

Monitoring Adverse Events during Seasonal Malaria Chemoprevention Campaigns for Children Aged 3 - 59 Months in Benin in 2023

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How to cite this paper: Affoukou, C., Aïkpon, R., Damiens, G., Biaou Boni, O.R., Padonou, G., Houndjo, W., Houetohossou, C., Sohizoun, E., Legba, T., Ogouyemi, A. and Aguemon, B. (2024) Monitoring Adverse Events during Seasonal Malaria Chemoprevention Campaigns for Children Aged 3 - 59 Months in Benin in 2023. *Open Journal of Epidemiology*, **14**, 579-589.

<https://doi.org/10.4236/ojepi.2024.144041>

Received: August 28, 2024

Accepted: November 2, 2024

Published: November 5, 2024

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Abstract

Background: Seasonal malaria chemoprevention (SMC) is crucial for reducing the burden of malaria in children. However, adverse events (AEs) can affect treatment adherence and efficacy. This study assesses the prevalence of AEs associated with SMC and identifies factors associated with treatment discontinuation. **Methods:** A cross-sectional study of 3115 children receiving SMC was conducted. The study was conducted in two departments in northern Benin. The prevalence of AEs and factors associated with discontinuation of treatment were analyzed. **Results:** Among the children, 578 (18.6%, 95% CI: 17.2 - 19.9) reported AEs, mainly vomiting (63.5%), fever (43.8%) and diarrhea (23.0%). Boys (51.9%) had slightly more AEs than girls (48.1%). The prevalence of AEs was higher in rural areas (64.0%) than in urban areas (36.0%). Only 2.8% of children stopped taking SMC because of AEs. There was no significant association between AEs and discontinuation of SMC ($p = 0.608$). Children referred to health centers for management of AEs were less likely to discontinue treatment ($p = 0.015$). **Conclusion:** AEs were common, but the rate of discontinuation of SMC due to AEs was low, indicating good treatment tolerance. Effective management of AEs in health centers reduces treatment interruptions.

Keywords

SMC, Adverse Events, Treatment Adherence, Benin

1. Introduction

Malaria is a major public health problem worldwide, particularly in sub-Saharan Africa, where the burden remains highest [1]-[3]. According to the WHO, around 94% of global cases (233 million cases) of malaria and 95% of global deaths (580,000 deaths) due to malaria were recorded in Africa in 2022 [4].

In Benin, malaria accounted for 21.7% of consultations or pathologies diagnosed in health centers, according to health statistics for 2021. The people most affected were children under 5 and pregnant women. Among infants under one year of age, the overall incidence was 39%, while among children aged 1 to 5 years, the trend was upwards, with an overall incidence of 44% [5]. Malaria remains the main reason for consultation in health services, accounting for 49.5% of cases in children under 5, with a specific death rate of 21.4% [6].

In order to reduce the burden of malaria, since 2012 the WHO has recommended the chemoprevention of seasonal malaria (SMC) in children under the age of 5 (7). This approach consists of a complete three-day course of treatment with Sulfadoxine pyrimethamine (SP) and Amodiaquine (AQ). The eligible children receive SP on the first day in the presence of a health worker. The next day and on day 3, a child receives AQ from a health worker or community health worker [7] [8]. SMC reduces the number of cases of uncomplicated malaria by at least 80% and severe malaria by 70% [1] [9] [10].

Benin has started implementing SMC in two health zones in 2019, and the positive results have led to the extension of the intervention to 4 other health zones in 2021. Each year, a mass SMC treatment campaign is organised in the health zones of Malanville-Karimama (MK), Kandi-Gogounou-Ségbana (KGS), Banikoara (BNK), Tanguiéta-Matéri-Cobly (TMC), Natitingou-Boukombé-Toucountouna (NBT), and Kouandé Kérou Péhunco (2KP) [8] [11].

The fact that dispensing agents did not inquire whether the child had recently been treated for malaria, or whether he or she had previously been allergic to SMC treatment, favored the occurrence of AEs in children targeted by SMC [12]. This often led to cessation [13] or misperception of SMC by the populations, to the detriment of the program, hence the importance of an effective AR monitoring system. However, Benin's surveillance system, like that of other sub-Saharan African countries, is characterized by low AEs notification rates [14].

The WHO recommends strengthening or implementing pharmacovigilance in order to detect, understand and prevent any risks associated with the use of SPAQ during SMC, with the aim of supporting the program with reliable efficacy and safety data, and guaranteeing the sustainability of the strategy [15].

The aim of this study is to describe the AEs reported during SMC and to

determine the frequency of discontinuation of SMC administration in children under the age of 5 in 2023.

