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Severe Malaria: The Role of Rapid Diagnostic Tests in Children Who Have Previously Received Presumptive Antimalarial Treatment

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Abstract

Background: Diagnosis of severe malaria by microscopy can be challenging in children who have previously received presumptive antimalarial treatment. **Objective**: To analyse the value of rapid diagnostic tests (RDTs) in the diagnosis and management of severe malaria in children who have received incomplete presumptive antimalarial treatment prior to admission. **Methods**: This was a prospective study which was carried out from December 2021 to April 2022 in the paediatric intensive care unit. Children admitted with suspected severe malaria and who had received incomplete presumptive antimalarial treatment prior to admission were included exhaustively. Microscopic examination of blood smears and RDTs was performed on all children. The p-value was set at 5% and the confidence interval at 95%. **Results**: In total, 97 (66.0%) of the 147 children admitted for suspected severe malaria met the inclusion criteria, including 49 (50.5%) girls. The median age was 48 months [IQR: 33.5 - 100.5]. The number of confirmed cases of severe malaria by TBS was 26 (26.8%) versus 84 (86.6%) by RDTs ($p < 0.0001$; OR 17.6 [8.4 - 36.9]). The RDTs helped prevent the misuse of antimalarials in 13.4% of the children. **Conclusion**: The irrational use of antimalarial drugs remains common, making it difficult to diagnose severe malaria by microscopy. In these conditions, malaria RDTs can provide a reasonable alternative for better case identification.

Keywords

Presumptive Treatment, Severe Malaria, Rapid Diagnostic Tests, Children

1. Introduction

Malaria is one of the major scourges in tropical countries and is responsible for significant mortality in its severe form, particularly among children in Africa. In 2022, the WHO estimated 608,000 malaria-related deaths, with 80% occurring in children living in sub-Saharan Africa [1]. In the Republic of Congo, according to national data, malaria is the leading cause of death, accounting for 28% of cases [2]. MOYEN and collaborators reported a case-fatality rate of 26.3% in Brazzaville hospitals [3]. Reducing the burden of malaria is a public health priority and is at the heart of Millenium Development Goals (MDG) 3 [4]. This involves specific preventive measures, rapid and accurate diagnosis of cases and effective treatment.

The diagnosis of severe malaria relies on clinical and biological criteria defined by the WHO in 2015 [5]. The identification of one of the Plasmodium species recognized as responsible for severe forms, (primarily Plasmodium falciparum in Congo), is essential for diagnosis via microscopy. However, microscopy methods (thick blood smear and blood films for Plasmodium detection), which form the basis of diagnosis, can be falsely negative in certain situations, such as in children who are incompletely treated, due to parasitic density falling below the detection threshold. In such cases, it becomes difficult to differentiate between poorly treated severe malaria and other conditions with similar symptoms. It is common practice to initiate presumptive antimalarial treatment in such situations.

However, this practice, which is contrary to the WHO recommendation to treat malaria cases with biological evidence, is not without its disadvantages [6]; not only does it delay the diagnosis and management of diseases other than malaria, but it also encourages the emergence and growth of drug resistance through the misuse of antimalarial drugs.

In light of the above, it would therefore be wise to propose an alternative diagnostic approach that would help to better identify cases of severe malaria in children who have a negative microscopy in the context of previous antimalarial drug use.

The best test under these conditions is PCR, but this is not yet available in our country and is rarely used in practice because of its prohibitive cost.

Immunochromatographic tests for malaria, also known as rapid diagnostic tests (RDTs) for malaria, particularly those targeting Plasmodium falciparum, may in our context constitute a reasonable alternative to PCR and a complement to the thick blood smear test (TBS) for diagnosing severe malaria. In addition to their outstanding diagnostic performance, RDTs remain positive for several weeks, even after anti-malarial treatment and parasite clearance. They also have the advantage of being inexpensive, easy to perform and rapid [7] [8].

We therefore conducted this study with the aim of improving the diagnosis and management of severe malaria in children.

Main Objective:

To study the relevance of malaria RDTs in the diagnosis of severe malaria in

children who have started presumptive antimalarial treatment prior to admission.

Secondary Objectives:

- Describe the sociodemographic characteristics of children admitted for severe malaria and those who started presumptive antimalarial treatment before admission.
- Compare diagnostic strategies with and without malaria RDTs in these children.
- Evaluate the impact of the diagnostic strategy using RDTs on the therapeutic management of these children.

Our working hypothesis is that malaria RDTs improve the diagnosis of severe malaria in children who have previously received presumptive antimalarial treatment.

2. Patients and Methods

2.1. Study Design, Duration, and Setting

We conducted a prospective cross-sectional analytical study from December 2021 to April 2022 (5 months) in the pediatric intensive care unit (PICU) of Brazzaville University Teaching Hospital (BUTC).

