

Hospital Based Surveillance of Severe Paediatric Malaria in Two Malaria Transmission Ecological Zones of Burkina Faso

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Abstract

Background

In the current context of tailoring interventions to maximize impact, it is important that current data of clinical epidemiology guide public health programs and health workers in the management of severe disease. This study aimed at describing the burden of severe malaria at hospital level in two areas with distinct malaria transmission intensity.

Methods

A hospital-based surveillance was established in two regional hospitals located in two areas exposed to different malaria transmission. Data on paediatric severe malaria admissions were recorded using standardized methods from August 2017 to August 2018 with an interruption during the dry season from April to June 2018.

Results

In total, 921 children with severe malaria cases were enrolled in the study. The mean age was 33.9 (± 1.3) and 36.8 (± 1.6) months in respectively lower malaria transmission (LMT) and higher malaria transmission (HMT) areas ($p=0.15$). The geometric mean of asexual *P. falciparum* density was significantly higher in the LMT area compared to the HMT area (22,861 trophozoites/ μL (95% CI 17,009.2-30,726.8) vs 11,291.9 trophozoites/ μL (95% CI 8,577.9-14,864.5)). Among enrolled cases, coma was present in 70 (9.2%) participants. 196 patients (21.8%) presented with two or more convulsions episodes prior to admission. Severe anaemia was present in 448 children (49.2%). Other clinical features recorded included 184 (19.9%) cases of lethargy, 99 (10.7%) children with incoercible vomiting, 80 (8.9%) patients with haemoglobinuria, 43 (4.8%) children with severe hypoglycaemia, 37 (4.0%) cases where child was unable to drink/suck, 11 (1.2%) cases of patients with circulatory collapse/shock, and 8 cases (0.9%) of abnormal bleeding (epistaxis).

The adjusted odds of presenting with coma, respiratory distress, haemoglobinuria, circulatory collapse/shock and hypoglycaemia were significantly higher (respectively 6.5 (95%CI 3.4-12.1); 1.8 (95%CI 1.0-3.2); 2.7 (95%CI 1.6-4.3); 5.9 (95%CI 1.3-27.9); 1.9 (95%CI 1.0-3.6)) in children living in the HMT area compared to those residing in the LMT area.

Overall, forty-four children died during hospitalization (case fatality rate 4.8%) with the highest fatalities in children admitted with respiratory distress (26.0%) and those with hypoglycaemia (25.0%).

Conclusion

The study showed that children in the HMT area have a higher risk of presenting with coma, shock/dehydration, haemoglobinuria, hypoglycaemia, and respiratory distress. Case-fatality rate is higher among patients with respiratory distress or hypoglycaemia. Hospital surveillance provides a reliable and

sustainable means to monitor the clinical presentation of severe malaria and tailor the training needs and resources allocation for case management.

Background

Despite the recent progress in malaria control in many countries across the globe, malaria remains the main public health threat in sub-Saharan Africa. Globally, there were an estimated 229 million malaria cases in 2019 in 87 malaria endemic countries, with about 94% of cases accounted for in the World Health Organization (WHO) African Region [1].

Burkina Faso is one of those countries where progress in controlling the disease has stalled despite full scale deployment of available interventions which include case management using Artemisinin Combination Therapy (ACT) drugs, vector control through large-scale distribution of Long-Lasting Impregnated Net (LLINs); and seasonal malaria chemoprevention (SMC) targeting the marked seasonality of the disease transmission. The country is one of the high-burden nations as defined by the WHO and is part of the high burden to high impact initiative [2].

The clinical epidemiology of severe, life-threatening malaria was characterised in Burkina Faso during the 1990s [3] at a time where current control tools were not yet deployed. These clinical features may no longer be relevant today. Indeed, there is evidence that some interventions such as LLINs had led to a decrease of anaemia among children in Kenya. It is possible that current interventions at scale may have changed the clinical presentation of severe malaria, by impacting on transmission intensity [4, 5].

To tailor interventions to maximize impact, it is important to obtain up to date information on the epidemiology of severe malaria. This study describes the current burden of severe malaria in children admitted at hospital level in two areas with distinct malaria transmission. The information on prevalence and lethality of severe malaria in hospitalized children is useful to the National malaria control programme, to health workers may contribute to fine tuning control strategies and resources allocation.

