Impact of the Introduction of Artesunate on the Management of Severe Malaria in Casamance (Senegal): A Comparative Analysis of Data From 2016 and 2020

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Abstract

Background: *the implementation of different control strategies, including the treatment of severe forms with injectable artesunate, has made it possible to significantly reduce malaria in Senegal. Despite everything, malaria remains a concern in Senegal, especially in the southern regions, hence the interest in studying these characteristics and their evolution over time.*

Objectives: *describe the epidemiological, clinical and evolving aspects of severe malaria before and after implementation of artesunate treatment.*

Patients and methods: *retrospective, cross-sectional, descriptive and analytical study focusing on cases of severe malaria admitted in two health structures in the Vélingara district in 2016 and 2020. The severity of diagnosis was made based on the current criteria of the WHO and confirmation made by thick blood smear and/or HRP2 rapid diagnostic test. The data was entered into Excel and analyzed with Epi-info version 7.2.6.*

Results: *In 2016, 357 cases of serious malaria were recorded from January 1st to December 31st, with 75.6% in October and December. The average age is 16.2 ± 12.9 years, with a predominance of the age group 6-15 years (38,94%). There was a male predominance and the sex ratio was 1.01. Coma (57%), convulsions (34%) and jaundice (14%) were the most common*

signs of severity. Under treatment with quinine salts (97%) and artemether (3%), the lethality was 5%. Factors significantly associated with death were rural origin (p:0.009), coma (p:0.000), hepatomegaly (p:0.03) and diffuse hemorrhages (p:0.03).

In 2020, 456 cases were collected from July 1st to December 31st, with 75.44% in October and November. The average age was 15.38±15.36 years (1 to 85 years) with a predominance of age group 6 to 15 years (46.49%). There was a male predominance and the sex ratio was 1.06. The signs of severity were dominated by prostration (52.63%), repeated convulsions (17.11%), coma (7.9%) and jaundice (7.2%). All patients were treated with injectable artesunate with a lethality of 3.5%. Death was significantly associated with coma (p:0.000) and the occurrence of respiratory failure (p:0.000).

Conclusion: *severe malaria remained a childhood pathology with neurological manifestations predominating in Vellingara. A drop in lethality is observed with the generalization of artesunate-based treatment.*

1. Introduction

Malaria remains a major public health issue, especially in sub-Saharan Africa [1] despite the financial support from major international initiatives such as the Global Fund, the American presidential initiative against malaria, the Roll Back Malaria program and the declaration of 'Abuja [2, 3], These investments made it possible to develop and implement controlling and preventive strategies, targeting pregnant women and children, which led to a significant reduction of the incidence of malaria [4].

The transition from quinine to artesunate represents an important step in improving the management of severe cases of malaria. Indeed, the WHO recommends artesunate as first-line treatment for severe Plamodium falciparum malaria in adults and children after the publication of results of comparative clinical trials which illustrated not only the superior effectiveness of artesunate, but also its better safety profile, in comparison with quinine which was the reference treatment for decades [5, 6].

In Senegal, malaria is mainly caused by P. falciparum, representing 98% of cases, followed by P. malariae and P. ovalae [7]. The WHO reported in 2020 that 0.7% of deaths worldwide due to malaria were recorded in Senegal [4].

The implementation by the national malaria control program (PNLP) of interventions with proven effectiveness as recommended by the WHO resulted at the operational level in an improvement in the access and the quality of treatment through access to the RDT rapid diagnostic test (HRP2), the dispensation of antimalarial drugs such as injectable artesunate for severe forms, acceptance of the use of insecticide-treated mosquito nets as a useful means of prevention, just like the use of intermittent preventive treatment (IPT) in pregnant women and chemo-prevention of seasonal malaria (CPS) in children aged 3 to 120 months. Despite the implementation of these different prevention strategies, malaria remains endemic throughout the national territory, particularly in the south-eastern regions of Senegal [8]. We conducted this study in that region to describe the epidemiological, clinical and evolving aspects of severe malaria before and after the implementation of artesunate treatment.

2. Material and Methods

Type and framework of the study: The study took place in two health structures in the department of Vélingara located in the region of Kolda, southeast of Senegal.

