

# Co-Infections among Children Hospitalised with Severe Plasmodium Falciparum Malaria in Gabon: A Retrospective Hospital-based Study

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## ABSTRACT

**Background:** Severe Plasmodium falciparum malaria remains a major cause of paediatric morbidity and mortality in sub-Saharan Africa and frequently occurs in association with other infections. Data on microbiologically documented co-infections and their clinical impact remain scarce in Central Africa, particularly in Gabon.

**Methods:** We conducted a retrospective, analytical, hospital-based study of children (<17 years) hospitalised with microscopically confirmed severe malaria at a tertiary referral hospital in Libreville, Gabon, between January 2021 and July 2022. Sociodemographic characteristics, consultation delay, vaccination status, documented co-infections, and clinical outcomes were analysed. Comparisons between isolated severe malaria and malaria with co-infection were performed using univariate analyses.

**Results:** Among 480 children included, 101 (21.0%) presented with at least one documented co-infection. Co-infected children were younger than those with isolated severe malaria (median age: 3.0 vs 5.0 years;  $p = 0.049$ ), and children under five years had higher odds of co-infection (OR 1.76, 95% CI 1.12–2.76). Co-infection was most frequent among children aged 37–59 months (25.8%) and infants under one year (20.0%). Respiratory infections were the most common co-infections (43.6%), followed by ENT infections (22.8%) and bacteraemia (14.9%). There a trend towards delayed health-seeking behaviour among co-infected children ( $p=0.054$ ). Co-infected children experienced longer hospital stays (median: 5.0 vs 4.0 days;  $p < 0.001$ ), while in-hospital mortality was low and limited to children with isolated severe malaria (0.8%).

**Conclusions:** Co-infections are common among Gabonese children hospitalised with severe malaria, particularly in younger age groups, and are associated with a trend towards delayed presentation and prolonged hospitalisation, underscoring the need for integrated syndromic management approaches.

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## Keywords

Severe malaria, Co-infection, Children, Consultation delay, Gabon.

## Introduction

Severe *Plasmodium falciparum* malaria remains a leading cause of paediatric morbidity and mortality in sub-Saharan Africa, despite the scale-up of effective antimalarial interventions. Children hospitalised with severe malaria frequently present with complex clinical syndromes that extend beyond parasitaemia alone, raising concern for concomitant infections that may modify disease severity, management, and outcomes. Increasing evidence suggests that severe malaria often occurs in the context of co-infections, particularly invasive bacterial infections, which may substantially worsen prognosis.

Bacterial co-infections have been consistently reported among African children with malaria and are associated with excess mortality. In a seminal review synthesising data from multiple African settings, invasive bacterial infections—most commonly due to non-typhoidal *Salmonella* and other Gram-negative organisms—occurred frequently in children with malaria and were associated with significantly higher mortality compared with malaria alone [1]. However, the authors also emphasised major methodological limitations across studies, including heterogeneous diagnostic approaches, inconsistent case definitions, and limited use of appropriate control groups, underscoring the need for well-designed, context-specific investigations.

At the clinical level, distinguishing severe malaria from malaria complicated by bacterial co-infection remains challenging. In a hospital-based study conducted in Ghana, bacterial co-infection among children with *P. falciparum* parasitaemia was associated with severe anaemia, leukocytosis, and splenomegaly, yet no single clinical or laboratory marker reliably discriminated malaria alone from malaria with bacteraemia [2]. More recent syntheses confirm that reliance on clinical features alone leads to both under-diagnosis of bacterial co-infections and inappropriate antimicrobial exposure [3]. These diagnostic challenges are particularly critical in referral hospitals where children often present late and with advanced disease.

Beyond bacterial pathogens, malaria frequently co-occurs with viral and parasitic infections in endemic regions. A meta-analysis reported that co-infection with dengue virus was associated with a markedly increased risk of severe malaria, with severe forms observed in approximately one-third of *Plasmodium*–DENV co-infected patients, and a higher frequency of complications compared with mono-infections [4]. Earlier studies have also documented the coexistence of helminthic and viral infections with malaria, illustrating the broader ecological and immunological context in which malaria occurs and reinforcing the concept of severe malaria as a syndromic condition rather than a single-pathogen disease [5].

