO criteria†	51/698 (7.3)	13/1146 (1.1)	79.7
2. Cerebral malaria and/or severe respiratory distress	49/277 (17.7)	15/1567 (1.0)	76.6
3. Impaired consciousness and/or any respiratory distress	54/501 (10.8)	10/1343 (0.7)	84.4
4. Prostration and/or any respiratory distress	58/650 (8.9)	6/1194 (0.5)	90.6
5. Prostration, any respiratory distress, hypoglycemia, jaundice, or any combination of these	59/693 (8.5)	5/1151 (0.4)	92.2

*See the Methods section and footnotes to Table 1 for definitions. Note that each level of severity includes all the more severe cases. For example, respiratory distress includes all cases of severe respiratory distress, and prostration includes all children with impaired consciousness, which in turn includes all children with cerebral malaria.

†Adapted from Warrell et al.¹

Table 2. Minimal-Effects Logistic-Regression Model for Major Predictors of Mortality in Inpatients with Malaria.*

PREDICTOR	CASE FATALITY RATE no. of deaths/ no. with predictor (%)	WITH BLOOD GLUCOSE CONCENTRATION		WITHOUT BLOOD GLUCOSE CONCENTRATION	
		P VALUE	RR (95% CI)	P VALUE	RR (95% CI)
Impaired consciousness	40/336 (11.9)	0.001	3.3 (1.6–7.0)	<0.001	6.3 (2.5–11.4)
Jaundice	10/84 (11.9)	0.031	2.6 (1.1–6.3)	0.05	2.2 (1.0–5.0)
Respiratory distress	35/251 (13.9)	<0.001	3.9 (2.0–7.7)	<0.001	5.5 (3.1–9.7)
Hypoglycemia	20/92 (21.7)	<0.001	3.3 (1.6–6.7)	—	—

*RR denotes relative risk, and CI confidence interval.

respiratory distress. Since the mortality rate was not significantly different between the group with and the group without plasma bicarbonate data (22 percent vs. 26 percent), there seems to have been no obvious bias toward sampling sicker children. Of the children with severe respiratory distress in whom plasma bicarbonate was measured, 81.4 percent had severe acidosis (plasma bicarbonate concentrations of <15 mmol per liter), and all 11 children who died had plasma bicarbonate concentrations below 10 mmol per liter.

Severe Anemia

There were 508 children (27.5 percent) with a primary diagnosis of malaria who had venous hemoglobin concentrations of less than 5 g per deciliter on admission. Of these, 320 had peripheral parasitemia with counts of 10,000 per cubic millimeter or more, thereby satisfying the WHO criteria for severe malarial anemia.¹ There was some overlap with other clinical groups: 28 children with severe malarial anemia also satisfied the WHO criteria for cerebral malaria, 59 satisfied the broader criteria of impaired consciousness, and 53 satisfied the criteria for severe respiratory distress. A total of 181 children with severe anemia (35.6 percent) received blood transfusions. The mortality rate in the group with severe malarial anemia as a whole was 4.7 percent, but in the majority, who had neither impaired consciousness nor severe respiratory distress, it was only 1.3 percent.

DISCUSSION

In many African hospitals, *P. falciparum* malaria is a leading cause of admission of children and the chief cause of their deaths. Surprisingly, there have been no comprehensive clinical descriptions of these patients, and the current definitions of severe and complicated malaria have not been validated in this group most at risk. Our starting point was with children admitted from among outpatients by clinical officers not involved in the study. During a concurrent study of non-severe malaria treated in outpatient settings, no deaths occurred within one week of treatment in 504 patients, and we are therefore confident that our findings do describe the complete spectrum of life-threatening disease presenting to health services in this setting.

A striking picture emerged from our analysis. Despite its pathophysiologic complexity,¹⁰ life-threatening