This is a cross-sectional, descriptive and analytical study covering 813 patients' files admitted to the two health centers in the Vélingara department, including 357 collected from January 1st to December 31st, 2016 in the Vélingara health center and 456 from July 1st, 2020 to December 31st, 2020) in the Medina Gounass health center.

In 2016, injectable quinine was the first-line treatment for severe malaria. Quinine base: 25 mg/kg/day divided into 3 infusions of 4 hours in 10% glucose serum to be repeated every 8 hours for 5 to 7 days then followed by quinine or ACTs as soon as the oral route is possible. Artemether: 3.2 mg/kg of body weight at admission then 1.6 mg/kg per day.

In 2020, the first-line treatment for severe malaria is injectable artesunate. Artesunate: 2.4 mg/kg body weight administered intravenously (IV) or intramuscularly (IM) at admission (t = 0), then 12 and 24 hours later and, thereafter, once daily until the patient is able to take their medication orally

3. Study Population

Inclusion criteria: all patients included were cases of severe malaria. The diagnosis of severity was made based on the current WHO criteria [9], namely: the presence of asexual forms of Plasmodium falciparum in the thick film and in the blood smear associated with one or more of the severity criteria of the WHO. In the absence of a thick film or smear, the diagnosis of severe malaria was made based on the positivity of the HRP2 rapid diagnostic test, and treatment for severe malaria was administered.

4. Non-Inclusion Criteria

We did not include suspected severe malaria not confirmed by parasitological examination or RDT, pregnant women, and all other patients whose medical records were incomplete or did not meet the diagnostic criteria for severe malaria.

Data collection: Data were collected from patients' medical records, hospitalization and treatment records.

Survey forms were completed based on information collected from patients' medical records and hospitalization records. For each patient, a form was established including socio-demographic aspects (age, sex, geographical origin), clinical aspects (date of consultation, clinical signs of severity of malaria, associated clinical signs), Para clinical aspects (biological signs of severity, other associated biological signs), therapeutic aspects (antimalarial treatment) and outcome aspects (duration of hospitalization, progressive modalities).

5. Statistical Analyses
Data were calculated using Excel 97-2003 and analyzed using Stata/Special 16 software (Stata Corporation, Texas and USA). Results were expressed as mean ± standard deviation for continuous variables and as proportion for categorical variables. Student's t test was used for mean comparisons and Pearson's chi-square test for comparison of categorical variables. P values <0.05 were considered significant for all analyses.

6. Results
Of the 813 cases of severe malaria included in this study, 459 cases observed in 2020 were treated with artesunate and 357 cases in 2016 were treated with quinine (97.20%) or artemether (2.80%). The average age of the patients did not differ significantly between the two groups (15.38±15.36 versus 14.86±16.72, p=0.643) and the age group of 6-15 years was predominant in the two groups (46.49% vs 38.94; p=0.031) (Table1). The number of cases was higher in the months of October (30.81% vs 27.41%), November (48.02% vs 31.37%) and December (9.42% vs 13.44%) with a peak of cases in November (Figure1).

The predominant signs of severity in 2016 and 2020 were represented by disturbances of consciousness (57% versus 32.5%, P= 0.029), repeated convulsions (34% versus 19.8%, P<0.001), and jaundice (14% versus 76.4%, P = 0.017). In addition to these serious signs, fever was noted in 350 cases (98%), vomiting in 134 cases (37.5%) and diarrhea (6.4%) (Figure2) . The average length of hospitalization was significantly lower in patients treated with artesunate (1.59 ± 0.78 vs 3.22 ± 1.99 days; (P < 0.0000) (Table 3).

Rapid diagnostic tests for malaria were performed in 100% of cases. The thick smear was performed in 240 patients or 67% in 2016 compared to 96 (21.05%) in 2020.

The average parasite density before starting treatment was significantly lower in patients diagnosed in 2020 (11833.88±22432.99 vs 34967.97± 62955.38; (p=0.0005) however, a significantly greater proportion of hyperparasitemia was observed in 2020 (78.51 % vs 48.18%; p =0.000).