2.2. Study Population

2.2.1. Inclusion Criteria

- Children admitted with suspected severe malaria (clinical picture combining fever and at least one of the WHO severity criteria) and having received incomplete presumptive antimalarial treatment prior to admission (insufficient dose and/or duration of antimalarial treatment).
- TBS is performed upon admission.
- Parental consent was obtained for the child's participation.

2.2.2. Exclusion Criteria

- Children who died on arrival.
- Children with a confirmed diagnosis of malaria or another infectious disease before admission.
- Children with a history of malaria or fever in the month preceding the current illness.

Eligible children were exhaustively included.

2.3. Study Procedures

Children meeting the inclusion criteria were initially seen in the paediatric emergency department of Brazzaville University Teaching Hospital, where, after an initial clinical examination, a paraclinical work-up was carried out, systematically including a TBS. Other paraclinical examinations were carried out depending on the clinical picture. Therapeutic management at this stage was decided by the paediatric emergency physician.

Children were then admitted to the PICU the same day, where they were examined afresh by a paediatrician, and an RDTs (Malaria Ag Pf, SD Bioline®) was systematically performed. The RDTs was performed according to the manufacturer's instructions. The test procedure is to add 5 µL of blood and two drops (60 µL) of buffer into the sample well and the diluent well, respectively. The result is read after 15 - 30 min. The presence of a control line ("C") within the result window indicates a negative result. The presence of two colored lines ("T" and "C") within the result window, regardless of indicates a positive result. If the control line ("C") is not visible within the result window after performing the test, the result is considered invalid.

If TBS and/or RDTs were positive, the diagnosis of severe malaria was confirmed, and antimalarial treatment was initiated or continued if started in the emergency department. Negative TBS and RDTs results ruled out malaria, and antimalarial treatment was discontinued if initiated in the emergency department. Follow-up TBS was performed on days 3 and 7 for all children.

The sociodemographic, clinical, paraclinical, therapeutic and developmental data for each child, obtained from interviewing the parents and the medical records, were collected on an anonymous, pre-established, standardised questionnaire.

2.4. Statistical Analysis

Data entry, management, and analysis were performed using Excel and Epi Info version 7.2.1.

Quantitative variables were expressed as mean with standard deviation or median with interquartile range (IQR), while qualitative variables were expressed as the number and frequency of each class.

Variable comparisons were made using Fisher's test, Chi-square test, and odds ratios. The p-value was set at 5%, and the confidence interval at 95%.

2.5. Ethical Considerations

Ethical approval for the study was obtained from the Health Research Ethics Committee of the Ministry of Scientific Research. We declare no conflicts of interest.

3. Results

3.1. Study Population Description

During the study period, 147 children were admitted for suspected severe malaria, and 97 (65.9%) had received antimalarial treatment before admission. Of these, 49 were girls (50.5%) and 48 were boys (49.5%) with a median age [IQR] of 48 months [33.5 - 100.5]. Table 1 summarizes the sociodemographic characteristics of the study population.

The antimalarials administered before admission were: artemether-lumefantrine (48.5%), artemether (18.6%), quinine (12.4%), artesunate (8.2%), with 14.4% of cases where the administered drug was not identified.

Table 2 shows the distribution of children according to the mode of prescription and the prescriber's grade.

Table 1. Description of the study population.

Variables	N	%
Sex		
Male	48	49.5
Female	49	50.5
Age (months)		
< 60	74	76.3
≥ 60	23	23.7
Socioeconomic level		
High	2	
Middle	23	23.7
Low	72	74.2
Source		
Health structure	65	67.0
Home	32	33.0
TBS on admission		
Negative	71	73.2
Positive	26	26.8

TBS: Thick Blood Smear

Table 2. Distribution of children according to the mode of prescription and the prescriber's grade.

Variables	N	%
Mode of prescription (N = 97)		
Self-medication	43	44.3
Heteroprescription	54	55.7
Prescriber's grade (n = 54)		
Paramedical agent	38	70.4
Non paediatrician	10	18.5
Paediatrician	3	5.6
Pharmacist	1	
Unknown	2	

3.2. TBS and RDTs Results

Thick blood smears performed on all children were positive in 26 (26.8%) children and negative in 71 (73.2%). The RDTs was positive in 84 (86.6%) children and negative in 13 (13.4%). All children with positive TBS also had positive RDTs results. Among the 71 children with negative TBS, 58 (81.7%) had a positive RDTs, and 13 (18.3%) had a negative RDTs.

Follow-up TBS was negative in all children.

3.3. Comparison of Malaria Diagnosis before and after RDTs

Before the RDTs, the diagnosis of severe malaria was confirmed in 26 children (26.8%) and considered probable in the other 71 (73.2%).