2. Framework and Methods

2.1. Study Framework

Benin's health system is pyramidal, with health zones at the base, topped by departmental health directorates at the intermediate level. At the top of the pyramid is the Ministry of Health and the various programmes. A health zone is made up of one (1) to three (3) communes. This study covered fifteen (15) of Benin's seventy-seven (77) communes, spread across six (06) health zones in north of the country, namely Banikoara (BNK), Kandi-Gogounou-Ségbana (KGS) and Malanville-Karimama (MK) in Alibori; Natitingou-Boukombé-Toucountouna (NBT), Kouandé-Kérou-Péhunco (2KP) and Tanguiéta-Matéri-Cobly (TMC) in Atacora.

The National Vigilance System of Health Products for Human Use was created by ministerial decree in 2021 in Benin and integrated into the epidemiological surveillance system. Its main function is to monitor AEs and events related to the use of healthcare products for human use.

Pharmacovigilance as applied to the SMC campaign is essentially based on the health zone, where the head of the epidemiological surveillance center is based, and who is responsible for supporting health professionals in reporting. For this reason, before the start of each year's SMC campaign, community workers, nurses and chief medical officers are trained in reporting.

Reporting of all AEs is mandatory for all healthcare professionals. Notification forms are collected by the pharmacist in charge of the zone hospital, in collaboration with the head of the epidemiological surveillance center of the health zone, then sent to the pharmacist at the departmental hospital center and finally to the Benin Pharmaceutical Regulation Agency. Notification is made to The National Malaria Control Program.

2.2. Type and Period of Study

It was a descriptive cross-sectional study. The data used were those from the 2023 SMC coverage survey, i.e. the July, August, September and October 2023 passages. The data collection period covered 15 days, i.e. from 30 November to 14 December 2023.

2.3. Study Population

The study population consisted of a primary and a secondary target group. The primary target was children (girls and boys) aged 3 to 59 months living in the study area at the time of the 2023 SMC campaign, and the secondary target was the respondents, i.e. the parents (mother or father) or guardians of the target children.

Children aged 3 to 59 months whose parents had lived in one of the six health zones for at least 6 months prior to the survey were included in the study.

2.4. Sampling Size and Technique

The sample size was calculated using the Schwartz formula, based on SMC coverage rate of 51.8% in 2022 with a desired margin of error of 2%, an alpha risk of 5% and a sampling technique effect of 1.4.

The minimum sample size was 3357 children.

Sampling was random in two stages. In the first stage, we selected 172 enumerations area (EA) by simple random selection, i.e. 11 to 12 EA in each of the 15 communes, based on data from the fourth General Population and Housing Census of 2013. Then, in each EA, all households in which children under the age of 5 were counted. The second stage consisted of randomly selecting 20 households in each EA. One eligible child was included in each household.

2.5. Data Collection Technique and Tools

The data collection technique was a structured interview between interviewer and respondent. The data collection tool was a standardized questionnaire administered to mothers or nannies. The questionnaire was digitized using the KoboToolbox platform and collected by using smartphones.

2.6. Study Variables

Our analysis used the preferred AE coding terms from the Medical Dictionary for Regulated Activities (MedDRA) used in VigiFlow®. The independent variables were the number of doses of SMC administered, the number of children who received at least one dose of SMC, age, sex, place of residence, therapeutic indication, nature of AE, corrective action of AE, and outcome of AE.

2.7. Data Processing and Analysis

The data were analyzed using Stata 11.2 and Minitab version 16 software. Variables were described by calculating proportions for qualitative variables and mean with standard deviations for quantitative variables following a normal distribution. Proportions were compared using Pearson's Chi-square test, with a significance level of 5%.

2.8. Ethical Considerations

The study was approved by the CER-ISBA Research Ethics Committee (decision N°190 of 06 December 2023). The survey was carried out after authorization for data collection had been granted by the two Departmental Directors of Health and the coordinating doctors of the health zones. In the field, the objectives of the survey were clearly explained to the participants and the questionnaires were administered after obtaining their written and free consent. The anonymity of the respondents was respected.

3. Results

A total of 3115 children had received at least one dose of SPC out of 3573 included

in the study, representing a coverage rate of at least one dose of 87.2%.

3.1. Characteristics of AEs

The occurrence of AEs was noted in 578 children, for a prevalence of SMC-related AEs of 18.6% IC95% = [17.2 - 19.9]. The most frequent AEs were vomiting (63.5%), fever (43.8%) and diarrhea (23.0%). The AEs reported during the 2023 SMC campaign in Benin are presented in **Figure 1** below.