The average hemoglobin level was similar in the two groups (8.93 ± 2.75 versus 8.93 ± 2.75, p = 0.9902). The proportion of cases of severe anemia with a hemoglobin level <7 g/dl was greater among patients in 2016 compared to 2020 but the difference was not significant (11.20% versus 7.46%; p: 0.065) (Figure 2).

The average blood sugar level was 1.09±0.42 g/l in 2016 with a proportion of 5% cases of hypoglycemia < 0.5 mg/l compared to 1.27±0.47 in 2020 with a proportion 1.97% of cases of hypoglycemia < 0.5 mg/l.

All cases collected in 2020 were treated with artesunate while the majority of cases included in 2016 were on injectable quinine and (2.80%) were on arthémeter (Table 3). The fatality rate was slightly lower in patients treated with artesunate in 2020 compared to those treated with quinine or artemether in 2016. Factors significantly associated with death in 2016 were coma (p:0.000) (Table5). In 2020, death was significantly associated with coma (p: 0.000) and the occurrence of respiratory failure (p: 0.000).

7. Discussion
This retrospective descriptive and analytical study aimed to describe the epidemiological, clinical and evolving aspects of severe malaria before and after the implementation of artesunate treatment.

In terms of frequency, our results are higher than those of Diop in 2010, who reported 181 cases over 4 years [10] and Wade, who reported 87 cases over a period of 2 years [11] in Dakar, Senegal. This reflects the geographic disparities in terms of transmission and incidence of malaria in Senegal, like many African countries. Indeed, the southeastern regions of Senegal are characterized by a Sudanian-type climate with longer and more intense rainy seasons favoring the reproduction of mosquito vectors. Our results are also superior to those of a study carried out in Ivory Coast which identified 274 cases over 14 years [12]. On the other hand, our results are similar to those of a study carried out in Congo by Ntabi et al. [13] who found 241 cases over one year or 31.2%.

The number of cases was higher in the months of October, November and December corresponding to the rainy season. This observation is found in several studies carried out on severe malaria in Africa [10, 12, 14,15]. Senegal is classified as a sub-Saharan African country where malaria is endemic, with seasonal transmission mainly during the rainy season, according to the National Malaria Control Program [8].

The age profile for the onset of serious malaria in our region remains young with a male predominance. These profiles are comparable with those obtained in other regions across our country and in sub-Saharan Africa [13,16]. Indeed, children in particular age groups 6-15 years and those under 5 years are more vulnerable to severe malaria due to their still developing immune systems, as well as increased exposure and susceptibility to higher parasite loads. The male predominance could be explained by the fact that boys are inclined to carry out activities with a greater risk of exposure to mosquitoes.

In our study, the reasons for consultation were dominated by fever, vomiting and headache. Regarding fever, it remains the most common reason for consultation in most studies [2,17].

The predominant signs of severity in 2016 and 2020 were represented by disturbances of consciousness (57% versus 32.5%, P= 0.029), repeated convulsions (34% versus 19.8%, P<0.001), and jaundice (14% versus 76.4%, P = 0.017). The predominance of cerebral malaria, especially in children over six months and under five years of age, has been noted by several authors [18,19].
Jaundice is often linked to liver damage, which is very common in adults, as highlighted by other authors [20,21]. These results could be influenced by traditional herbal medicine, which lengthens consultation times [20,21].

The rate of severe anemia was higher in 2016 compared to 2020. Our results are lower than those found by several authors in the sub-region [10,23, 24]. Anemia is linked to the lysis of parasitized red blood cells but also to the release of plasma toxins [25]. In addition, there is said to be deficiency anemia in sub-Saharan Africa among children under five years of age, to which malaria is linked [26]. It is considered as a poor prognostic factor [27].
Cases of respiratory distress represented only 4% in 2016 and 0.8% in 2020 in our series. Respiratory distress during malaria can result mainly from metabolic acidosis which is probably underestimated because the measurement of respiratory gases blood was not systematically available in our public services, which could constitute a bias. This result is much lower than the result of Wade [11] [9] who obtained 38% in a study of 87 patients. Respiratory distress is aggravated by severe anemia and disseminated intravascular coagulation, linked to hyperparasitemia and Plasmodium falciparum infection.

