

Risk factors of mortality related to severe malaria among children in Referral Hospitals of Kisangani

ABSTRACT

Aims: This study aimed at determining the factors associated with mortality in childhood severe malaria in Kisangani. For Democratic Republic of Congo is one of African countries with highest mortality rate of under five children.

Study design: cross-sectional study.

Place and Duration of Study: Data were collected from medical folders of all children of 6 months to 16 years-old, hospitalized in 4 general reference hospitals (GRH) of Kisangani town, from January to December, 2015. We selected only children with severe malaria confirmed by a positive thick blood smear and/or positive rapid diagnosis test.

Methodology: Sociodemographic and clinical data of deceased children were compared to those of alive or controls. Association of severity criteria and other factors to fatal prognosis was assessed by chi-square or Yate's adjustment. Bivariate analysis used odds ratio to evaluate the risk of dying. Means were compared by test t of student.

Results: Among 3410 children hospitalized for miscellaneous causes, 1194 had clinical and 845 confirmed severe malaria. The sex ratio M/F was 1.34. Most of children were under 5 years old (73.1%) and the most frequent severity criterion of malaria was pallor, followed by respiratory distress, icterus and coma. Quinine was used in 84.3%. Twenty-nine out of 845 children died (3.43%) and factors associated to this fatality were male sex ($P = .04$), age under 5 years-old ($P = .002$). The risk of dying was high when children had circulatory collapse or shock ($P < .001$), coma ($P = .0008$), icterus ($P = .003$), and ≥ 2 severity criteria ($P = .005$). Sixty-six percent received antibiotics without any microbiological exam.

Conclusion: The malaria-related mortality is still high and associated with avoidable factors. Supervising health workers in GRH and providing them with more technical assistance to address complications in severe malaria can help to save more children.

Keywords: severe malaria, children, risk factors, mortality

1. INTRODUCTION

Malaria is one of the main causes of morbidity and mortality in children of low income countries. In 2015, WHO noticed that cases of deaths related to malaria diminished but diminution was low in countries with high prevalence. The global burden of malaria-related mortality is dominated by sub-Saharan countries. Among them, Nigeria and Democratic Republic of Congo (DRC) represent more than 34% of world-wide deaths related to malaria [1]. These deaths are due to severe malaria. Losimba *et al* determined that the limited available technical tools of the General Reference Hospitals (GRH) of Kisangani and the organization of the patient care may result in an under-estimation of metabolic complications in severe malaria and of other severe infections in young children, even when effective drugs were available. In the same study, the case specific fatality rate was 7.7% in confirmed cases [2]. Since 2012, Democratic Republic of Congo changed policy of severe malaria treatment from intravenous quinine to intravenous artesunate, according to WHO guidelines [3]. Studies showed that the new policy was acceptable and feasible [4]. This study was conducted in order to determine the factors associated with death among children hospitalized with severe malaria in GRH of Kisangani.

2. MATERIAL AND METHODS

2.1 Study design and area

33 This was a cross-sectional study conducted in four GRH (out of five) of Kisangani town: Lubunga,
34 Kabondo, Mangobo and Makiso-Kisangani.

35 36 2.2 Duration of the study

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38 Collected data concerned a period of 12 months, from January to December 2015. Data were
39 collected retrospectively.

40 41 2.3 Sample size

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43 Were included in the study medical files that matched these criteria: (i) children of 6 months old to 16
44 years old (ii) hospitalized in the 4 GRH cited above, (iii) with the clinical diagnosis of severe malaria
45 according to WHO case definition [5, 6], (iv) confirmed by a positive rapid diagnosis test (RDT) or a
46 positive thick blood smear (TBS).

47 The RDT used was manufactured by Standard Diagnostics Bioline® (Malaria antigen P.f/Pan). All
48 GRH used the same national policy, that recommends the management of severe malaria by
49 intravenous artesunate (Artesun®, Guilin Pharmaceutical Co. Ltd. China) or intravenous quinine when
50 the former was unavailable in stock. Files of children that did not match inclusion criteria were
51 excluded.

