

# Original Research Article

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

### ABSTRACT

**Aims:** This study was aimed to find out which factors were associated to mortality of severe malaria in children of Democratic Republic of Congo, among the highest in Africa.

**Study design:** This study was descriptive and analytic cross-sectional.

**Place and Duration of Study:** Data were collected from medical folders of all children of 6 months to 16 years-old, hospitalized in four 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:** We first described sociodemographic and clinical data. Then we compared data of deceased children 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 if necessary. We also used Odds ratio to evaluate the risk of dying. Means were compared by test t of student.

**Results:** Out of 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 choque ( $P < .001$ ), coma ( $P = .0008$ ), icterus ( $P = .003$ ), and  $\geq 2$  severity criteria ( $P = .005$ ). Sixty-six percent received antibiotics without any microbiological exam.

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

**Keywords:** severe malaria, children, mortality, Kisangani

### 1. INTRODUCTION (ARIAL, BOLD, 11 FONT, LEFT ALIGNED, CAPS)

Malaria is one of the main causes of morbidity and mortality of children in 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) 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, detrimental to patients, even when effective drugs were available. In the same study, they found that the case specific fatality rate was 7.7% in confirmed cases [2].

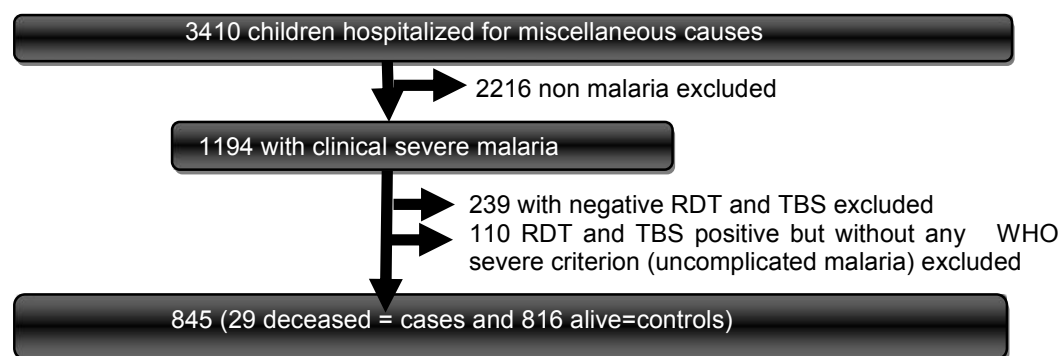
Since 2012, Democratic Republic of Congo changed policy of severe malaria treatment from intravenous quinine to intravenous artesunate, according to WHO guidelines [3]. Studies showed that the new policy was acceptable and feasible [4]. This study was realized in order to determine which factors were associated to death among children hospitalized with severe malaria in GRH of Kisangani.

### 2. MATERIAL AND METHODS

This descriptive and cross-sectional study was realized within four GRH (out of five) in Kisangani town: Lubunga, Kabondo, Mangobo and Makiso-Kisangani. Collected data concerned the period from 1st January to 31st December 2015. We included in the study (i) children of 6 months-old to 16 years-old (ii) hospitalized in the 4 GRH cited above, (iii) for the clinical diagnosis of severe malaria