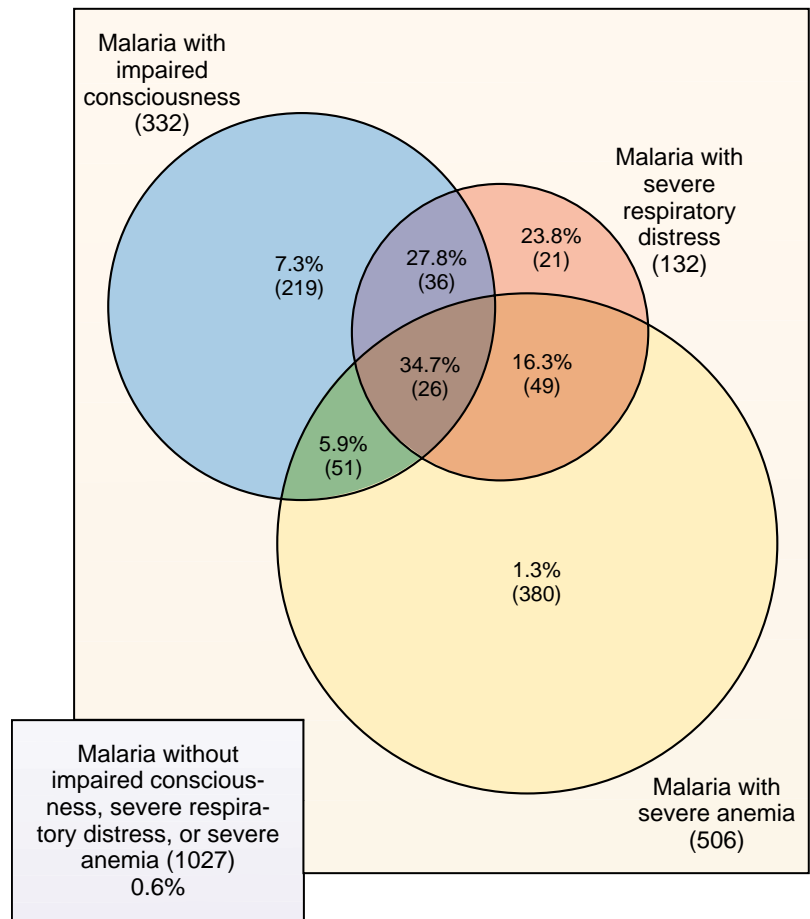


Figure 1. Prevalence, Overlap, and Mortality for Major Clinical Subgroups of Severe Malaria.

Total numbers are given in parentheses, and mortality is given as a percentage. Slight discrepancies between totals in the figure and in the text are due to missing values, as indicated in Table 1. Thus, 26 children did not have their hemoglobin concentrations recorded on admission; of these, 1 had severe respiratory distress and 4 had disturbed consciousness. Two children for whom hemoglobin concentrations were recorded did not have the severity of their respiratory distress recorded.

malarial disease in African children, as defined by poor outcome in the presence of good standard management, fell into two overlapping clinical syndromes: malaria with impaired consciousness and malaria with respiratory distress. Malaria with impaired consciousness is, of course, a well-recognized syndrome, although the exact definition of cerebral malaria is controversial.⁹ By contrast, respiratory distress has received little attention as a feature of life-threatening malaria in children, although milder respiratory signs and symptoms are common in less severe malaria.¹¹ Recently, respiratory distress has been reported to be of prognostic importance in African children with malarial anemia.⁸

Respiratory distress could potentially result from several underlying processes acting alone or in combination. In nonimmune adults with severe malaria, respiratory distress is a grave sign, often reflecting the development of pulmonary edema, which may lead to the adult respiratory distress syndrome.¹² This does not

seem to be the case in African children. The acute severe dyspnea that we observed in young children with malaria would, in many cases, probably be considered typical of heart failure due to severe malarial anemia.^{8,13} However, several factors lead us to question the assumption that this is the principal or only cause. First, the clinical signs commonly used to identify cardiac failure in young children are nonspecific; tachycardia, tachypnea, and hepatic enlargement are common in febrile children with malaria. Second, no studies documenting pulmonary edema or impaired cardiac function have been performed in children with malaria. Third, as can be seen in Figure 1, many children with severe respiratory distress were not severely anemic, and the outcome did not appear to depend on whether they were or not.

The predominant finding in children with respiratory distress, regardless of hemoglobin concentration, was severe metabolic acidosis. Taylor et al. have recently documented the prognostic importance of metabolic acidosis in Malawian children with malaria,¹⁴ and Krishna et al. have reported that persisting lactic acidemia is a predictor of death in Gambian children with severe malaria.¹⁵ We hypothesize that the development of metabolic acidosis is a fundamental process in severe malaria that cuts across other diagnostic categories, and that respiratory distress is commonly its most obvious clinical manifestation. By impairing tissue oxygenation, severe anemia is one factor likely to contribute to the development of acidosis, and in areas of high transmission where anemia is the dominant feature of malaria, it may become the chief factor. Nonetheless, it is vital that the relative roles of primary cardiac failure and acidosis in producing the clinical syndrome of respiratory distress in children with malaria be distinguished, since the implications for management are quite different. If acidosis is the principal problem, then the current practice of slow blood transfusion, often with diuretic agents, would amount to serious undertreatment, especially since such a large proportion of deaths occur in the first six hours after admission. On the other hand, rapid volume expansion, a rational part of the management of severe acidosis, could be disastrous if there is genuine impairment of cardiac function.

A major aim of this study was to validate the current criteria for severe and complicated malaria. In applying these criteria it became clear that in some cases definitions are either inapplicable or inappropriate. For the purpose of identifying children at high risk for death, we found that the WHO criteria can be simplified to require only simple bedside assessments of neurologic involvement and respiratory distress.