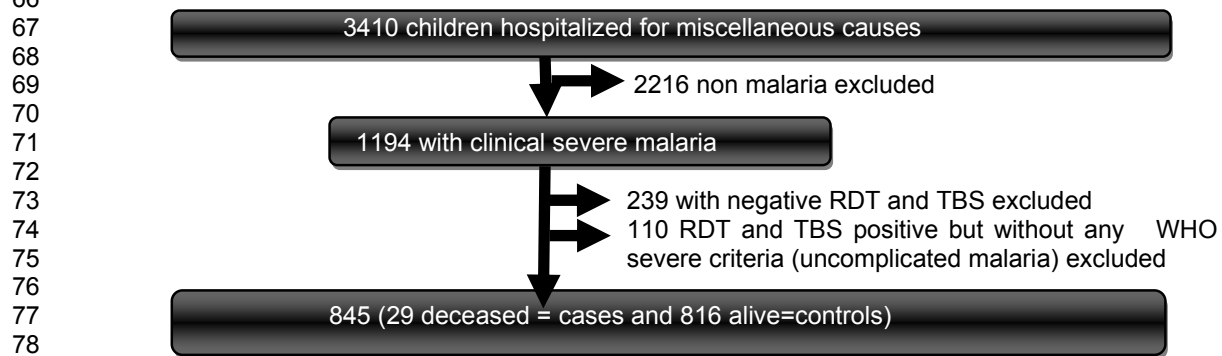
52 A former study about childhood severe malaria in the same town found, five years earlier, a
53 prevalence of 13.4 % [2]. Therefore, the sample for this study was calculated by this formula: $n = (z^2 \times$
54 $p \times q) / d^2$ with an error risk of 5%. Data of dead children (cases) were compared with those of alive
55 (controls) in order to determine the risk factors associated with death in childhood severe malaria.

56 57 2.4 Data analysis and ethics

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59 Data were encoded and analyzed by Epi info™ 7.2.1.0. To describe the sample, we used arithmetic
60 mean, standard deviation and percentages. Bi- and multivariate analysis were realized by Pearson's
61 chi-square, Fisher exact, t test of student, and odds ratio.

62 This study had the agreement of Research authorities of the Faculty of Medicine and Pharmacy of the
63 University of Kisangani. Data were anonym and not available to people stranger to the study.

64 65 3. RESULTS AND DISCUSSION



81 Figure 1. Flow chart of selected patients.
82 The malaria-related mortality was 3.43 %.

83 84 85 3.1 Descriptive data

86
87 Table 1. Socio-demographic and clinical data of children with severe malaria
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		Frequency %	
Age	6 months to 5 years-old	618	73.14%

	6 - 10 years old	151	17.87%
	11 - 16 years old	76	8.99%
Sex	Boys	485	57.40%
	Girls	360	42.60%
Address	Makiso	299	35.38%
	Kabondo	163	19.29%
	Lubunga	133	15.74%
	Mangobo	114	13.49%
	Tshopo	84	9.94%
	Kisangani	52	6.15%
Severity signs	Pallor	607	71.83%
	Respiratory distress	574	67.93%
	Icterus	140	16.57%
	Seizures	110	13.02%
	Coma	66	7.81%
	Hemoglobinuria (Coca-Cola like urines)	29	3.43%
	Circulatory collapse or shock	26	3.08%
	Bleeding	12	1.42%
Antimalarials	Quinine	713	84.38%
	Artesunate	132	15.62%
Other treatment	Blood transfusion	463	54.79%
	Antibiotics	560	66.27%

Children of less than 5 years-old were the most numerous and quinine was more used than artesunate in the management of severe malaria in GRH Kisangani.

The mean temperature at admission was 38.1°C (37.6 – 41.3°C). About clinical forms, the most frequent form was anemia (N=612; 72.4%), neurologic manifestations (N=142; 16.8%), respiratory (N=47; 5.6%), icteric (45; 5.3%), digestive (N=35; 4.1%), hemoglobinuria (N=25; 2.9%), haemorrhage (N=1; 0.1%). Note that in 62 cases we had two severity criteria: 49 with both anemia and neurologic manifestations, 9 with both anemia and hemoglobinuria, 4 with neurologic manifestations and hemoglobinuria.

3.2 Analytic data

Table 2. Factors associated with mortality

		Alive	Deceased	OR (95% CI)	P
Age	≤ 5 years-old	592	26		
	6 – 10 years-old	148	3		.04*
	10 – 16 years-old	76	0		
Sex	Boys	460	25		.002*
	Girls	356	4	.2 (.07- .5)	

* Yate's correction

Mortality related to malaria was associated with sex and age. Hemoglobin mean of dead children (5.3 ± 1.5 g/dl) was significantly lower than that of alive children (7.3 ± 2 g/dl): $t(843) = 5.02$; $P < .0001$.

