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Standardized data collection for multi-center clinical studies of severe malaria in African children: establishing the SMAC network

Terrie Taylor^a, Christopher Olola^b, Clarissa Valim^c, Tsiri Agbenyega^d, Peter Kremsner^e, Sanjeev Krishna^f, Dominic Kwiatkowski^g, Charles Newton^{b,h}, Michel Missinou^e, Margaret Pinderⁱ, David Wypij^c, and on behalf of the SMAC network

a Department of Internal Medicine, College of Osteopathic Medicine, Michigan State University, E. Lansing MI, USA

b Centre for Geographic Medicine Research-Coast, Kenya Medical Research Institute, Kilifi, Kenya

c Children's Hospital, Clinical Research Program, 300 Longwood Avenue, Boston, MA 02115 USA

d Department of Physiology, School of Medical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

e Albert Schweitzer Hospital, Lambaréné, Gabon and Department of Parasitology, Institute of Tropical Medicine, University of Tübingen, Germany.

f Department of Cellular and Molecular Sciences (Infectious Diseases), St. George's Hospital Medical School, London SW17 0RE, UK

g Wellcome Center for Human Genetics, Roosevelt Drive, Oxford OX3 7BN, UK

h Institute of Child Health, London, United Kingdom

i Medical Research Council Laboratories, Malaria Research Programme, PO Box 273, The Gambia

Abstract

The Severe Malaria in African Children (SMAC) network was established to conduct mortality-based trials. Although falciparum malaria kills more than one million children each year, single centers cannot enroll enough patients to detect reductions of 20–30% in mortality rates. Our aim was to quantify and describe severe malaria across a variety of epidemiological settings so that we could design intervention studies with more precise sample size estimates. We used a standardized surveillance mechanism to capture clinical, laboratory, and outcome data on all parasitemic children admitted to hospital.

Between December 2000 and December 2003, 20,333 patients were enrolled in five sites. The frequency of severe malaria syndromes (cerebral malaria, severe malarial anemia and acidosis) differed between sites, as did the syndrome-specific mortality rates. Intervention studies targeted at reducing mortality in one or a combination of severe malaria syndromes would require 3–4 years to complete within the existing network.

These data provide more accurate estimates of the disease burden of children hospitalized for malaria in sub-Saharan Africa. Networks are required to recruit enough patients for mortality-based studies and to encompass the epidemiological diversity of malaria in sub-Saharan Africa. SMAC represents the first effort to develop this capacity.

Keywords

malaria; children; Africa; clinical trials; severe malaria; falciparum; network

Introduction

Malaria kills over a million African children each year, but there are few definitive studies of lifesaving interventions. The disease is distributed widely across the continent and a hospital that treats 10,000 children with malarial illness may see only 100–200 fatal cases each year (Greenwood et al., 1991). Individual research centers cannot recruit sufficient numbers of patients for large-scale clinical trials capable of detecting 20–30% reductions in case fatality rate. In addition, few surrogate markers for a fatal outcome have been identified and animal models do not mimic human disease closely enough to reliably evaluate new treatments (Newton et al., 1998). For these reasons, multi-center studies are required to identify interventions that reduce mortality.

The importance of establishing pan-African networks to study various aspects of malaria was recognized at an international, multidisciplinary meeting held in Senegal in 1997 (Bruno et al., 1998). We identified all clinical malaria research groups in Africa that had published intervention studies involving children with severe falciparum malaria in peer-reviewed journals and invited them to join a clinical trials network. Five sites responded, and with support from a U.S. National Institutes of Health-funded planning grant, representatives from each participated in a series of meetings in 1997 and 1998, culminating in a research proposal to the NIH in September 1998. The award to support “Severe Malaria in African Children (SMAC): A Clinical Network” was made through a cooperative agreement mechanism in September 1999.

The main objective of the network is to reduce the mortality of severe malaria in African children by supporting the conduct of definitive clinical trials across the continent. Published comparative studies indicate that there is considerable variation in the frequencies and mortality rates of different severe malaria syndromes (Snow et al., 1997). Because children with severe malaria require treatment with parenteral drugs, the network population consists of hospitalized children. This is a select, heterogeneous group, but these patients do reflect severe malaria in each setting, they represent the group most likely to participate in future clinical trials, and they encompass much of the epidemiological diversity of malaria across the continent (Snow et al., 1994).