Study Methods

Study sites

The study was conducted at two regional referral hospitals, the Regional Hospital of Koudougou and the Regional Hospital of Banfora, respectively.

The Regional Hospital of Koudougou (lower transmission area, LMT) is located 100 km Centre West of the capital city of Ouagadougou. Malaria transmission in this central part of the country is markedly seasonal and intense during the rainy season from June to October. The entomological inoculation rate was estimated at 31.4 infective bites/person/year in a study conducted in the neighbouring zone of Saponé [6].

The Banfora Regional Hospital (higher transmission area, HMT) is located within a very highly endemic area where transmission occurs throughout the year, with a peak during the rainy season (from June to October). The entomological inoculation rates (EIR) ranges from 55 to 400 infected bites/person/year (Tiono et al, unpublished data).

In both areas, the main malaria vectors are *Anopheles gambiae*, *An. arabiensis* and *An. funestus* and *P. falciparum* is responsible for more than 90% of all clinical malaria cases [7, 8].

Recruitment and management of study participants

The recruitment of children took place from August 2017 to August 2018 with an interruption from April to June 2018 (representing the dry season). For all consecutive children presenting at the paediatric emergency room at any time with a clinical presentation suggestive of severe malaria, an informed consent was obtained by study personnel from parents/legal representatives. Patients were further assessed by paediatric ward clinicians (who benefited from a refresher protocol specific training prior to the study start) and observations recorded using a standardized case report form. Data collected included the medical history, vital signs, a complete physical examination for signs of severity (affecting the airway, respiratory, circulatory, and neurological systems). Finger prick blood sample was taken for malaria diagnosis (Rapid diagnosis test (SD Bioline Malaria Ag Pf® (Histidin Rich Protein 2, HRP2)) and malaria smear (Method for microscopy examination of blood smears and criteria for diagnosis of severe malaria are given below), haemoglobin and glucose measurements using point of care devices (HemoCue® Hb 201+ and HemoCue® Glucose 201+; HaemoCue AB, Ängelholm, Sweden). If the RDT was positive, antimalarial treatment was immediately initiated based on the National Malarial Control Programme (NMCP) guidelines.

Children received parenteral artesunate at 2.4 mg/kg body weight on admission (time zero), then after 12 and 24 hours and then once a day, or artemether Injection at 3.2 mg/kg on admission, then 1.6 mg/kg body weight per day. In both cases, parenteral administration continued until the child improved and was able to take full course of oral artemisinin-based combination therapy (ACT), artemether-lumefantrine or artesunate-amodiaquine. Supportive therapy recommended for severe malaria includes the treatment of hypoglycaemia with dextrose when glucose <2.2 mmol/l, blood transfusion for children with haemoglobin less than 5 g/dL. All treatments were free of charge. No adjusted dose of parenteral artesunate for children weighing less than 20 kg was adopted by the NMCP at the time of the study conduct.

Blood smears reading

Blood films were managed as described elsewhere [9]. All RDT positive children had blood smears taken and examined by light microscopy. In brief, smears were air-dried and Giemsa-stained for examination by a light microscope fitted with 100 X oil immersion lens at a single laboratory. At least two hundred thick film fields were examined before a slide was declared negative. If *Plasmodium* asexual forms were found, a total of two hundred thick film fields were screened for *Plasmodium* species other than *P. falciparum*. If

P. falciparum was present, a count of asexual forms against leukocytes was made using a tally counter. Counting was conducted based on at least two hundred leukocytes in consistence with WHO standards. If less than 10 parasites were identified from the two hundred leukocytes screened, the count was extended to 1,000 leukocytes. On the other hand, if *P. falciparum* gametocytes were seen, a gametocyte count was performed against 1,000 leukocytes. All slides were read by two independent microscopists with a third reading in case of discordant results. The final result was based on the two most concordant readings. All readers are certified competent/expert by an external quality assurance system with Clinical Laboratory Services (<http://www.cls.co.za>), South Africa.