Table 3. Severity criteria related to fatal prognosis

Severity criterion	Alive	Deceased	OR (95% CI)	P
Circulatory collapse	17	9	.04 (.01- .1)	< .0001
Coma	59	7	.2 (.1 - .5)	.0008[†]
Seizures	103	7	.4 (.1 - 1)	.07
Dyspnea	554	20	.9 (.4 – 2.1)	.4
Icterus	129	11	.03 (.1 - .6)	.003
Pallor	652	23	1.03 (.4 – 2.5)	.4
Hemoglobinuria	29	0	1.03 (1.02 -1.05)*	.6
≥ 2 criterion	56	6	.2 (.1 – .7)	.005

* Risk Ratio instead of Odds ratio (OR); †: Yate's correction

Fatal prognosis was associated with circulatory collapse, coma, icterus and the association of 2 or more severity criteria.

3.3 Discussion

The mortality rate was 3.43%. Children under 5 years old were the most numerous. Quinine was more used than artesunate in the management of severe malaria in GRH Kisangani (Table 1). These results can be due to low compliance of physicians to national policy. Intravenous artesunate might have been unavailable in the GRH. Ntuku conducted a study in DRC and found that implementation of intravenous artesunate was possible and feasible [4]. But the study concerned only 2 provinces out of 26 in the DRC, amongst those where roads are in better state.

The most frequent form was anemia. Our results are close to those found by Kunuanunua in Kinshasa, DRC: mortality rate 4%, predominance of under five, anemia as the most frequent form [7]. These results show that infant mortality due to malaria is decreasing because, four years earlier, in the same town, Losimba found 7.7% [2]. Our rate is higher than the 1.2% found by Saravu in India [8], and the 2.1% by Bouyou-Akotet in Gabon [9]. That can be explained by the fact that GHR in Kisangani have poor laboratory medicine to help management of metabolic complications due to severe malaria, fact noticed by other researchers [10].

The rate of hemoglobinuria was lower than 19.1% found by Ajetunmobi in Nigeria [11] and 25.4% by cKunuanunua in DRC [7]. This might be due to the low predictive value of clinical appreciation that was used in GRH Kisangani. Only too obvious cases could be noticed, leading to underestimation. Respiratory distress cases were higher than 40% [12]: severe anemia, metabolic acidosis, undetected bacterial pneumonia might be the cause.

Factors associated with mortality

Mortality related to malaria was associated with sex and age (Table 2): most of children who died were male under 5 years old, fact confirmed by numerous scientific papers [2, 5, 7, 8]. Even though hemoglobin level of dead children was significantly lower than that of alive, pallor was not associated with high risk of death. This emphasizes the role of laboratory where clinical appreciation alone may confound pallor due to severe anemia with that due to circulatory collapse and others complications. Fatal prognosis was associated to presence of choque, coma, icterus and to association of 2 or more severity criteria (Table 3). Jallow, in Gambia, found coma and jaundice [13] other found anemia, neurologic manifestations, respiratory distress and jaundice as most predictive of malaria lethality [2, 7, 8, 14].

Apart from poor technical supplies to address metabolic complications, we noticed that 8 children out of 10 still received quinine instead of intravenous artesunate. Many studies had stated that intravenous artesunate was superior, less expensive than quinine and saved more lives [3, 4, 14, 15, 16, 17]. This was an actual avoidable but big concern for national malaria program to check out whether intravenous artesunate availability mattered or doctors had low compliance to national policy. Biai found that supervising healthcare workers to adhere to a standardized treatment protocol was associated with greatly reduced in-hospital mortality [14]

Limits

Biological or microbiological data were not recorded to rule out bacterial infections among children hospitalized or died with severe malaria diagnosis because none of GRH had C reactive protein tests or bacteriology. About icteric children, no serological and transaminase results were found that could help to rule out associated hepatitis. Therefore, it is not sure that the 29 children died with severe malaria alone. Losimba found that poor technical support caused an underestimation of metabolic complications [2]. The lack of laboratory devices that provides evidence for ruling out associated sepsis or other bacterial infections leads to unnecessary use of antibiotics [4].

4. CONCLUSION

The malaria-related mortality of children in DRC is still high and associated to avoidable factors. Supervising health workers in GRH Kisangani and giving to them more technical assistance to address complications in severe malaria can help to save more children.

ETHICAL APPROVAL

This study had the agreement of research authorities of the Faculty of Medicine and Pharmacy. Data collected were anonym and inaccessible to people stranger to the medical research team.