In this paper, we describe the mechanisms employed to establish the network and to assess data quality. We also compare the characteristics of the patients and the pattern of severe malaria across study sites.

Methods

Organization

SMAC was funded under a cooperative agreement awarded by the National Institute of Allergy and Infectious Diseases (30 Sept 1999–31 Aug 2004). The primary awardee, Michigan State University, subcontracted to the participating field sites: Banjul (Medical Research Council Laboratories, Malaria Research Programme, Banjul, The Gambia), Blantyre (Blantyre Malaria Project, Queen Elizabeth Central Hospital, Blantyre, Malawi), Kumasi (University of Science and Technology, School of Medical Science, Kumasi, Ghana), Kilifi (Kenya Medical Research Institute for Geographic Medicine Research-Coast (KEMRI/CGMR), Wellcome Trust Research Laboratories, Kilifi, Kenya), and two sites in Gabon, Lambaréné and Libreville, both

administered by the Medical Research Unit, Albert Schweitzer Hospital, Lambaréné, Gabon. A subcontract was also awarded to the biostatistical core (Children's Hospital, Clinical Research Program, Boston, Massachusetts).

Michigan State University served as the administrative coordinating center and was responsible for arranging travel, managing the list serve, tracking various versions of protocols, developing case report forms, expediting communication, and overseeing finances. Each site was responsible for its data collection and entry; assistance was provided by the Data Coordinator (CO), based at the SMAC site in Kilifi, Kenya.

The first task was to develop a core database in order to identify all parasitemic children admitted to the hospitals at each study site, and to document the distribution of the established disease syndromes (cerebral malaria, severe malarial anemia, acidosis) and their outcomes (survived, died or absconded).

Identifying all children admitted with malaria infection (i.e., with *P. falciparum* parasitemia) requires a constant presence in the admissions area and the ability to stain and interpret blood films around the clock. Additional SMAC staff members were required in some sites to ensure that all parasitemic children admitted to each hospital were identified and, if informed consent was forthcoming, were included in the database.

The patient populations were expected to differ across sites. The Albert Schweitzer Hospital in Lambaréné is a private hospital with 30 beds for children. The hospitals in Banjul, Libreville, Kumasi and Blantyre are all government teaching institutions for local medical schools and have 158, 65,184, and 200 inpatient pediatric beds, respectively. Kilifi District Hospital is the first and only source of in-patient hospital care in the district, and has 41 beds for children. Peak transmission seasons are established in each site (Fig. 1).

Design

We aimed to enroll the entire pediatric malaria population at each participating hospital, capturing the defining features of severe malaria at each site (WHO, 2000). All children who were suspected of having a malaria illness and who were sick enough to be admitted to hospital were screened, with a peripheral blood film, for the presence of *P. falciparum* parasitemia. Those with a positive blood film who were under the age of 180 months were invited to join the study. Informed consent was sought from the accompanying parent or guardian. The content of the consent form was conveyed first in the appropriate local language; the parent/guardian could indicate their consent by signing the consent form, or by verbally agreeing in the presence of a witness. The SMAC consent forms differed slightly at each site, but each version was approved by the local Institutional Review Board (IRB), by the Michigan State University IRB, and by the protocol review group at the National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases.

Data management procedures

If consent was provided, data were collected on a standardized case report form. Patients were followed throughout their hospitalization, and once the outcome was known, the completed form was submitted to the data entry team at each site. Two different people performed data entry. An automated verification program generated an error file, and queries were created for data outside of the pre-defined allowable ranges. All discrepancies and queries were resolved manually by the clerks and data managers at each site; once double-entered, checked, and verified, the data from each site were sent by e-mail or courier to the Data Coordinator, who was responsible for maintaining the pooled database for the network and for ensuring its security.

Because age and parasitemia status were the two pre-admission eligibility criteria, every effort was made to retrieve these variables when they were missing. If either one could not be retrieved, the record in question was excluded from the final analysis database.