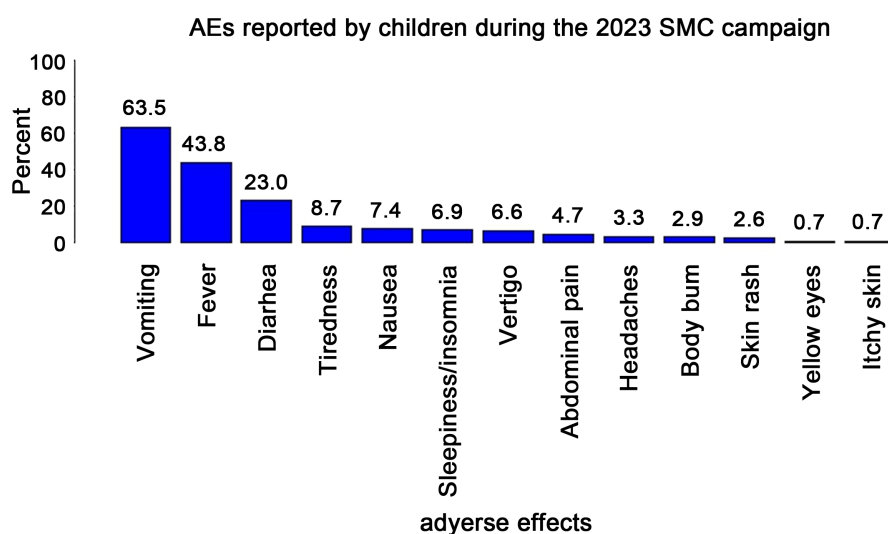


Figure 1. Adverse events reported by children aged 3 - 59 months during the 2023 SMC campaign in Benin.

The median age of children with at least one AE was 28 months (interquartile ranges 16 and 44 months). Among them, 19.4% were aged between 3 and 11 months, and 80.6% between 12 and 59 months. Boys (51.9%) were more affected than girls (48.1%). There were more children with AEs in rural areas (64.0%) than in urban areas (36.0%). The 2KP health zone recorded more cases of AEs (30.3%). However, these differences were not statistically significant.

Just over a third (34.8%) of children with AEs were referred to a health center for treatment. Factors associated with the occurrence of AEs are presented in **Table 1**.

3.2. Frequency of Discontinuation of SMC

A total of 63 children discontinued SMC, including 16 for reasons related to AEs, i.e. 2.8% of children with AEs. There was no significant association ($p = 0.608$) between the proportion of children who stopped SMC after vomiting (1.9%) and the proportion who stopped SMC for other reasons (4.3%). Children referred to a health center were less likely to stop treatment than those who were not referred to a health center ($p = 0.015$). The proportion of children who stopped treatment due to AE in health zones 2KP (5.7%) and TMC (4.0%) was significantly higher than that of children who stopped treatment in the other health zones due to AE ($p = 0.034$).

Table 2 below shows the results of the bivariate analysis.

Table 1. Distribution of children aged 3 - 59 months receiving SMC in 2023 in Benin according to AEs occurrence.

	Occurrence of AEs		p-value
	Yes (%)	No (%)	
Health zone			0.000
BNK	20 (10.0)	181 (90.0)	
KGS	93 (16.8)	462 (83.2)	
2KP	175 (28.9)	431 (71.1)	
MK	108 (24.3)	336 (75.7)	
NTB	81 (14.5)	478 (85.5)	
TMC	101 (13.5)	649 (86.5)	
Place of residence			0.060
Rural	370 (17.5)	1748 (82.5)	
Urban	208 (20.9)	789 (79.1)	
Children's age in months			0.667
3 - 11	112 (20.4)	436 (79.6)	
12 - 59	466 (18.2)	2101 (81.8)	
Gender of children			0.146
Male	300 (18.0)	1371 (82.0)	
Female	278 (19.3)	1166 (80.7)	
SMC strategy			0.548
One supervised plug	229 (16.4)	1166 (83.6)	
Three supervised plugs	349 (20.3)	1371 (79.7)	

Table 2. Distribution of children aged 3 - 59 months receiving SMC in 2023 in Benin according to the management and treatment discontinuation.