Sociodemographic determinants further shape malaria risk, severity, and outcomes. Factors such as young age, low

socioeconomic status, maternal education, and place of residence have been consistently associated with malaria infection among children in sub-Saharan Africa [6]. These same determinants are likely to influence exposure to additional pathogens, access to preventive measures, and health-seeking behaviour. In particular, delays in consultation after symptom onset may increase the risk of secondary bacterial infection and worsen clinical outcomes, yet this dimension remains insufficiently explored in many endemic settings.

The World Health Organization has long highlighted the problem of over-diagnosis of malaria and under-recognition of invasive bacterial disease in children presenting with severe febrile illness, particularly in high-transmission settings where parasitaemia is common [7]. Recent research initiatives, including the Mal-CoChild project, further suggest that the burden of co-infection in African children is likely underestimated, especially where microbiological investigations are limited or inconsistently applied.

In Gabon, although several studies have described the epidemiology and clinical spectrum of paediatric severe malaria, data specifically addressing microbiologically documented co-infections and their prognostic impact remain scarce. Molecular investigations have demonstrated the co-circulation of *Plasmodium* and bacterial DNA in febrile Gabonese children, providing biological evidence that concomitant bacterial infections do occur in this setting [8]. However, these studies did not assess clinical outcomes or integrate key determinants such as consultation delay or preventive factors. To date, no hospital-based study in Gabon has systematically examined the association between sociodemographic characteristics, consultation delay, microbiologically confirmed co-infections, and clinical outcomes among children hospitalised with severe malaria.

Against this background, the present study aimed to identify sociodemographic and clinical factors associated with microbiologically documented co-infections among children hospitalised with severe malaria in Gabon, and to assess their impact on clinical outcomes, with particular attention to consultation delay and vaccination status.

## Methods

### Study design and setting

This was a retrospective, analytical, health facility-based study conducted through a review of medical records of paediatric patients hospitalised for confirmed malaria between January 2021 and July 2022. The study was carried out at the Centre Hospitalier Universitaire Mère-Enfant Fondation Jeanne Ebori (CHUME-FJE), a tertiary referral university hospital dedicated to maternal and child health and located in Libreville, the capital city of Gabon. The Paediatric Department of CHUME-FJE includes general paediatrics, neonatal medicine, paediatric surgery, paediatric emergency care, and paediatric outpatient consultation units. In the general paediatrics ward, approximately 1,500 children are hospitalised annually. Data were collected from the general

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paediatrics ward, in conjunction with records from the emergency department and the intensive care unit (ICU), allowing inclusion of children across the full spectrum of disease severity.

### Eligibility criteria

Medical records were eligible for inclusion if patients were aged under 17 years and had been hospitalised for a microscopically confirmed *Plasmodium falciparum* infection. Only records with available haematological and biochemical laboratory results were included, in accordance with World Health Organization recommendations for the diagnosis and management of malaria.

Records were excluded if they concerned neonates admitted to the neonatal unit or children hospitalised for febrile illnesses other than malaria. Medical files with missing key information on consultation delay, co-infection status, or clinical outcome were also excluded from the analysis.

### Data collection and variables

Data were extracted retrospectively from eligible medical records using a standardised electronic data collection form developed with Research Electronic Data Capture (REDCap). Each patient was assigned a unique anonymised identification code to ensure confidentiality.

Sociodemographic data collected included age at admission, expressed both as a continuous variable in years and categorised into age groups, as well as sex. Age was further classified into predefined paediatric categories, including infants and children under five years of age, to reflect the epidemiological profile of severe malaria.

Consultation delay was defined as the time elapsed between the reported onset of symptoms and hospital admission. This variable was recorded as a continuous variable in days and categorised into clinically meaningful intervals, including delays of three days or less, four to seven days, and more than seven days, as documented in the medical records.

Clinical data included body temperature at admission, the primary diagnosis of malaria, and the presence of associated infections. Associated infections were recorded based on clinical and laboratory documentation in the medical files. Co-infection status was defined according to bacteriological evidence and classified as malaria alone or malaria with at least one documented co-infection.

Vaccination status was extracted from vaccination cards or medical records when available and classified as age-appropriate vaccination completed, incomplete vaccination, or undocumented vaccination status. This variable was analysed as an indicator of access to preventive healthcare services rather than pathogen-specific immunity.