REFERENCES

1. WHO, World malaria report 2017, Geneva, 2017
2. Losimba L.J, D'Alessandro U, Donnenc P., Wilmet Dramaix M, Clinical aspects and outcome of suspected severe pediatric malaria, *Médecine et maladies infectieuses*. 2012, 42, 315–320
3. National Malaria Program (Programme National de Lutte contre le Paludisme PNLP). National Guidelines on malaria management in Democratic Republic of Congo, Public Health Ministry; 2012.
4. Ntuku H, Ferrari G, Burri C, Tshefu A, Kalemwa D, Lengeler C, Feasibility and acceptability of injectable artesunate for the treatment of severe malaria in the Democratic Republic of Congo, *Malar J* 2016, 15:18 DOI 10.1186/s12936-015-1072-x
5. WHO, Guidelines for the treatment of malaria, third edition, Geneva, 2015
6. WHO, WHO malaria terminology, Geneva, 2016

- 189 7. Kunuanunua TS, Nsibu CN, Bodi JM, Tshibola TK, Makusi Bura M, Magoga K, Ekila MB, Severe
190 malaria in children: A descriptive report from Kinshasa, the Democratic Republic of Congo. *J*
191 *Trop Pediatr*. 2015, 61(4):272-8.
- 192 8. Saravu K, Rishikesh K, Kamath A, Determinants of mortality, intensive care requirement and
193 prolonged hospitalization in malaria - a tertiary care hospital based cohort study from South-
194 Western India. *Malar J*. 2014, 13:370.
- 195 9. Bouyou-Akotet MK, Mawili-Mboumba DP, Kendjo E, Eyang Ekouma A, Abdou Raouf O,
196 Complicated malaria and other severe febrile illness in a pediatric ward in Libreville, Gabon. *BMC*
197 *Infect Dis*. 2012, 13; 12:216.
- 198 10. Maitland, Management of severe paediatric malaria in resource-limited settings, *BMC Medicine*
199 2015, 13:42
- 200 11. Ajetunmobi WA, Orimadegun AE, Brown BJ, Afolabi NK, Olabiyi FA Haemoglobinuria among
201 children with severe malaria attending tertiary care in Ibadan, Nigeria. *Malar J*. 2012, 5; 11:336.
- 202 12. Taylor WR, Hanson J, Turner GD, White NJ, Dondorp AM, Respiratory manifestations of
203 malaria., *Chest*. 2012;142(2):492-505.
- 204 13. Jallow M, Casals-Pascual C, Ackerman H, Walther B, Walther M, Pinder M, Sisay-Joof F, Clinical
205 features of severe malaria associated with death: a 13-year observational study in the Gambia.
206 *PLoS One*. 2012;7(9): e45645.
- 207 14. Biai S, Rodrigues A, Gomes M, Ribeiro I, Sodemann M, Alves F, Aaby P. Reduced in-hospital
208 mortality after improved management of children under 5 years admitted to hospital with malaria:
209 randomized trial. *BMJ*. 2007, 27;335(7625):862.
- 210 15. Dondorp A, Fanello C, Hendriksen I, Artesunate versus quinine in the treatment of severe
211 falciparum malaria in African children (AQUAMAT): an open-label, randomised trial, *Lancet*.
212 2010; 376(9753): 1647–1657.
- 213 16. Sinclair D, Donegan S, Lalloo DG, Artesunate versus quinine for treating severe malaria.
214 *Cochrane Database Syst Rev*. 2012, 13;6:CD005967.
- 215 17. Abdallah TM, Elmardi KA, Elhassan AH, Omer MB, Elhag MS, Desogi MA, Comparison of
216 artesunate and quinine in the treatment of severe Plasmodium falciparum malaria at Kassala
217 hospital, Sudan. *J Infect Dev Ctries*. 2014 14;8(5):611-5.
- 218 18. Hildenwall H, Ben Amos, Mtove G, Muro F, Cederlund K, Causes of non-malarial febrile illness in
219 outpatients in Tanzania, *Trop Med Int Health*, 2016, 21:1, 149–156 2016
- 220 19. Hildenwall H, Muro F, Jansson J, Mtove G, Reyburn H, Point-of-care assessment of C-reactive
221 protein and white blood cell count to identify bacterial aetiologies in malaria-negative paediatric
222 fevers in Tanzania, *Trop Med Int Health*. 2017; 22(3): 286–293