The effect of using different definitions of neurologic involvement or respiratory distress on the proportions of all hospital patients singled out for more intensive treatment and the value of the criteria for predicting deaths are shown in Table 3. In each case it is clear that the more stringent a definition the greater the predictive value for poor outcome. For the clinical purpose of identifying children requiring more intensive treat-

ment, the broadest definition is necessary; for specific therapeutic or epidemiologic studies, a more restrictive definition may be more appropriate. For example, the use of severe respiratory distress as a criterion rather than simply any respiratory distress allowed a marked increase in selectivity (133 instead of 251 children identified, with only two deaths not included), but it is very likely that action taken as a result of applying the broader classification (usually blood transfusion or rehydration) averted a number of deaths.

This approach has obvious advantages for most centers managing inpatient malaria: it is simple, rapid, easily taught, and avoids reliance on laboratory measurements, which are often unavailable or unreliable. Clearly, children without the poor prognostic features may nonetheless have benefited from the extra attention they received in this study. However, we doubt that this detracts from the general applicability of the approach. Since the end of the study these criteria (number 4 in Table 3) have been used at Kilifi District Hospital to identify children to be referred for parenteral therapy and close monitoring. The other 70 percent of young patients with malaria receive simple care on the general ward at a level typical of that at any busy district hospital. Case fatality rates in the two groups remain unchanged from those observed during the study period.

We draw several major conclusions from this study. First, most children who die of malaria in hospitals fall into two easily defined groups, one of which — those with respiratory distress — has not been adequately recognized previously. The fact that most deaths occur within 24 hours of admission implies that efforts to lower the case fatality rate should focus on understanding the pathophysiologic processes underlying these syndromes. Second, we concur with the authors of the WHO guidelines on severe malaria that no single definition of severe disease will be satisfactory or relevant in all situations. Two sorts of definitions are now required for African children: the first should aim to define in detail the pathophysiologic elements of severe disease, and will be used primarily for research purposes. A second definition is required for clinical management, therapeutic studies, and epidemiologic surveillance; here the criteria need to be simple, robust, and capable of identifying high-risk groups. In our experience, bedside observation of neurologic involvement and respiratory distress fulfills these requirements.

We are indebted to Dr. D. Koech, the director of KEMRI, for permission to publish these results; to all our colleagues at the KEMRI unit, Kilifi, and at the Kilifi District Hospital, particularly nursing and laboratory staff, for their skilled work and collaboration; and to the many colleagues who have provided helpful advice and comments, in particular Dr. J. Crawley, Dr. S. Murphy, Dr. M. English, Dr. C. Nevill, and Prof. D. Warrell.

REFERENCES

1. Warrell DA, Molyneux ME, Beales PF. Severe and complicated malaria. *Trans R Soc Trop Med Hyg* 1990;84:Suppl 2:1-65.
2. World Bank. World development report 1993: investing in health. Oxford, England: Oxford University Press, 1993.

3. Snow RW, Schellenberg JR, Peshu N, et al. Periodicity and space-time clustering of severe childhood malaria on the coast of Kenya. *Trans R Soc Trop Med Hyg* 1993;87:386-90.
 4. Molyneux ME, Taylor TE, Wirima JJ, Borgstein A. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. *Q J Med* 1989;71:441-59.
 5. Brewster DR, Kwiatowski D, White NJ. Neurological sequelae of cerebral malaria in children. *Lancet* 1990;336:1039-43.
 6. Pasvol G, Newton CR, Winstanley PA, et al. Quinine treatment of severe falciparum malaria in African children: a randomized comparison of three regimens. *Am J Trop Med Hyg* 1991;45:702-13.
 7. Newton CR, Kirkham FJ, Winstanley PA, et al. Intracranial pressure in African children with cerebral malaria. *Lancet* 1991;337:573-6.
 8. Lackritz EM, Campbell CC, Ruebush TK II, et al. Effect of blood transfusion on survival among children in a Kenyan hospital. *Lancet* 1992;340:524-8.
 9. Newton CRJC, Pasvol G, Winstanley PA, Warrell DA. Cerebral malaria: what is unrousable coma? *Lancet* 1990;335:472.
 10. Warrell DA. Pathophysiology of severe falciparum malaria in man. *Parasitology* 1987;94:Suppl:S53-S76.
 11. O'Dempsey TJD, McArdle TF, Laurence BE, Lamont AC, Todd TE, Greenwood BM. Overlap in the clinical features of pneumonia and malaria in African children. *Trans R Soc Trop Med Hyg* 1993;87:662-5.
 12. White NJ. Pathophysiology. *Clin Trop Med Commun Dis* 1986;1:55-90.
 13. Molyneux ME. Malaria — clinical features in children. *J R Soc Med* 1989;82:Suppl 17:35-8.
 14. Taylor TE, Borgstein A, Molyneux ME. Acid-base status in paediatric plasmodium falciparum malaria. *Q J Med* 1993;86:99-109.
 15. Krishna S, Waller DW, ter Kuile F, et al. Lactic acidosis and hypoglycaemia in children with severe malaria: pathophysiological and prognostic significance. *Trans R Soc Trop Med Hyg* 1994;88:67-73.
-