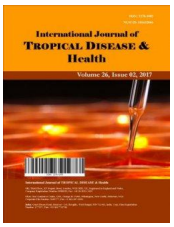

*International Journal of TROPICAL DISEASE & Health*

*31(2): 1-6, 2018; Article no.IJTDH.40898*
*ISSN: 2278–1005, NLM ID: 101632866*

# Risk Factors of Mortality Related to Severe Malaria among Children in Referral Hospitals of Kisangani

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***Authors' contributions***

*This work was carried out in collaboration between all authors. Author BGM designed the study, performed the statistical analysis, wrote the protocol, and the first draft of the manuscript. Author KVM contributed to bibliography research reviewing and analysis of results. Author OA edited the study design, methods and results analysis. All authors read and approved the final manuscript.*

***Article Information***

DOI: 10.9734/IJTDH/2018/40898
Editor(s):
(1) Dr. Paul M. Southern, Professor, Department of Pathology and Internal Medicine, University of Texas Southwestern Medical Center at Dallas, USA.
Reviewers:
(1) Iragbogie Al-Mustapha Imoudu, Federal Medical Centre, Nigeria.
(2) K. Abdullahi, Usmanu Danfodiyo University, Nigeria.
(3) Ali Mahmud Umar, Kano University of Science and Technology, Nigeria.
(4) Taratisio Ndwiga, Moi University, Kenya.
Complete Peer review History: http://www.sciencedomain.org/review-history/25343

***Original Research Article***

***Received 21st March 2018***
***Accepted 28th May 2018***
***Published 30th June 2018***

## 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 diagnostic 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.

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**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 worldwide 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, especially GRH of Kabondo and GRH Makiso-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 artésunate, 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. MATERIALS AND METHODS

### 2.1 Study Design and Area

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

### 2.2 Duration of the Study

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

### 2.3 Sample Size

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

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

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

### 2.4 Data Analysis and Ethics

Data were encoded and analyzed by Epi info™ 7.2.1.0. To describe the sample, we used arithmetic mean, standard deviation and percentages. Bi- and multivariate analysis were

realized by Pearson's chi-square, Fisher exact, t-test of student, and odds ratio.

This study had the agreement of Research authorities of the Faculty of Medicine and Pharmacy of the University of Kisangani, where as informed consent is also taken. Data were anonym and not available to people stranger to the study.

## 3. RESULTS AND DISCUSSION

The malaria-related mortality was 3.43 %.

### 3.1 Socio-demographic Features

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 both anemia and neurologic manifestations, 9 both anemia and hemoglobinuria, 4 neurologic manifestations and hemoglobinuria.

### 3.2 Risk Factors

Sex and age were associated to death with severe ml. There was association between sex and age. Haemoglobin means 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 1. Socio-demographic and clinical data of children with severe malaria**

| | | Frequency | % |
|---|---|---|---|
| Age | 6 months to 5 years | 618 | 73.14% |
| | 6 - 10 years | 151 | 17.87% |
| | 11 - 16 years | 76 | 8.99% |
| Sex | Boys | 485 | 57.40% |
| | Girls | 360 | 42.60% |
| Address | Makiso | 299 | 35.38% |
| | Kabongo | 163 | 19.29% |
| | Lubunga | 133 | 15.74% |
| | Manobo | 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% |

**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*

**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*

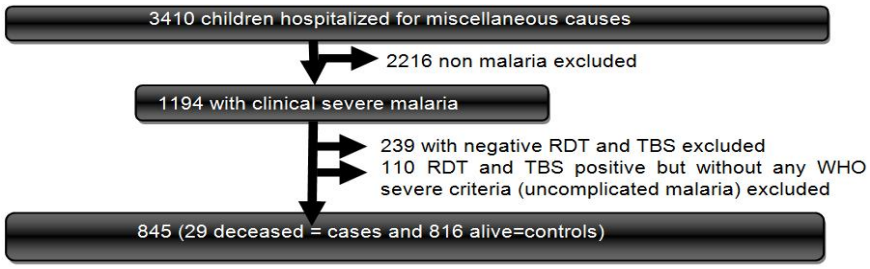


**Fig. 1. Flowchart of selected patients**

The 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 five 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 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 two provinces out of 26 in the DRC, amongst those where roads are in the better state.

The most frequent form was anaemia. Results in this study are close to those found by Kunuanunua in Kinshasa, DRC: mortality rate 4%, predominance of under five, anaemia 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 has poor laboratory medicine to help management of metabolic complications due to severe malaria, the 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 apparent cases could be noticed, leading to underestimation.