Hospitalisation data included duration of hospital stay, recorded as a continuous variable in days and categorised into length-of-stay intervals. Clinical outcome at discharge was recorded as survival or in-hospital death.

### Definitions

Severe malaria was defined according to World Health Organization criteria, based on the presence of *Plasmodium falciparum* parasitaemia associated with at least one clinical or biological criterion of severity.

Co-infection was defined as the presence of a documented infection associated with malaria, supported by routine bacteriological investigations when available and recorded in the medical file. Clinical suspicion of infection without laboratory documentation was not considered sufficient to define co-infection for analytical purposes.

Consultation delay referred exclusively to the pre-hospital delay, measured from symptom onset to hospital admission, and did not include in-hospital diagnostic or treatment delays.

### Statistical analysis

Data were analysed using appropriate statistical software (to be specified). Continuous variables were summarised using means and standard deviations or medians and interquartile ranges, depending on their distribution. Categorical variables were expressed as frequencies and percentages.

Comparisons between children hospitalised with malaria alone and those with malaria and documented co-infection were performed using chi-square or Fisher's exact tests for categorical variables and Student's *t* test or Mann–Whitney *U* test for continuous variables, as appropriate.

Multivariable logistic regression analyses were conducted to identify factors independently associated with the presence of co-infection and with in-hospital mortality. Variables entered into multivariable models were selected based on clinical relevance and results of univariable analyses. Adjusted odds ratios with 95% confidence intervals were reported, and statistical significance was set at a two-sided *p* value of less than 0.05.

## Results

### Characteristics of the study population

A total of 480 children hospitalised with severe malaria were included in the analysis. Among them, 379 (79.0%) had severe malaria without any documented co-infection, while 101 (21.0%) children presented with at least one associated co-infection during hospitalisation.

Overall, the median age of the study population was 4.0 years (IQR: 2.0–9.0). Children with co-infection were significantly younger than those with isolated severe malaria. Children under five years of age accounted for half of the cases (52.5%) overall and were more frequently represented among co-infected children (than among those without co-infection (Table 1). The sex distribution was balanced, with a male predominance in the overall population and the sex ratio did not differ significantly between children with co-infection (49/101; 48.5% male) and those without co-infection (198/379; 52.2% male).

Vaccination status was available for the majority of patients. Age-appropriate vaccination was documented in 257 children (53.5%), while 223 children (46.5%) had incomplete or undocumented vaccination status. The proportion of incomplete or undocumented vaccination was similar among children with co-infection (0.43) and those with isolated severe malaria (0.47).

The median consultation delay for the entire cohort was 4.0 days. Overall, 203 children (42.3%) consulted within three days of symptom onset, 219 (45.6%) between four and seven days, and 34 children (7.1%) after more than seven days. Delays longer than seven days were more frequent among co-infected children (Table 1).

Among the 101 co-infected children, respiratory infections were the most frequently documented, accounting for 44 (43.6%) cases, followed by ear, nose and throat infections (n=23; 22.8%), bacteraemia (n=15; 14.9%), urinary tract infections (n=9; 8.9%), and central nervous system infections, including meningitis or meningo-encephalitis (n=7; 6.9%). Less frequent infections accounted for the remaining cases.

#### Age-related distribution of severe malaria and co-infection

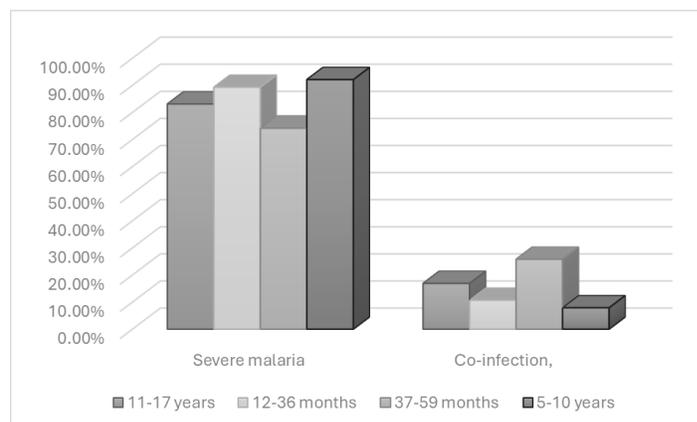
The distribution of isolated severe malaria and malaria with co-infection differed significantly across age categories ( $\chi^2$  test,  $p = 0.006$ ). Marked heterogeneity was observed in the proportion of co-infected cases according to age.