The following data were collected from all enrollees:

- Identifiers: study number, site number, ethnic group (site-specific codes).
- Demographic details: date of birth or age, gender, weight.
- History of present illness: date/time of admission, convulsions prior to admission, vomiting prior to admission.
- Physical findings on admission: temperature and site of measurement, Blantyre Coma Score (Molyneux et al., 1989), respiratory status (deep breathing, rate, intercostal recessions, irregular breathing), and prostration (difficulty or inability to suck, sit up, stand up or walk unaided). Clinical observations were standardized on collective ward rounds involving the lead SMAC clinicians as the protocol was being developed.
- Laboratory investigations: For parasitemia, all sites examined Giemsa-stained thick smears, either for 200 white blood cells (WBC) (Kumasi and Blantyre) or for 100 high-powered fields (hpf) (all other sites) before recording a negative result. Asexual parasitemia was estimated from the number of parasites per hpf on thick films in Banjul (Greenwood and Armstrong, 1991) and in Lambaréné and Libreville (Planche et al., 2001). The remaining sites counted parasites per 200 WBC and estimated the concentration by assuming 8000 WBC/ μ l (Blantyre and Kumasi) or using the measured WBC count (Kilifi). In Blantyre, Kumasi and Kilifi, thin films were used when the parasite:WBC ratio exceeded 50:1. Other measurements included hematocrit only (Blantyre, microhematocrit centrifuge), hemoglobin and hematocrit (colorimetric method and microhematocrit centrifuge in Banjul; Coulter counter in Kilifi, Kumasi, Lambaréné and Libreville) glucose (mmol/l) from capillary or venous blood using handheld glucose analyzers, lactate (mmol/l) from capillary or venous blood (Arkay Lactate Pro LT-1710 portable lactate analyzer in Banjul, Blantyre, Lambaréné, and Libreville; 2300 Stat plus analyzer, YSI Corporation, Yellow Spring, Ohio, USA in Kumasi), blood gas analysis (base excess) from capillary or venous blood (Stat Profile[®] pHox Blood Gas/Oximeter, Nova Biomedical Corporation, Waltham, Massachusetts, USA in Blantyre and Kilifi). Hematocrit values were used in the analyses that follow, except when only hemoglobin values were available.
- Outcome measures: died, survived, absconded or unknown.

Quality control

Standard operating procedures were developed at each site. Before data collection began, at least one laboratory technician from each site attended a workshop and was trained in operating and maintaining the two instruments that were new and common to all five sites (the blood gas analyzers and the handheld lactate analyzer). The Data Coordinator visited each site before data collection commenced. The starts were staggered, beginning with Lambaréné and Libreville in December 2000, and continuing with Kumasi (February 2001), Blantyre (April 2001), Kilifi (June 2001), and Banjul (March 2002). The Principal Investigator (TT) visited each site over the course of the study, addressing site-specific issues. A meeting for all local Data Managers was held in February 2003; this provided a good opportunity to ensure that data quality was maintained.

Ranges for double-checking quantitative data were developed, based on a consensus of the study investigators. Allowable ranges (Blantyre Coma Score 0–5; temperature 34°C–43°C;

parasitemia 1–2,500,000/ μ l; hematocrit 3–60%; hemoglobin 0.9–20g/dL; glucose 0–20 mmol/l; base excess –30 to +20; lactate 0–20 mmol/l; weight-for-age Z-score –10 to +4) were established. Individual variables outside the allowable ranges were set to missing, but the records remained in the data base.

Clinical case definitions

The criteria are based on data collected at admission from parasitemic patients. Enrollees with a Blantyre Coma Score ≤ 2 were classified as having cerebral malaria. Those whose hematocrit was $< 15\%$ (or, in the absence of a hematocrit value, whose hemoglobin was < 5 gm/dL) were categorized as severe malarial anemia, and those with at least one of the following were said to have acidosis: deep breathing, base excess ≤ -8 , or whole blood lactate > 5 mmol/l. Individual patients may have been classified as having more than one of these syndromes.