36 according to WHO case definition [5-6], (iv) with a parasitological confirmation by a positive rapid  
 37 diagnostic test (RDT) or a positive thick blood smear (TBS).  
 38 The RDT used was manufactured by Standard Diagnostics Bioline® (Malaria antigen P.f/Pan). All  
 39 GRH used the same national protocol of management of severe malaria and cases were managed  
 40 either by intravenous artesunate (Artesun®, Guilin Pharmaceutical Co. Ltd. China) or intravenous  
 41 quinine when the former was unavailable in stock. All children who did not match inclusion criteria  
 42 were excluded.  
 43 A former study in the same town found, five years earlier, a prevalence of 13,4 % of confirmed severe  
 44 malaria [2]. Therefore, we had to settle a sample equal or greater than 179 cases, on the basis of the  
 45 formula  $n \geq (z^2 * p * q) / d^2$  with an error risk of 5%. We then compared data of dead children (cases) with  
 46 that of alive (controls) in order to find out risk factors of dying with malaria.  
 47 We encoded data and analyzed them by Epi info™ 7.2.1.0. To describe the sample, we used  
 48 arithmetic mean, standard deviation and percentages. Bi- and multivariate analysis were realized by  
 49 Pearson's chi-square, Fisher exact, t of student, odds ratio.  
 50 About ethics, this study had the agreement of Research authorities of the Faculty of Medicine and  
 51 Pharmacy of the University of Kisangani. Data were anonym and not available to people stranger to  
 52 the study.  
 53

### 54 3. RESULTS AND DISCUSSION



70 Fig. 1. Flow of selected patients.  
 71 The malaria-related mortality was 29 out of 845 (3,43%)

#### 74 3.1 Descriptive data

76 Table 1. Socio-demographic and clinical data of children with severe malaria

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

### 3.2 Analytic data

Table 2. Factors associated to 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        | 0,2 (0,07-0,5) |       |

\* 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                         |
|--------------------|-------|----------|--------------------|---------------------------|
| Choque             | 17    | 9        | 0,04 (0,01-0,1)    | <b>&lt; 0,0001</b>        |
| Coma               | 59    | 7        | 0,2 (0,1 - 0,5)    | <b>0,0008<sup>†</sup></b> |
| Seizures           | 103   | 7        | 0,4 (0,1 - 1)      | 0,07                      |
| Dyspnea            | 554   | 20       | 0,9 (0,4 - 2,1)    | 0,4                       |
| Icterus            | 129   | 11       | 0,03 (0,1 - 0,6)   | <b>0,003</b>              |
| Pallor             | 652   | 23       | 1,03 (0,4 - 2,5)   | 0,4                       |
| Hemoglobinuria     | 29    | 0        | 1,03 (1,02 -1,05)* | 0,6                       |
| ≥ 2 criterion      | 56    | 6        | 0,2 (0,1 – 0,7)    | <b>0,005</b>              |

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

Fatal prognosis was associated to presence of choque, coma, icterus and to association of 2 or more severity criteria.

### 3.3 Discussion

#### 3.1.1 Descriptive data

We found a mortality rate of 3.43%. Children under 5 years-old were the most numerous and quinine was more used than artesunate in the management of severe malaria in GRH of Kisangani (table 1). The most frequent form was anemic. Our results are close to those found by Kunuanunua et al in Kinshasa, DRC: mortality rate 4%, predominance of under five years-old, of anemic forms [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 that 1.2% found by Saravu in India [8], or 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 emphasized by other researchers [10].

Our rate of hemoglobinuria was lower than 19.1% found by Ajetunmobi in Nigeria [11] and 25.4% by Kunuanunua in DRC [7]. Clinical appreciation has its weaknesses: only too obvious cases can be noticed, leading to underestimation.

Respiratory distress cases were higher than 40% [12]: we must consider additional respiratory disorders due to severe anemia and metabolic complications.

#### 3.1.2 Factors associated to 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 to high risk of death. This emphasize the role of laboratory where clinical appreciation alone may confound pallor due to severe anemia with that due to choque 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, also found coma and jaundice [13] but many others found anemia, neurologic, pulmonary and icteric form 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. This is 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]

## 137 Limits

138 We did not record biological or microbiological data to rule out bacterial infection among children  
 139 hospitalized or died with malaria diagnosis because none of GRH had C reactive protein tests nor  
 140 bacteriology. We did not find biochemical exams to check out hypoglycemia. About icterus, we did not  
 141 find serological and transaminase results to rule out liver associated diseases or hepatitis. Because of  
 142 all this, we cannot say, *stricto sensu*, that the 29 children who died had malaria alone. This is due, like  
 143 Losimba et al found it, to poor technical support that result in underestimating the metabolic  
 144 complications [2]. This leads to overuse of antibiotics like found in this study (table1) and in Hiden's  
 145 [4]. Further studies must focus on this issue with evidence-based exams to find out the actual.