Severe malaria case definitions

Severe malaria was defined based on presence of one or more criteria outlined in box 1 with a malaria positive RDT result. Only haemoglobin and glucose were measured in study participants. Therefore, it was not possible to assess the incidence of other clinical features as defined by the WHO; among others the hyperlactataemia, hyperbilirubinemia, metabolic acidosis, renal failure.

Passing dark urine was considered as a proxy of haemoglobinuria. As per country NMCP guidelines, we have also included in severe cases definitions children with incoercible vomiting, lethargy, and inability to drink or suck.

Data were entered into a MS ACCESS database and analysed using STATA software (Version 14.0, College Station, TX: StataCorp; 2015). Analysis included all paediatric admissions meeting the study eligibility criteria.

Ethical and regulatory approvals

The study protocol and associated documents were reviewed and approved by CNRFP institutional bioethics committee (approval reference N° 2015/007/MS/SG/CNRFP/CNRFP/CIB), the Ministry of Health Ethical Committee for Biomedical Research (approval reference N° 2015-7-092). All study participants' parents or legal representatives gave documented informed consent before any study procedures were performed. The study was conducted according to the principles of the declaration of Helsinki and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines.

Results

Population characteristics

Characteristics of enrolled children are presented in Table 1. A total of 921 severe malaria cases were admitted based on RDT positivity. Among them, only 448 (48.6%) were confirmed positive by microscopy. At admission, 46.8% and 39.0% have received an antimalarial treatment pre-referral respectively in the LMT and the HMT area ($p = 0.017$). Among those who were microscopy negative at admission, 43.3% had received an antimalarial treatment pre-referral to the hospital. Injectable artesunate was the most

administered drug (87.0%), followed by artemether-lumefantrine (AL) (11.5%). Few numbers of cases (2.5%) have received both injectable artesunate then oral AL.

The mean time before hospital admission was 3.0 days (95% CI 2.7–3.4) and 4.0 days (95% CI 3.5–4.5) in respectively the LMT and the HMT areas.

A high proportion of children admitted (38.4%) had also received a beta lactam antibiotic prior to hospital admission. There was a statistically significant difference between the HMT and LMT areas (25.6% vs 34.4% respectively; $p = 0.01$). Antibiotics administered include Ceftriaxone (59.2%); ampicillin (29.6%) and amoxicillin (8.5%).

Overall, almost half (43.1%) of children who had received an antimalarial were also given an antibiotic.

The age of recruited children was 33.9 (± 1.3) and 36.8 (± 1.6) months in respectively LMT and HMT areas ($p = 0.15$). For children enrolled with convulsions, the mean age was 29.5 months in LMT area compared to 38.3 in the HMT area. The difference was statistically significant.

The geometric mean of asexual *P. falciparum* density was significantly higher in the LMT area compared to the HMT area (22,861 trophozoites/ μ L (95% 17,009.2–30,726.8) vs 11,291.9 trophozoites/ μ L (95% CI 8,577.9–14,864.5)). In total 58 (6.3%) of enrolled cases were harbouring *P. falciparum* gametocytes. The proportion of patients with gametocytaemia were 4.9% and 7.9% respectively in LMT and HMT areas ($p = 0.06$). The geometric mean of gametocytes density was 44.7 gametocytes/ μ L (95% CI 25.4–78.7) and 81.3 gametocytes/ μ L (95%CI 52.2-126.5) respectively in the LMT and HMT areas.

Clinical presentation of severe malaria cases

Among enrolled cases, coma was present in 70 (9.2%) participants. There were 291 children presenting convulsions prior to admissions. The number of convulsive episodes ranged from 1 to 10. Two or more convulsions prior to admissions were recorded in 196 patients (21.8%).

The mean haemoglobin level was 5.7 (± 2.7) g/dL in study participants. Severe anaemia was present in 448 children (49.2%). Other clinical features recorded included 8 cases (0.9%) of abnormal bleeding (epistaxis), 11 (1.2%) cases of circulatory collapse/shock, 80 (8.9%) patients with haemoglobinuria, 99 (10.7%) children with incoercible vomiting, 184 (19.9%) cases of lethargy, 37 (4.0%) children unable to drink/suck. Among those with haemoglobinuria, only 7 (13.9%) have reported Quinine intake during the episode.