Statistical analyses

Assessments of outcome, data quality, and site profiles were based on descriptive statistics, including means and standard deviations, medians and interquartile ranges, and proportions. Statistical tests for comparisons across study sites were based on Pearson chi-square tests or extensions of Fisher's exact tests for categorical variables, and on analysis of variance or Kruskal-Wallis tests for continuous variables. Data analyses were performed using SAS version 9 (SAS Institute, Inc., Cary, North Carolina, USA).

Results

From the first enrollment (December 2000) through December 2003, 20,733 children were screened. Consent was withheld for 400 patients (206 (51%) from Kilifi, and 187 (47%) from Blantyre), and 20,333 patients were enrolled. Of these, 71 (0.35%) were excluded from the analysis data set because either parasitemia ($n=1$) or age ($n=40$) was outside the agreed range, or because age was missing ($n=29$) or the subject was declared 'dead on admission' ($n=1$). The analysis data set thus included 20,262 cases, and 892 of these (4.4%) died (Table 1). Data on outcome were unknown for 205 patients; 41 (0.2%) were untraceable, and 164 patients (0.8%) absconded from hospital before their outcome status could be determined. For these 205 patients, outcome was set to "missing" in the analysis data set. To evaluate the possibility that these patients represented groups which could have biased our case fatality rates and associations between various predictors and outcome, we compared the demographic and clinical profiles of those who absconded and those for whom the outcome was unknown with those who remained in the hospital until they were discharged (Table 2). For most characteristics, the absconders and those who could not be traced were similar to the survivors. For base excess and hyperlactatemia, the absconders were similar to the survivors, but the untraceable patients resembled those who died. Only three sites were able to maintain blood gas analyzers (Blantyre, Kilifi and Kumasi) and in even in those sites, it was difficult to maintain the analyzer continuously; the missing blood gas values represented 42.2%, 8.5% and 20.0% of admissions, respectively.

For between-site comparisons, we chose a twelve-month period in which data were available from all sites (Table 3). A single twelve-month period is the minimum length of time needed for these analyses, because it must encompass the complete malaria transmission period in each site. During this time, a total of 7,205 patients were eligible for analysis. Study sites were heterogeneous with respect to all variables except gender (p -values of the heterogeneity tests were < 0.001). The differences in some clinical characteristics (respiratory symptoms, history of vomiting, inability to sit, peripheral parasitemia) were statistically significant, but are almost certainly too small, in absolute terms, to be clinically significant.

The sites also differed in terms of the clinical presentation of severe malaria and the associated mortality risks (Table 4). The overall mortality risk in the twelve-month cohort in whom the outcomes were known was 4.9%, ranging between 2.0 and 3.9%, except in Banjul, where the mortality risk among children admitted with parasitemia was 9.7%. In all sites, severe malarial anemia was more common than cerebral malaria, and the associated case fatality rate was lower. It was considerably more common in Banjul, Kumasi and Libreville, but the highest case fatality risks for those with severe anemia were in Banjul, Blantyre and Kilifi. The proportion of cases with cerebral malaria was similar in all sites, but the highest case fatality risks were recorded in Banjul (28.4%) and Blantyre (27.0%). Data from the four sites using the handheld lactate analyzer showed that hyperlactatemia (whole blood lactate > 5 mmol/l) occurred in 32.5% of admissions overall, and was homogeneously distributed across those four sites. Overall, 10.4% of the patients were admitted with deep breathing; the distribution of this clinical sign was uneven, ranging from 2.5% in Libreville to 15.0% in Kumasi. Acidosis as measured by base excess was also unevenly distributed, ranging from 4.0% in Blantyre to 39.6% in Kilifi. The overall one-year mortality risks for hyperlactatemia, deep breathing, and base excess ≤ -8 were 12.0%, 18.7%, and 9.3% respectively.