The average parasite density before starting treatment was significantly lower in patients diagnosed in 2020 (11833.88±22432.99 p/µL vs 34967.97± 62955.38 p/µL; (p=0.0005) (Table 2) however there was a proportion of cases of significantly greater hyperparasitemia in 2020 (78.51% vs 48.18%; p = 0.000). In several studies carried out in Senegal, the parasite density remains high [28,29]. A study conducted by Kotepui .M and al [30] and Rodriguez. P and al [31] showed an increase in parasite density with correlation to signs of severity.

The average length of hospitalization was significantly lower in patients treated with artesunate (1.59 ± 0.78 vs 3.22 ± 1.99 days). This reduction in the duration of hospitalization under artesunate was observed in the study of Cissé VPM et al. in Dakar. Clinical trials had already established that the use of injectable artesunate results in reduced mortality and shortened hospital stays, as this leads to faster elimination of parasites [32,33].

The case fatality rate was slightly lower in patients taking artesunate in 2020 compared to those treated with quinine or artemether in 2016. This rate of 5% in 2020 is lower than the results of other previous studies carried out in Senegal by Diop [10], Lawson [34] and Cissé [17] who found 17.1% and 18% and 10.9% respectively. This trend observed in our study is clearly in line with current WHO data, which shows a reduction in case fatality in recent years, from 896,000 cases in 2000 to 558,000 cases in 2019 [4].

In Senegal, the number of deaths fell from 526 to 260, a reduction of 51% over the period from 2016 to 2019 [8]. In addition, injectable artesunate, the currently first-line treatment for severe malaria, was the only antimalarial used in all patients included in 2020. Clinical trials had already established that the use of injectable artesunate reduced mortality and shortened hospital stays, as it led to faster elimination of parasites [32,33].

We also looked for risk factors for death: in 2016, the factors significantly associated with death were coma (p: 0.000), hepatomegaly (p: 0.03) and diffuse hemorrhage (p: 0.03). In 2020. Death was significantly associated with coma (p: 0.000) and the occurrence of respiratory failure (p: 0.000).
Disorders of consciousness, particularly coma, have been found as a factor independently associated with death in several studies [17, 35,36]. In Brunel's study [20], 21% of surviving patients had impaired consciousness, compared to 62% of deceased patients, with a statistically significant difference. The severity of cerebral malaria is linked to the sequestration of red blood cells, leading to vital dysfunction, which is mainly the prerogative of Plasmodium falciparum.

8. Conclusion
Serious malaria remains a public health problem in Senegal, especially in the South-Eastern regions, which are characterized by a persistence of serious forms of malaria, especially in children, with a predominance of neurological signs of severity. Access to RDT has improved early diagnosis and the use of injectable artesunate has helped reduce mortality. Optimizing early diagnosis of signs of malaria severity and strengthening the technical platform in intensive care units, as well as increasing preventive efforts, can improve outcomes for patients.

Table 1: Socio-demographic characteristics of severe malaria among patients Vélingara's two health centers in 2016 and 2020.