The mean glucose level was 5.8 mmol/l (± 2.8). Severe hypoglycaemia was present in 43 (4.8%) children.

Clinical presentation of severe malaria clinical in the two study sites

The association between clinical presentation and malaria endemicity is presented in Table 2. The odds of presenting with coma, prostration, respiratory distress, haemoglobinuria, circulatory collapse/shock, and hypoglycaemia were significantly higher in children living in the HMT area compared to those

residing in the LMT area. The odd remains higher after adjusting for antimalarial treatment (pre-referral) and parasite density on admission.

Case fatality in study participants with various severe malaria clinical features

Table 3 summarizes the case fatality ratio for each clinical presentation of severe malaria. Overall, forty-four children died during hospitalization (case fatality rate 4.8%). Among them, 11 (25%) were microscopically negative at admission. In total 80% of death were recorded in children younger than 5 years. 81.8% of deaths occurred within the first 2 days of admission. Overall, case-fatality rates were highest among children with respiratory distress (26.0%), hypoglycaemia (25.0%); circulatory collapse/shock (18.8%) and those with inability to drink/suck (19.4%). The coma was also associated with a high case fatality rate (16.7%) and the case fatality for children with two or more convulsions at admission was 7.4%. The case fatality was much lower for children with prostration (7.6%), haemoglobinuria (5.3%), incoercible vomiting (4.1%), lethargy (4.5%) and anaemia (3.6%). No death was recorded in children with abnormal bleeding at admission.

Discussion

This study investigated the burden of severe malaria in two hospitals located in two areas with different malaria transmission covered by same malaria control strategies as deployed the country NMCP.

The predominant clinical presentations were anaemia (49.2%) and convulsions (21.8%); almost at the same level as reported in Burkina more than 20 years before by Modiano et al [10]. This is unexpected given the context of seasonal malaria chemoprevention implementation (SMC) and the high coverage reported [11].

SMC consists of 4 rounds of administration of sulphadoxine/pyrimethamine + Amodiaquine given at intervals of one month to children aged between 3–59 months during the peak transmission season (July to October). This strategy has been shown to drastically reduce incidence of uncomplicated and severe malaria due to *P. falciparum* infection and prevalence of malaria-related anaemia [12–14] in children who benefit. However, only the first dose of the three-day treatment regimen is given under direct observation.

The odd of presenting with coma was significantly higher in children living in the higher malaria transmission area compared to those in lower malaria transmission area. This finding is in line with the inversely correlated geometric mean parasite. These findings are not in line with previous studies conducted in sub-Saharan Africa which have shown that cerebral malaria (CM) is mostly predominant in low transmission intensity area as compared to high transmission areas [10, 15, 16]. It was hypothesized that the level of acquired immunity is an important determinant of susceptibility to CM [17]. However, the apparent conflict in results could also underline the fact that the relationships between malaria transmission intensity and disease clinical presentation is probably more complex than previously argued. It is also possible that the SMC which maintains children under prophylaxis during the high transmission season altered the naturally acquired, *Plasmodium falciparum* erythrocyte membrane

protein 1 (PfEMP1) specific immunity which has been described to play a significant role in the susceptibility to CM [18].

Shock/dehydration was the second clinical presentation more observed in HMT area compared to LMT area (adjusted OR = 5.3 (1.1–24.6)). There are many potential causes of hypotension or shock in severe malaria. These include secondary bacterial sepsis, dehydration from vomiting or fever, haemorrhage from gastrointestinal bleeding, splenic rupture, and cardiac dysfunction. This was an unexpected finding which calls for further investigations to understand the potential causes of the difference if confirmed.