Discussion

Patterns of severe disease are different between sites, reflecting disparate patient and parasite populations as well as different admission criteria and health care systems. The various manifestations of severe malaria also have different associations with mortality in each site. Are the discrepancies due to differences in the management of severe malaria, or are there more fundamental distinctions between the hospitalized populations at each site? Different transmission patterns and intensities may produce different proportions of incidental parasitemias in these cohorts of patients with coma, anemia and acidosis. The variation in these standardized observations represents an opportunity to generate a number of testable hypotheses related to the natural history and outcome of severe pediatric malaria (e.g., which clinical features are the best prognostic features? Which measure of acid/base status is most useful? Is there a standard age-related parasitemia threshold for severe malaria, and does it vary by site?), and these will be addressed in subsequent analyses of these data as well as in future SMAC studies.

The most likely source of error in this data set is overestimating the contribution of malaria illness to the syndromes and outcomes observed in children with malaria infection (peripheral parasitemia). An ongoing autopsy study suggests that even with a stringent clinical case definition, 23% of children who were thought to have died of cerebral malaria actually died for other reasons; the peripheral parasitemia in each case was incidental, and unrelated to the cause of death (Taylor et al., 2004).

Methodological differences could be a source of error. We took care to standardize the laboratory estimations and clinical observations, and are reasonably confident that the differences observed between sites (e.g., incidence of seizures, prevalence of chest indrawing and acidosis) represent true differences rather than discrepancies in definitions or observations.

Another potential contributor to error is selection bias introduced by unknown outcome status (absconders or patients for whom outcome information was completely missing). Our analysis suggests that for most variables, the patients with unknown outcomes were similar to survivors; this would tend to underestimate associations between candidate predictors and risk of death.

There were two variables for which the patients with missing data were more similar to patients who died: base excess and hyperlactatemia. This effect was noted only in a small group of patients for whom the outcome was unknown, and could have occurred by chance. Any bias

introduced in this way could potentially overestimate the odds ratios between candidate predictors and the risk of death, but since the numbers involved are very small, this bias is likely to be negligible.

The combined data set can be used to generate more precise sample size calculations. For instance, an intervention study, using a two-sided 0.05 level test, powered at 80% and addressing studying patients with hyperlactatemia (SMAC annual admissions: 1,576; mortality risk 12.0%) would need to enroll 5,250 patients to detect a 20% decrease in mortality, or 2,218 patients to detect a 30% decrease in mortality risk. If patients with cerebral malaria (Blantyre Coma Score ≤ 2) (Molyneux et al., 1989) were targeted (SMAC annual admissions: 643; mortality rate 19.3%), 2,958 patients would need to be enrolled to detect a 20% decrease in mortality, and 1,278 patients would be required to discern a 30% drop. For a network-wide intervention involving one of these target groups, 3–4 years would probably be required to enroll a sufficient number of patients.

Future plans include refining our surveillance activity by deleting the less helpful variables, evaluating new variables (i.e., pulse oximetry), standardizing more variables (i.e., deep breathing, parasitemia), and developing a secure, on-line data repository. We aim to begin mortality-based intervention studies by 2006.

Conclusions

Standardized data on severe pediatric malaria, collected across sub-Saharan Africa, can provide more accurate estimates of the disease burden and improved descriptions of the different patterns of severe malaria. The data also support the generation of hypotheses about pathogenesis and treatment, and allow for more precise sample size calculations and clinical trial timelines. This clinical network should be able to develop evidence-based guidelines for the diagnosis and treatment of severe malaria using readily available methods, and we anticipate that it could play a key role in assessing the impact of novel interventions in African children on the mortality rates associated with the various syndromes that comprise severe and complicated malaria.

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Total enrollment, mortality, and mortality risk through December 2003 of 20,262 African children with malaria and peak transmission season(s), overall and by study site.

Study Site	Total Enrollment	Mortality (n)	Mortality Risk (%) ^a	Peak Transmission Season(s)											
				Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Overall	20,262	892	4.4										↔		
Banjul, The Gambia	2,720	255	9.6										↔		
Blantyre, Malawi	4,362	109	2.5			↔									
Kilifi, Kenya	5,274	191	3.6		→					↔					←
Kumasi, Ghana	4,969	245	5.0							↔					
Lambaréné, Gabon	1,436	20	1.4						↔						
Libreville, Gabon	1,501	72	4.9						↔						

^a Calculation of mortality risks excludes study subjects who absconded or who could not be traced.