After the RDTs, the diagnosis of severe malaria was confirmed in 84 (86.6%) children and ruled out in the remaining 13 (13.4%).

The number of confirmed severe malaria cases increased from 26 (26.8%) before the RDTs to 84 (86.6%) after the RDTs ($p < 0.0001$; OR 17.6 [8.4 - 36.9]).

The number of ruled-out severe malaria cases increased from 0 before the RDT to 13 after the RDTs.

3.4. Comparison of Therapeutic Management before and after RDT

Before the RDTs, all children received antimalarial treatment regardless of the TBS result. Afterward, therapeutic management in the ICU was based on TBS and RDTs results. Table 3 compares therapeutic strategies before and after RDTs.

Table 3. Comparison of the therapeutic strategy before and after RDTs.

Antimalarial treatment	RDTs (N = 97)		P-value	OR
	Before	After		
	n (%)	n (%)		
Yes	97 (100.0)	84 (86.6)	0.0001	0.4 [0.3 - 0.5]*
No	00	13 (13.4)		

*: statistically significant difference.

3.5. Outcomes

The overall outcome was favourable in 92 (94.8%) children, with death in 5 (5.2%). In the group of children with a positive RDTs (n = 84), 80 (95.2%) had a favourable outcome and 4 (4.8%) died. In the group of children with negative RDTs (n = 13), 12 had a favourable outcome and 1 died.

4. Discussion

This work is one of the few to have studied the value of RDTs in the diagnosis of severe malaria, with most studies in the medical literature being focused on the diagnosis of the simple form of the disease [9]-[11]. The present study shows that a significant proportion of children hospitalised for severe malaria were still treated presumptively before hospitalisation. Moyen *et al.* reported a proportion of 35.5% in a study carried out in hospitals in the city of Brazzaville [3]. The abuse of presumptive antimalarial treatment has already been highlighted by other authors [12]-[14]. Presumptive antimalarial treatment for children suspected of malaria has long been the norm in many African countries and is recommended by the WHO [15]. However, in 2010, considering changes in malaria's epidemiological profile, the availability and effectiveness of diagnostic methods such as RDTs, and the risk of spreading resistance to artemisinin-based combination therapies, the WHO modified its recommendation, stating that "all suspected cases of malaria should be confirmed before treatment is initiated" [6]. This paradigm shift has not always been understood or accepted by all. In our study, parents practising self-medication and paramedical staff were the

most likely to continue presumptive treatment, possibly due to being less informed or resistant to change.

Children under 5 years old and those from low socioeconomic households were the majority, a typical profile for children hospitalized with severe malaria [16] [17]. However, in 2015, OKOKO reported a predominance of children over 5 years old, attributing this to better disease prevention in younger children [18]. The same explanation could account for the underrepresentation of children from high socioeconomic households [19].

Presumptive antimalarial treatment, especially when incomplete, can make it challenging to diagnose malaria by microscopy. Our study confirms this for severe forms of malaria. In fact, in the vast majority (73.2%) of our study population, the diagnosis of severe malaria was uncertain because of the negativity of TBS in the context of previous antimalarial treatment. In this situation, the WHO recommends repeating the TBS 6 to 12 hours later, or performing an RDTs to confirm or exclude the diagnosis of malaria [5]. In our opinion, the 6 - 12 hour delay in repeating the TBS is too long for such a serious pathology, which needs to be treated as an emergency, and the RDTs is the most suitable option because of the rapid delivery of results (15 - 30 minutes) [7]. The use of RDTs in this study helped to better identify cases of severe malaria; the diagnosis of severe malaria was confirmed in 81.7% of cases, compared with 26% before RDT.

From a therapeutic point of view, the prescription of an antimalarial drug for all children before the RDTs, despite a negative TBS result in some, was justified by the diagnostic uncertainty of such a result in a child who had previously received incomplete antimalarial treatment and the seriousness of the clinical picture. However, this approach exposes the child to over-treatment, the risk of drug resistance and delayed diagnosis of other diseases. The introduction of RDTs has had the advantage of improving diagnosis and, as a result, limiting the prescription of antimalarial drugs to malaria-infected children, thereby avoiding the overuse of antimalarial drugs in 13.4% of children.

The diagnostic and therapeutic approach proposed in this study was not associated with increased lethality compared to previous studies; 5.2% versus 26.3% and 6.5% reported by MOYEN and OKOKO, respectively [3] [18].

5. Limitations of This Study

The monocentric design of our study makes it difficult to extrapolate our results to all children of Brazzaville. However, as the PICU receives the majority of children presenting with severe malaria, we feel that our results are fairly representative of the situation in children in Brazzaville.

6. Conclusion

The presumptive use of antimalarial drugs remains common, making it challenging to diagnose severe malaria using microscopy alone. Combining RDT with microscopy enables better identification of cases and appropriate treatment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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