Among infants under one year of age, co-infection accounted for 20.0% of cases, while 80.0% presented with isolated severe malaria. In children aged 12-36 months, the proportion of co-infection was lower (10.7%), with 89.3% of cases corresponding to isolated severe malaria. The highest proportion of co-infection was observed in children aged 37-59 months, among whom 25.8% had malaria with co-infection, compared with 74.2% with isolated severe malaria.

In older children, co-infection was less frequent. Among those aged 5-10 years, only 7.9% of cases were co-infected, whereas 92.1% had isolated severe malaria. Similarly, in adolescents aged 11-17 years, co-infection represented 16.9% of cases, with 83.1% presenting with severe malaria alone (Figure 1).

Overall, co-infection was disproportionately concentrated in younger age groups, particularly among children aged 37-59 months and infants under one year, while isolated severe malaria

predominated increasingly with advancing age.



**Figure 1:** Age-related distribution of isolated severe malaria and malaria with co-infection among hospitalised children.

#### Univariate analysis of factors associated with co-infection

In univariate analysis, age under five years was significantly associated with the presence of co-infection among children hospitalised with severe malaria. Children aged <5 years had a 1.76-fold higher odds of co-infection compared with older children (Table 2).

A prolonged consultation delay exceeding seven days tended to be associated with an increased likelihood of co-infection ( $p = 0.063$ ), indicating a trend towards delayed health-seeking behaviour among co-infected children. Sex and vaccination status were not associated with co-infection.

**Table 2:** Univariate analysis of factors associated with co-infection.

	Crude OR (95% CI)	p value
Age <5 years	1.76 (1.12-2.76)	0.019
Male sex	0.86 (0.56-1.34)	0.580
Consultation delay >7 days	2.31 (1.01-5.31)	0.054
Incomplete/undocumented vaccination	0.82 (0.53-1.28)	0.442

#### Clinical outcomes according to co-infection status

Clinical outcomes differed according to the presence of co-infection. Children with malaria and associated co-infection experienced a significantly longer hospital stay compared with those hospitalised for isolated severe malaria. The median length

**Table 1:** General characteristics of the study population.

Characteristics	Total (N=480)	Severe Malaria (n=379)	Co-infection (n=101)	p value
Age, years, median (IQR)	4.0 (2.0-9.0)	5.0 (2.0-9.0)	3.0 (1.5-8.0)	0.049
Age <5 years, n (%)	252 (52.5)	188 (49.6)	64 (63.4)	0.019
Male sex, n (%)	247 (51.5)	198 (52.2)	49 (48.5)	0.580
Consultation delay, days, median (IQR)	4.0 (3.0-6.0)	4.0 (3.0-6.0)	5.0 (3.0-7.0)	0.063
Consultation delay >7 days, n (%)	34 (7.1)	24 (6.3)	10 (9.9)	0.063
Incomplete/undocumented vaccination, n (%)	223 (46.5)	180 (47.5)	43 (42.6)	0.442
Length of hospital stay, days, median (IQR)	4.0 (3.0-5.0)	4.0 (3.0-4.0)	5.0 (4.0-8.0)	<0.001

of hospitalisation was 5.0 days (IQR: 4.0-8.0) among co-infected children, versus 4.0 days (IQR: 3.0-4.0) in children without co-infection ( $p < 0.001$ ).

In-hospital mortality was low overall. Three deaths were recorded among children with isolated severe malaria (3/379; 0.8%), whereas no deaths occurred among children with co-infection (0/101; 0.0%). Given the small number of events, no statistical comparison of mortality was performed.

Overall, these findings indicate that, while co-infection was not associated with increased in-hospital mortality in this cohort, it was associated with a greater burden of care, reflected by a significantly prolonged duration of hospitalisation.

## Discussion

This hospital-based study provides new evidence on the epidemiology and clinical impact of co-infections among children hospitalised with severe *Plasmodium falciparum* malaria in Gabon. Approximately one in five children (21.0%) presented with at least one documented co-infection, highlighting that severe malaria in this setting frequently occurs as part of a broader infectious syndrome rather than as an isolated parasitic disease. Co-infected children were significantly younger, experienced longer delays before hospital presentation, and required prolonged hospitalisation, although no excess in-hospital mortality was observed.