Demographic, clinical and laboratory variables through December 2003 of 20,262 African children with malaria, by outcome.

Table 2

Variables	Outcome		
	Survival (N = 19,165)	Death (N = 892)	Absconded (N = 164)
			Unknown (N = 41)
Demographic			
Age (months)	35 ± 31	37 ± 32	30 ± 27
Weight (kg)	12 ± 5	11 ± 6	11 ± 5
Male (%)	54	53	58
Clinical			
Seizures prior to admission (%)	29	45	18
Vomiting prior to admission (%)	48	61	41
Deep breathing (%)	9	43	7
Chest indrawing (%)	10	35	9
Irregular breathing (%)	4	27	4
Unable to sit (%)	34	81	29
Blantyre Coma Score ≤ 2 (%)	8	41	4
Temperature (° C)	38.1 ± 1.2	37.8 ± 1.2	38.1 ± 1.2
Laboratory			
Parasitemia / 10 ³ median (interquartile range)	60 (10,192)	43 (3, 211)	41 (6, 121)
Hematocrit (%)	23.4 ± 8.1	20.9 ± 9.2	22.8 ± 8.5
Hemoglobin (g/dL)	7.2 ± 2.6	6.6 ± 3.1	6.7 ± 2.6
Glucose (mmol/l)	5.4 ± 2.3	5.7 ± 5.4	5.6 ± 2.2
Base excess	-4.8 ± 5.8	-11.3 ± 7.4	-2.6 ± 5.1
Lactate (mmol/l)	4.3 ± 3.4	8.8 ± 5.4	3.8 ± 2.4

Table 3

Comparing demographic, clinical and laboratory variables across study sites from January–December 2003 in 7205 African children with malaria. ^a Data from 71 subjects who absconded or who could not be traced are included in these analyses.

Variables	Study Site					
	Banjul (N = 1739)	Blantyre (N = 1228)	Kilifi (N = 2076)	Kumasi (N = 1452)	Lambaréné (N = 344)	Libreville (N = 366)
<i>mean ± SD, or %</i>						
Demographic						
Age (months)	42 ± 35	37 ± 32	33 ± 28	31 ± 28	39 ± 35	31 ± 24
Weight (kg)	13 ± 7	12 ± 6	11 ± 5	11 ± 5	13 ± 6	12 ± 5
Male (%)	52	54	54	55	56	51
Clinical						
Seizures prior to admission (%)	41	22	11	44	25	45
Vomiting prior to admission (%)	72	48	32	56	53	54
Deep breathing (%)	11	6	11	15	4	2
Chest indrawing (%)	11	4	13	21	8	3
Irregular breathing (%)	10	5	2	4	5	3
Unable to sit (%)	46	33	27	45	25	52
Blantyre Coma Score ≤ 2 (%)	9	6	10	11	9	8
Temperature (°C)	37.8 ± 1.1	38.6 ± 1.1	38.2 ± 1.2	37.9 ± 1.1	38.3 ± 1.3	38.6 ± 1.1
Laboratory						
Parasitemia / 10 ³ median (interquartile range)	19 (2, 72)	76 (32, 171)	38 (3, 202)	95 (18, 296)	48 (10, 162)	73 (27, 234)
Hematocrit (%)	20.8 ± 9.0	26.8 ± 7.7	25.3 ± 7.5	19.1 ± 6.9	23.3 ± 7.1	20.7 ± 7.6
Hemoglobin (g/dL)	6.4 ± 2.8	^b	7.7 ± 2.4	6.4 ± 2.4	7.6 ± 2.4	6.6 ± 2.4
Glucose (mmol/l)	6.5 ± 3.1	5.6 ± 2.1	5.4 ± 2.7	5.3 ± 2.4	4.4 ± 1.7	5.2 ± 2.2
Base excess	^c	2.7 ± 5.0	-7.5 ± 4.9	-4.8 ± 5.1	^c	^c
Lactate (mmol/l)	5.5 ± 4.0	4.7 ± 3.6	^d	4.6 ± 3.5	4.1 ± 2.4	4.8 ± 3.6

^a To compare study sites, Pearson chi-square tests were used to compare proportions, the Kruskal-Wallis test was used to compare parasitemia levels, and analysis of variance was used to compare other continuous variables. *P*-values for each comparison were < 0.001, except for gender (*P* = 0.40).