Haemoglobinuria was one of the clinical syndromes significantly associated with the transmission intensity. The odds of presenting with haemoglobinuria was almost 3 times in HMT area although the overall incidence was similar to what was reported elsewhere in west Africa [19]. A number of factors including the immune hypersensitivity in long-term residents of *P. falciparum*-endemic areas who took quinine, the glucose-6-phosphate dehydrogenase (G6PD) deficiency have been described as potential causes of haemoglobinuria. Occurrence of haemoglobinuria have also been described in patients with normal erythrocyte G6PD activity who were administered quinine for severe malaria [20, 21]. However, in our study, all patients who report quinine intake was recorded in the LMT area. Also, in previous, work the prevalence of G6PD deficiency by enzymatic test was higher in LMT area compared the HMT area [22]. Another trigger is an antibiotic induced haemolysis. Indeed, Ceftriaxone has been found to induce haemolysis in many reports [23, 24]. In the current study, it was the most prescribed antibiotic (59.2%), although, predominantly in the LMT area (34.4%vs 25.6%).

The overall case fatality rate recorded in our study is relatively high (5.3%) However, it was reduced by half compared to previous reports in Burkina [10] this may be due to the improved quality of care during these last 20 years in the country.

Case-fatality rate was the highest in children with respiratory distress (26.0%) and those presenting with hypoglycaemia (25%). CFR was also high in children with shock/severe dehydration. In this study we were not able to perform blood culture and initiate adequate antibiotics treatment. It is possible that bacterial co-infections may have been overlooked.

Although most predominant, the case-fatality rate associated with severe malaria anaemia was among the lowest, in line with what previously observed by Marsh K. et al [25].

More than half (51.4%) of cases referred by peripheral health clinics, who were admitted and managed as severe malaria cases based on HRP2 RDT results turned out to be negative by microscopy probably due to the high proportion (44.1%) of children who had received pre-referral antimalarial treatment or alternatively to the low specificity of the HRP2 based RDT in our geographical context [9, 26, 27]. The high proportion of microscopically negative cases may have potential deleterious consequences for the appropriate management of hospitalized children. It is indeed possible that these children with false-positive RDT are suffering from other underlying causes to their conditions which were undetected given the focus of the clinical team on severe malaria [15]. The training of the health staff at the tertiary level of

the health system on these risks of mismanagement need to be emphasized; so that appropriate complementary investigations are undertaken whenever needed.

Conclusion

In two areas of Burkina Faso with different ecology of malaria transmission, hospital-based surveillance of severe malaria clinical presentations has shown that children in the HMT are more significantly at risk of presenting with coma, prostration, shock/dehydration, haemoglobinuria, hypoglycaemia, and respiratory distress. Case-fatality rates are high among patients with respiratory distress and those with hypoglycaemia. Hospital surveillance provides a reliable and sustainable means to monitor the clinical presentations and lethality of severe and tailor the training needs for health workers at the frontline of cases management in different transmission patterns.

Abbreviations

ACT: Artemisinin Combination Therapy drugs

CFR: Case Fatality Rate

CM: Cerebral Malaria

EIR: Entomological inoculation rate

G6PD: Glucose-6-phosphate dehydrogenase

HMT: Higher Malaria Transmission Area

HRP2: Histidine Rich Protein 2

LLIN: Long-Lasting Impregnated Net

LMT: Lower Malaria Transmission Area

RDT: Rapid Diagnosis Test

SMC: Seasonal malaria chemoprevention

WHO: World Health Organisation

Declarations

- **Ethics approval and consent to participate**

The study protocol and associated documents were reviewed and approved by CNRFP institutional bioethics committee (approval reference N° 2015/007/MS/SG/CNRFP/CNRFP/CIB), the Ministry of

Health Ethical Committee for Biomedical Research (approval reference N° 2015-7-092). All study participants' parents or legal representatives gave documented informed consent before any study procedures were performed. The study was conducted according to the principles of the declaration of Helsinki and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines.

- **Availability of data and materials**

The datasets analysed during the current study are available from the corresponding author on reasonable request.

- **Consent for publication**

Not applicable

- **Competing interests**

The authors have declared that no competing interests exist.

- **Funding**

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- **Authors' contributions**

SBS, ATK, AD and DK developed the protocol in consultation with ABT, INO, AO, FP and DM. ABT performed the data analysis in collaboration with SBS. ABT drafted the manuscript, which was edited by SBS, ATK, DK, INO, AO, AD, FP and DM. All authors read and approved the final manuscript.