### Burden and spectrum of co-infections in severe malaria

The frequency of co-infection observed in our cohort is consistent with reports from other sub-Saharan African settings, where bacterial and other infectious co-morbidities are commonly identified among children with severe malaria [1,9]. In line with previous studies, respiratory infections constituted the most frequent associated infections, followed by ENT infections and bacteraemia. This distribution likely reflects both true epidemiological patterns and the relative availability of diagnostic investigations for respiratory and bloodstream infections in routine hospital practice.

Importantly, although bacteraemia accounted for less than 15% of co-infections in our study, its presence remains clinically significant given its well-documented association with increased morbidity and mortality in African children with malaria [1,10]. The lower proportion observed in our cohort may reflect underdiagnosis related to limited blood culture use or prior antibiotic exposure, suggesting that the true burden of invasive bacterial infections is likely underestimated.

### Young age as a major determinant of co-infection

A key finding of this study is the strong association between young age and co-infection. Children under five years of age had a significantly higher likelihood of presenting with co-infection, with the highest proportions observed among children aged 37–59 months and infants under one year. This age-related gradient has been reported in other African cohorts and is biologically plausible

given the immaturity of the immune system, higher exposure to respiratory and enteric pathogens, and increased vulnerability to severe disease in early childhood [2,6].

The particularly high proportion of co-infection observed among children aged 37–59 months is noteworthy and suggests a critical transitional period in which waning maternal immunity, increased social exposure, and incomplete acquisition of protective immunity may converge. This age group may therefore warrant heightened clinical vigilance and targeted diagnostic strategies.

### Consultation delay and health-seeking behaviour

Children with co-infection tended to present later than those with isolated severe malaria, and a consultation delay exceeding seven days was associated with more than a twofold increase in the odds of co-infection, although this association did not reach conventional statistical significance. Similar associations between delayed care-seeking and severe malaria outcomes have been described elsewhere in sub-Saharan Africa [11,12].

Delayed presentation may increase the risk of secondary bacterial infection through prolonged parasitaemia, anaemia, and immune dysregulation, while also reflecting structural barriers to timely healthcare access. These findings underscore the importance of community-level interventions aimed at early recognition of severe illness and prompt referral, particularly for young children.

### Vaccination status and access to preventive care

In this cohort, vaccination status was not significantly associated with the presence of co-infection. While this finding might appear counterintuitive, it is consistent with previous studies suggesting that routine childhood vaccination primarily reflects broader access to healthcare services rather than direct protection against the pathogens most commonly implicated in malaria-associated co-infections [6].

Nevertheless, the high proportion of children with incomplete or undocumented vaccination highlights persistent gaps in preventive healthcare coverage and reinforces the need to interpret vaccination status as a contextual marker rather than a causal determinant in this setting.

### Clinical outcomes and implications for case management

Although co-infection was not associated with increased in-hospital mortality in our study, co-infected children experienced significantly longer hospital stays, indicating a greater burden of care. This finding aligns with previous reports showing that co-infections complicate clinical management, prolong recovery, and increase healthcare resource utilisation even in the absence of excess mortality [2,3].

The absence of excess mortality among co-infected children should be interpreted cautiously, given the low overall number of deaths and the retrospective nature of the study. It may also reflect effective in-hospital management, including early empirical antibiotic treatment in severely ill children, as recommended by

international guidelines [7].

This study benefits from a relatively large hospital-based cohort and the integration of key sociodemographic and clinical variables, including consultation delay, which is infrequently examined in studies of malaria co-infection. However, several limitations must be acknowledged. The retrospective design and reliance on routine diagnostic practices likely led to under-ascertainment of co-infections, particularly invasive bacterial disease. Additionally, the absence of multivariable analysis limits causal inference.

Future prospective studies incorporating systematic microbiological testing and longitudinal follow-up are needed to better quantify the true burden of co-infection and to refine diagnostic and therapeutic algorithms for children presenting with severe malaria.

### Conclusion

In summary, co-infections are common among Gabonese children hospitalised with severe malaria, particularly in young age groups, and are associated with delayed presentation and prolonged hospitalisation. These findings support the need for integrated, syndromic approaches to the management of severe malaria that extend beyond antimalarial treatment alone.

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