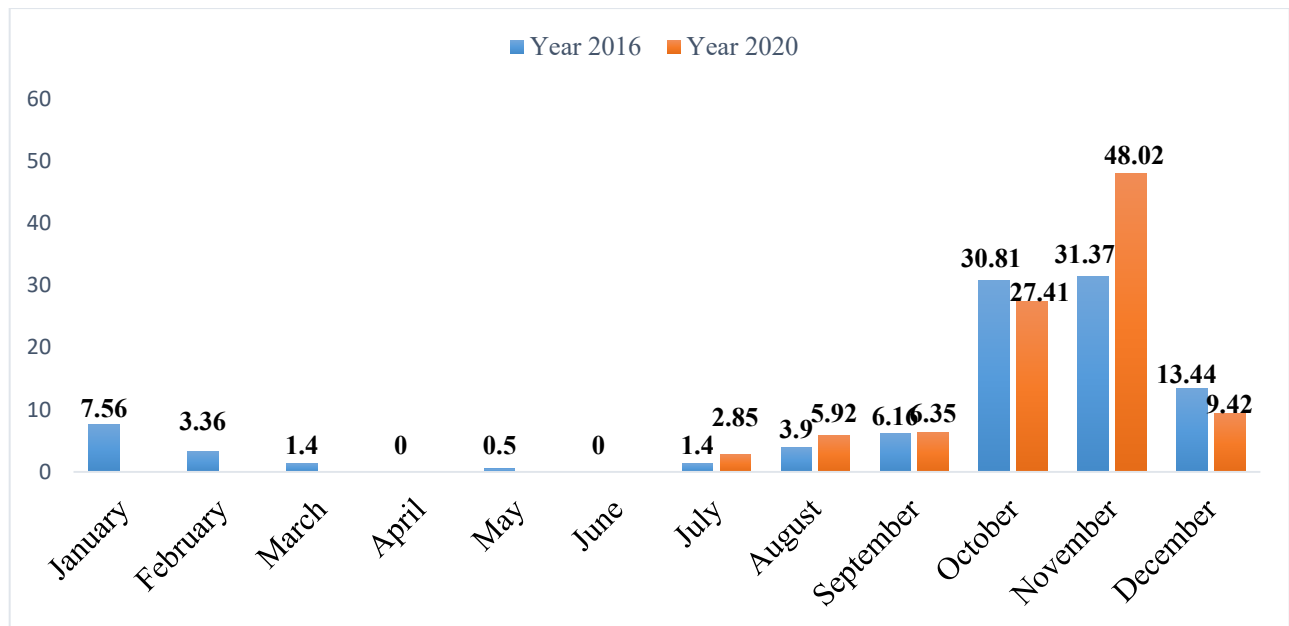| Variables	Année 2016 (N=357)	Année 2020 (N=456)	P-value
Gender			
Female	178 (49.86)	221 (48.46)	0.693
Male	179 (50.14)	235 (51.54)	
Age (years)			
0 - 5	121 (33.89)	107 (23.46)	0.001
6 - 15	139 (38.94)	212 (46.49)	0.031
16 - 50	77 (38.94)	115 (38.94)	0.224
>50	69 (21.57)	93 (25.22)	0.619
Mean age	14.86±16.72	15.38±15.36	0.643

Figure 1: Patients' received for severe malaria based on different months in Vélingara's two health centers in 2016 and 2020.
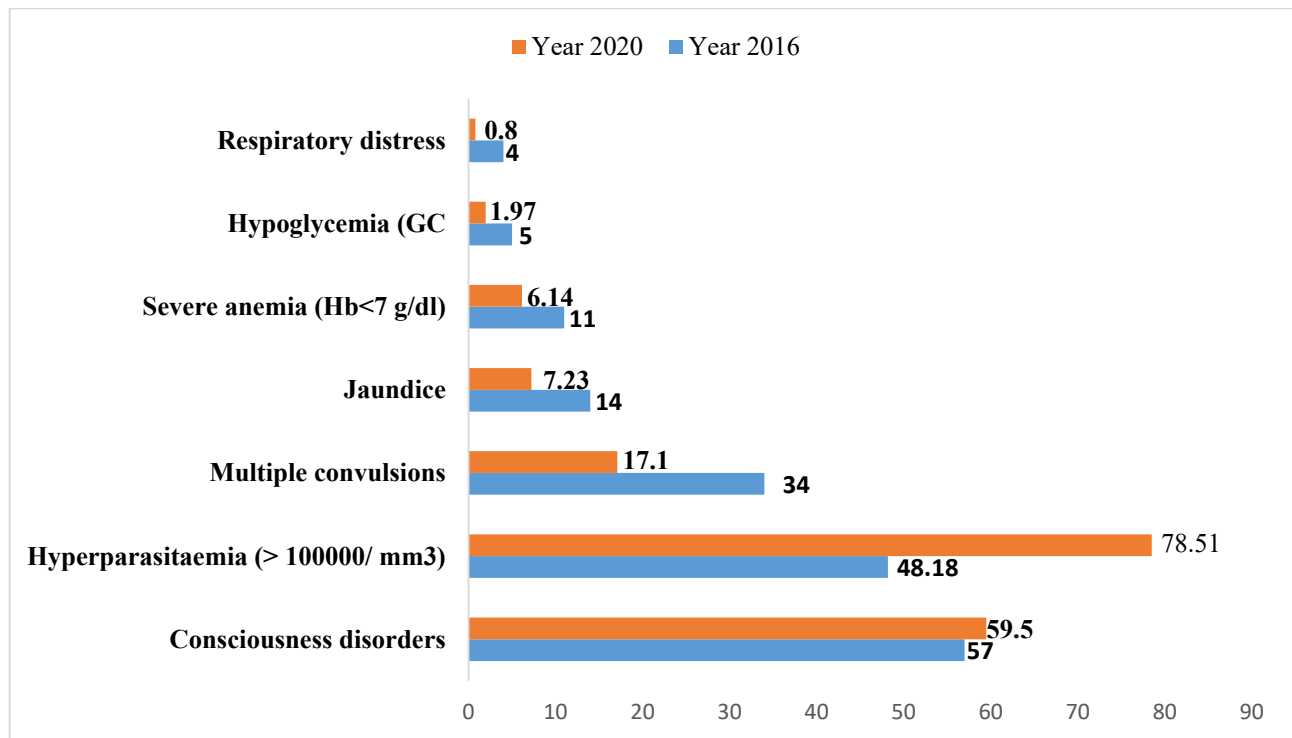
Figure 2: Table 2. Clinical and biological manifestations of severe malaria Vélingara's two health centers in 2016 and 2020.