^b Hemoglobin data are not available from this site.

^c Base excess data are not available from these sites.

^d Lactate data are not available from this site.

Table 4

Comparing patterns of severe malaria across study sites from January–December 2003 in 7134 African children with malaria. ^a Data from 71 subjects who absconded or who could not be traced are excluded from these analyses.

Enrollment	N	Study Site						Overall 7134
		Banjul 1702	Blantyre 1212	Kilifi 2063	Kumasi 1447	Lambaréné 344	Libreville 366	
Mortality Risk	(%)	9.7	3.3	3.4	3.9	2.0	2.7	4.9
Severe malaria syndromes								
Cerebral Malaria	N	148	74	201	159	32	29	643
(BCS ^b ≤ 2)	(%)	8.7	6.1	9.7	11.0	9.3	8.0	9.0
	CFR ^b	28.4	27.0	13.4	17.6	9.4	13.8	19.3
	(%)							
Severe Anemia	N	576	91	222	469	49	99	1506
(PCV ^b < 15%)	(%)	34.0	7.5	10.8	32.4	14.3	27.1	21.2
	CFR	11.6	14.3	8.6	4.7	0	6.1	8.4
	(%)							
Acidosis								
Hyper-lactatemia	N	580	379	— ^c	422	78	117	1576
(lactate > 5 mmol/l)	(%)	38.9	31.4	-	29.2	22.9	32.5	32.5
	CFR	19.0	8.2	-	8.5	2.6	8.6	12.0
	(%)							
Deep Breathing	N	194	73	232	217	14	9	739
(present)	(%)	11.4	6.0	11.3	15.0	4.1	2.5	10.4
	CFR	29.4	27.4	14.2	11.5	7.1	22.2	18.7
	(%)							
Base Excess	N	— ^d	21	712	320	— ^d	— ^d	1053
(BE ^b ≤ -8)	(%)	-	4.0	39.6	23.5	-	-	28.5
	CFR	-	42.9	11.6	7.3	-	-	9.3
	(%)							
Number of severe malaria syndromes^e								
None	N	558	755	1541	656	213	176	3899
	(%)	37.6	62.5	74.8	45.4	63.0	49.6	56.6
	CFR	2.2	0.3	1.4	1.1	1.4	0	1.2
	(%)							
1	N	553	334	397	447	91	119	1941
	(%)	37.3	27.7	19.3	30.9	26.9	33.5	28.2
	CFR	9.2	3.3	5.0	3.6	1.1	1.7	5.2
	(%)							
2	N	279	81	108	228	24	54	774
	(%)	18.8	6.7	5.2	15.8	7.1	15.2	11.2
	CFR	18.3	14.8	23.2	5.3	8.3	9.3	13.8
	(%)							
≥ 3	N	93	38	14 ^f	114	10	6	275
	(%)	6.3	3.2	0.7	7.9	3.0	1.7	4.0
	CFR	37.6	39.5	21.4	18.4	0	50	28.0
	(%)							

^aTo compare risk of severe malaria syndromes and case fatality risks across study sites, Pearson chi-square tests were used. *P*-values for all comparisons across study sites were < 0.005, except *p* = 0.01 for comparing mortality risks across study sites for subjects with no severe malaria syndromes.

^bCFR = case fatality risk; BCS = Blantyre Coma Score; PCV = packed cell volume; BE = base excess.

^cLactate data are not available from this site.

^dBase excess data are not available from these sites.

^eNumber of severe malaria syndromes is based on cerebral malaria, severe malarial anemia, hyperlactatemia and deep breathing. Base excess was not used in this definition because these data were not available from three sites.

^fSince there are no lactate data from this site, the category ≥ 3 means exactly three syndromes, i.e. cerebral malaria, severe malarial anemia and deep breathing.