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Tables

Table 1
Characteristics of enrolled children

Characteristics	Lower transmission area	Higher transmission area	Overall
Number enrolled	506 (54.9%)	415 (46.1%)	921 (100%)
Gender			
Male	272 (53.7%)	241 (58.1%)	513 (55.7%)
Female	234 (46.3%)	174 (41.9%)	408 (44.3%)
Mean time of illness before hospital admission in days (95%CI)	3.0 (2.7–3.4)	4.0 (3.5–4.5)	3.5 (3.2–3.8)
Proportion who received antimalarial treatment before admission (95% CI)	46.8% (42.4–51.3)	39.0% (34.3–43.9)	43.3% (40.0–46.6)
Proportion with fever at admission (95% CI)	79.2% (75.4–82.7)	75.2% (70.7–79.3)	77.4% (75.5–80.0)
Mean age in months (95% CI)			
Coma	48.6 (33.9–64.1)	36.9 (30.9–42.8)	39.0 (33.5–44.6)
Convulsions	29.5 (25.5–33.5)	38.3 (32.1–44.5)	33.7 (30.0–37.3)
Prostration	39.3 (34.1–44.6)	41.9 (37.6–46.2)	40.9 (37.5–44.2)
Respiratory Distress	32.1 (17.2–47.0)	29.3 (16.8–41.9)	30.5 (21.2–39.7)
Abnormal bleeding	66.8 (31.2–102.4)	-	-
Circulatory collapse/shock	9 (6.0–47)	42.4 (18.3–66.6)	36.4 (15.4–57.3)
Haemoglobinuria	50.6 (34.7–66.4)	45.3 (36.1–54.5)	46.9 (39.1–54.8)
Incoercible vomiting	34.9 (28.1–41.8)	39.0 (30.2–47.8)	36.7 (31.3–42.0)
Lethargy	35.1 (30.2–40.0)	47.8 (37.0–58.5)	37.6 (33.1–42.1)
Inability to drink /suck	37.7 (21.9–53.5)	41.7 (27.8–55.5)	39.6 (29.6–49.7)
Severe anaemia	30.9 (27.3–34.5)	31.6 (27.8–35.5)	31.2 (28.6–33.8)

Characteristics	Lower transmission area	Higher transmission area	Overall
Hypoglycaemia	29.2 (14.5–43.9)	26.2 (19.9–32.6)	27.4 (20.8–34.0)
Proportion of microscopically confirmed <i>P. falciparum</i> infection (95% CI)	42.7% (38.3–47.1)	55.9% (50.9–60.7)	48.6% (45.4–51.9)
Geometric mean of <i>P. falciparum</i> count (trophozoits/μL) (95% CI)	22,861.3 (17,009.2–30,726.8)	11,291.9 (8,577.9–14,864.5)	15,865.8 (12,946.4–19,443.6)
Ethnicity (95% CI)			
Fulani	4.3% (2.7–6.5)	9.6% (7.0–12.9)	6.7% (5.2–8.5)
Other ethnic groups	95.7% (93.5–97.2)	90.4% (87.1–93.0)	93.3% (91.4–94.8)
Proportion with recent history of malaria/fever episode (current malaria season)	42.5% (38.1–46.9)	70.1% (65.5–74.5)	54.9% (51.7–58.2)