Table 2: Clinical manifestations of severe malaria Vélingara's two health centers in 2016 and 2020.

Signes cliniques	Year 2016	Year 2020
Fever	351 (98.32)	393 (86,18)
Vomiting	131(36.69)	213 (46,71)
Headach	13 (3.64)	107 (23,46)
Algie diffuse	16 (4.48)	56 (12,28)
Diarrhée	17 (4,76)	37 (8,11)
Saignement anormal	8 (2,2)	0 (0,00)

Table 3: Repartion of patients based on therapeutic and evolving aspects in Vélingara's two health centers in 2016 and 2020.

Aspects thérapeutiques	Year 2016	Year 2020	p-value
Artesunate inj	0 (0,00)	456 (100)	
Quinine inj	347 (97.20)	0 (0,00)	
Artheméter in	10 (2.80)	0 (0,00)	
Hospitalization length (days)			
Mean	3.22 ± 1.99	1.59 ± 0.78	0.0000
< 4	257 (72.19)	445 (97.59)	
4- 7	85 (23.88)	11 (2.41)	

> 7	14 (3.93)	0 (0,00)	
Evolution			
Healing	**324 (91)**	**433 (95)**	
Deaths	**19 (05)**	**16 (3,5)**	
Transfert	**14 (04)**	**07 (1,54)**	

Table 4: Repartition of death cases due to severe malaria based on age, sex, severity signs.

Variables	Death	
Year	2016	2020
Sex		
Male	6 (3.35)	13 (5.53)
Female	13 (7.30)	10 (4.52)
Age range (years)		
0-5	9 (7.44)	9 (8.41)
6-15	7 (5.04)	13 (6.13)
15-50	2 (2.60)	0 (0,00)
> 50	1 (5.00)	1 (4.55)
	19 (5.32)	23 (5.04)
Gravity symptoms		
Coma	9/189 (4,76)	5/14 (35,71)
Multiples convulsions	8/128 (6.25)	8/78 (10.26)
Jaundice	4/54 (7.41)	1/38 (2.56)
Hyperparasitaemia (> 100000/ mm3	13/172 (7.56)	20/358 (5.59)

Table 5: Risk factors for death of severe malaria Vélingara's two health centers in 2016 and 2020.

Année	Variables	OR	p-value	IC 95%
2016	**Consciousness disorders**	**15,35**	**0,000**	**[3,74 –62,89**
	Respiratory distress	**15,10**	**0,031**	**[1,27 - 179]**
2020	**Consciousness disorders**	**13,5**	**0,00**	**[5,6 – 35]**

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