Respiratory distress cases were higher than 40% [12]: severe anaemia, metabolic acidosis, undetected bacterial pneumonia might be the cause.

Mortality related to malaria was associated with sex and age (Table 2): most of the children who died were male under five years old, the fact confirmed by numerous scientific papers [2,5,7,8]. Even though haemoglobin level of dead children was significantly lower than that of alive, pallor was not associated with high risk of death. This emphasises the role of the laboratory where clinical appreciation alone may confound pallor due to severe anaemia with that due to circulatory collapse and others complications.

The fatal prognosis was associated to the presence of choque, coma, icterus and the association of 2 or more severity criteria (Table 3). Jallow, in the Gambia, found coma and jaundice [13] other found anaemia, neurologic

manifestations, respiratory distress and disease as most predictive of malaria lethality [2,7,8,14].

Apart from poor technical supplies to address metabolic complications, we noticed that eight 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 [3,4,14,15,16,17,18,19]. 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 domestic policy. Biai found that supervising healthcare workers to adhere to a standardised treatment protocol was associated with significantly reduced in-hospital mortality [14].

## 4. LIMITS

Biological or microbiological data were not recorded to rule out bacterial infections among children hospitalised 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 of 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].

## 5. CONCLUSION

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

## CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

## ETHICAL APPROVAL

This study had the agreement of research authorities of the Faculty of Medicine and Pharmacy of the University of Kisangani.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES

1. WHO, World malaria report 2017, Geneva; 2017.
2. Losimba LJ, 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.
7. Kunuanunua TS, Nsibu CN, Bodi JM, Tshibola TK, Makusi Bura M, Magoga K, Ekila MB, Severe malaria in children: A descriptive report from Kinshasa, the Democratic Republic of Congo. J Trop Pediatr. 2015;61(4):272-8.
8. Saravu K, Rishikesh K, Kamath A, Determinants of mortality, intensive care requirement and prolonged hospitalization in malaria - A tertiary care hospital based cohort study from South-Western India. Malar J. 2014;13:370.
9. Bouyou-Akotet MK, Mawili-Mboumba DP, Kendjo E, Eyang Ekouma A, Abdou Raouf O. Complicated malaria and other severe febrile illness in a pediatric ward in Libreville, Gabon. BMC Infect Dis. 2012;13:12:216.
10. Maitland. Management of severe paediatric malaria in resource-limited settings. BMC Medicine. 2015;13:42.
11. Ajetunmobi WA, Orimadegun AE, Brown BJ, Afolabi NK, Olabiyi FA. Haemoglobinuria among children with severe malaria attending tertiary care in Ibadan, Nigeria. Malar J. 2012;5(11):336.

12. Taylor WR, Hanson J, Turner GD, White NJ, Dondorp AM, Respiratory manifestations of malaria. Chest. 2012;142(2):492-505.
13. Jallow M, Casals-Pascual C, Ackerman H, Walther B, Walther M, Pinder M, Sisay-Joof F. Clinical features of severe malaria associated with death: A 13-year observational study in the Gambia. PLoS One. 2012;7(9):e45645.
14. Biai S, Rodrigues A, Gomes M, Ribeiro I, Sodemann M, Alves F, Aaby P. Reduced in-hospital mortality after improved management of children under 5 years admitted to hospital with malaria: randomized trial. BMJ. 2007;27;335(7625):862.
15. Dondorp A, Fanello C, Hendriksen I. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): An open-label, randomised trial. Lancet. 2010;376(9753): 1647–1657.
16. Sinclair D, Donegan S, Lalloo DG, Artesunate versus quinine for treating severe malaria. Cochrane Database Syst Rev. 2012;13(6):CD005967.
17. Abdallah TM, Elmardi KA, Elhassan AH, Omer MB, Elhag MS, Desogi MA. Comparison of artesunate and quinine in the treatment of severe *Plasmodium falciparum* malaria at Kassala hospital, Sudan. J Infect Dev Ctries. 2014;8(5): 611-5.
18. Hildenwall H, Ben Amos, Mtove G, Muro F, Cederlund K, Causes of non-malarial febrile illness in outpatients in Tanzania, Trop Med Int Health. 2016;21(1):149–156.
19. Hildenwall H, Muro F, Jansson J, Mtove G, Reyburn H, Point-of-care assessment of C-reactive protein and white blood cell count to identify bacterial aetiologies in malaria-negative paediatric fevers in Tanzania. Trop Med Int Health. 2017;22(3):286–293.



*Peer-review history:*
*The peer review history for this paper can be accessed here:*
*http://www.sciencedomain.org/review-history/25343*