## 146 4. Conclusion

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

## 150 ETHICAL APPROVAL

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

## 153 REFERENCES

- 154 1. WHO, *World malaria report 2017*, Geneva, 2017
- 155 2. Losimba L.J, D'Alessandro U, Donnenc P., Wilmet Dramaix M, Clinical aspects and outcome of  
 156 suspected severe pediatric malaria, *Médecine et maladies infectieuses*. 2012, 42, 315–320
- 157 3. National Malaria Program (Programme National de Lutte contre le Paludisme PNLP). National  
 158 Guidelines on malaria management in Democratic Republic of Congo, Public Health Ministry;  
 159 2012.
- 160 4. Ntuku H, Ferrari G, Burri C, Tshetu A, Kalemwa D, Lengeler C, Feasibility and acceptability of  
 161 injectable artesunate for the treatment of severe malaria in the Democratic Republic of Congo,  
 162 *Malar J* (2016) 15:18 DOI 10.1186/s12936-015-1072-x
- 163 5. WHO, Guidelines for the treatment of malaria, third edition, Geneva, 2015
- 164 6. WHO, WHO malaria terminology, Geneva, 2016
- 165 7. Kunuanunua TS, Nsibu CN, Bodi JM, Tshibola TK, Makusi Bura M, Magoga K, Ekila MB, Severe  
 166 malaria in children: A descriptive report from Kinshasa, the Democratic Republic of Congo. *J*  
 167 *Trop Pediatr*. 2015 Aug;61(4):272-8. doi: 10.1093/tropej/fmv029.
- 168 8. Saravu K, Rishikesh K, Kamath A, Determinants of mortality, intensive care requirement and  
 169 prolonged hospitalization in malaria - a tertiary care hospital based cohort study from South-  
 170 Western India. *Malar J*. 2014 Sep 19; 13:370. doi: 10.1186/1475-2875-13-370.
- 171 9. Bouyou-Akotet MK, Mawili-Mboumba DP, Kendjo E, Eyang Ekouma A, Abdou Raouf O,  
 172 Complicated malaria and other severe febrile illness in a pediatric ward in Libreville, Gabon. *BMC*  
 173 *Infect Dis*. 2012 Sep 13; 12:216. doi: 10.1186/1471-2334-12-216.
- 174 10. Maitland, Management of severe paediatric malaria in resource-limited settings, *BMC Medicine*  
 175 (2015) 13:42
- 176 11. Ajetunmobi WA, Orimadegun AE, Brown BJ, Afolabi NK, Olabiyi FA Haemoglobinuria among  
 177 children with severe malaria attending tertiary care in Ibadan, Nigeria. *Malar J*. 2012 Oct 5;  
 178 11:336. doi: 10.1186/1475-2875-11-336.
- 179 12. Taylor WR, Hanson J, Turner GD, White NJ, Dondorp AM, Respiratory manifestations of  
 180 malaria., *Chest*. 2012 Aug;142(2):492-505. doi: 10.1378/chest.11-2655.
- 181 13. Jallow M, Casals-Pascual C, Ackerman H, Walther B, Walther M, Pinder M, Sisay-Joof F, Clinical  
 182 features of severe malaria associated with death: a 13-year observational study in the Gambia.  
 183 *PLoS One*. 2012;7(9): e45645. doi: 10.1371/journal.pone.0045645.
- 184 14. Biai S, Rodrigues A, Gomes M, Ribeiro I, Sodemann M, Alves F, Aaby P. Reduced in-hospital  
 185 mortality after improved management of children under 5 years admitted to hospital with malaria:  
 186 randomized trial. *BMJ*. 2007 Oct 27;335(7625):862.