Table 2
Association between clinical presentation and malaria endemicity

Clinical presentation	Total	Lower transmission area	Higher transmission area	Odd ratio (OR)	
				Unadjusted OR (with 95% CI)	Adjusted OR (with 95% CI)
Coma	70	13 (2.6%)	57 (13.7%)	6.0 (3.2–11.2)	6.5 (3.4–12.1)
Convulsions	196	105 (20.8%)	91 (21.9%)	1.0 (0.8–1.5)	1.1 (0.8–1.5)
Prostration	385	162 (32.0%)	223 (53.7%)	2.5 (1.9–3.2)	2.5 (1.9–3.3)
Respiratory Distress	53	22 (4.3%)	31 (7.5%)	1.8 (1.0-3.1)	1.8 (1.0-3.2)
Abnormal bleeding	8	7 (1.4%)	1 (0.2%)	0.2 (0.02–1.4)	0.2 (0.1–1.3)
Circulatory collapse/shock	11	2 (0.4%)	9 (2.2%)	5.6 (1.2–26.0)	5.9 (1.3–27.9)
Haemoglobinuria	80	26 (5.1%)	54 (13.0%)	2.8 (1.7–4.5)	2.7 (1.6–4.3)
Incoercible vomiting	99	57 (11.2%)	42 (10.1%)	0.9 (0.6–1.4)	0.9 (0.6–1.3)
Lethargy	184	149 (29.4%)	35 (8.4%)	0.2 (0.1–0.3)	0.2 (0.1–0.3)
inability to drink /suck	37	19 (3.7%)	18 (4.3%)	1.2 (0.6–2.2)	1.1 (0.6–2.2)
Severe anaemia	448	252 (50.7%)	196 (47.5%)	0.9 (0.7–1.1)	0.9 (0.7–1.1)
Hypoglycaemia	43	17 (3.4%)	26 (6.4%)	1.9 (1.0-3.6)	1.9 (1.0-3.6)

Table 3

Case fatality rates associated with the different clinical presentations

Clinical presentation	CFR (% , 95%CI)		
	Lower transmission area	Higher transmission area	Overall
Coma	2/13 (15.3%, 1.9%-45.4%)	9/53 (16.9%, 8.1%-29.8%)	11/66 (16.7%, 8.6%-27.9%)
Convulsions	7/102 (6.9%, 2.8%-13.6%)	7/86 (8.1%, 3.3%-16.0%)	14/188 (7.4%, 4.1%-12.2%)
Prostration	10/154 (6.5%, 3.1%-11.6%)	18/213 (5.1%-13.0%)	28/367 (7.6%, 5.1%-10.8%)
Respiratory Distress	5/21 (23.8%, 8.2%-47.2%)	8/29 (27.6%, 12.8%-47.2%)	13/50 (26.0%, 14.6%-40.3%)
Abnormal bleeding	-	-	-
Circulatory collapse/shock	0/2 (-)	2/9 (22.2%, 2.8%-60.0%)	2/11 (18.2%, 2.3%-51.8%)
Haemoglobinuria	1/23 (4.3%, 0.1-21.9%)	3/53 (5.7%, 1.2-15.7%)	4/76 (5.3%, 1.4%-12.9%)
Incoercible vomiting	3/56 (5.4%, 1.1%-14.9%)	1/42 (2.4%, 0.1%-12.6%)	4/98 (4.1%, 1.1%-10.1%)
Lethargy	5/144 (3.5%, 1.1%-7.9%)	3/34 (8.8%, 1.8%-23.7%)	8/178 (4.5%, 1.9%-8.7%)
Inability to drink /suck	5/18 (27.8%, 9.7%-53.5%)	2/18 (11.1%, 1.4%-34.7%)	7/36 (19.4%, 8.2%-36.0%)
Severe anaemia	7/243 (2.9%, 1.2%-5.8%)	8/180 (4.4%, 1.9%-8.6%)	15/423 (3.5%, 2.0%-5.8%)
Hypoglycaemia	3/17 (17.6%, 3.8%-43.4%)	7/23 (30.4%, 13.2-52.9%)	10/40 (25%, 12.7%-41.2%)

Box

Box 1: Features of Severe malaria

Clinical features of severe malaria

- Impaired consciousness (including unrousable coma);
- Prostration, i.e. generalized weakness so that the patient is unable to sit, stand or walk without assistance
- Multiple convulsions: more than two episodes within 24h;
- Acute pulmonary oedema and acute respiratory distress syndrome.
- Circulatory collapse or shock, systolic blood pressure
- Clinical jaundice plus evidence of other vital organ dysfunction
- Abnormal bleeding.
- Haemoglobinuria (dark urine or coca cola);

Laboratory findings

- Hypoglycaemia (< 2.2mmol/l or < 40mg/dl);
- Severe anaemia (haemoglobin < 5g/dl)

Danger signs as per NMCP guidelines

- Incoercible vomiting
- Lethargy
- Inability to drink or suck.