Health zone	AEs referred to the Health Center		p-value	SMC shutdown due to AEs		p-value
	Yes (%)	No (%)		Yes (%)	No (%)	
			<0.001			0.034
BNK	4 (20.0)	16 (80.0)		0 (0.0)	20 (100.0)	
KGS	23 (24.7)	70 (75.3)		0 (0.0)	93 (100.0)	
2KP	46 (26.3)	129 (73.7)		10 (5.7)	165 (94.3)	
MK	64 (59.3)	44 (40.7)		2 (1.9)	106 (98.1)	
NTB	49 (60.5)	32 (39.5)		0 (0.0)	81 (100.0)	
TMC	15 (14.9)	86 (85.1)		4 (4.0)	97 (96.0)	

Continued

Place of residence			0.060		0.145
Rural	139 (37.6)	231 (62.4)		13 (3.5)	357 (96.5)
Urban	62 (29.8)	146 (70.2)		3 (1.4)	205 (98.6)
Children's age in months			0.667		0.331
3 - 11	37 (33.0)	75 (67.0)		1 (0.9)	111 (99.1)
12 - 59	164 (35.2)	302 (64.8)		15 (3.2)	451 (96.8)
Gender of children			0.146		0.877
Male	96 (32.0)	204 (68.0)		8 (2.7)	292 (97.3)
Female	105 (37.8)	173 (62.2)		8 (2.9)	270 (97.1)
SMC strategy			0.548		0.860
One supervised plug	83 (36.2)	146 (63.8)		6 (2.6)	223 (97.4)
Three supervised plugs	118 (33.8)	231 (66.2)		10 (2.9)	339 (97.1)
Nature of AEs					
Vomiting			<0.001		0.096
Yes	162 (44.1)	205 (55.9)		7 (1.9)	360 (98.1)
No	39 (18.5)	172 (81.5)		9 (4.3)	202 (95.7)
Fever			<0.001		0.608
Yes	108 (42.7)	145 (57.3)		6 (2.4)	247 (97.6)
No	93 (28.6)	232 (71.4)		10 (3.1)	315 (96.9)
Diarrhea			0.002		0.848
Yes	61 (45.9)	72 (54.1)		4 (3.0)	129 (97.0)
No	140 (31.5)	305 (68.5)		12 (2.7)	433 (97.3)
Tiredness			0.293		0.212
Yes	14 (28.0)	36 (72.0)		0 (0.0)	50 (100.0)
No	187 (35.4)	341 (64.6)		16 (3.0)	512 (97.0)
Sleepiness/insomnia			0.288		0.618
Yes	23 (57.5)	17 (42.5)		0 (0.0)	40 (100.0)
No	354 (65.8)	184 (34.2)		16 (3.0)	522 (97.0)
Abdominal pain			0.505		0.766
Yes	11 (40.7)	16 (59.3)		0 (0.0)	27 (100.0)
No	190 (34.5)	361 (65.5)		16 (2.9)	535 (97.1)
Vertigo			0.001		1.000
Yes	4 (10.5)	34 (89.5)		1 (2.6)	37 (97.4)
No	197 (36.5)	343 (63.5)		15 (2.8)	525 (97.2)

Continued

Headaches			0.031		1.000
Yes	11 (57.9)	8 (42.1)		0 (0.0)	19 (100.0)
No	190 (34.0)	369 (66.0)		16 (2.9)	543 (97.1)
Body burns			0.009		1.000
Yes	11 (64.7)	6 (35.3)		0 (0.0)	17 (100.0)
No	190 (33.9)	371 (66.1)		16 (2.9)	545 (97.1)
Referred to health center for treatment					0.015
Yes				1 (0.5)	200 (99.5)
No				15 (4.0)	362 (96.0)

4. Discussion

SMC campaigns contribute to the increase in AEs reporting in Benin. The prevalence of SMC-related AEs observed in this study was 18.6%, which is consistent with data available in the scientific literature [16]. The AEs presented in this study are mentioned in the summary of product characteristics used for SMC and mentioned in other studies [1] [3] [17]-[20]. Vomiting was the most frequent AE, both in our study and in the literature. Ndiaye *et al.*, in Senegal in 2016 [20] and Ouoba *et al.* in 2023 in Burkina [18], also identified vomiting as a common reaction. This similarity may be attributed to amodiaquine, which is known to cause nausea and vomiting. The high prevalence of vomiting suggests that it may be beneficial to explore alternative formulations or administration strategies to reduce this adverse reaction. Fever was the second most frequent adverse reaction in our study. Dicko *et al.*, also reported similar rates of fever, highlighting that this reaction may be due to a normal immune response or a reaction to the drug [17]. Proactive management of side effects, including fever and diarrhea, is essential to improve acceptability and adherence to treatment.

Children in rural areas appear to be more affected by AEs, which could be attributed to environmental and nutritional conditions, which are often less favorable in rural areas and may play a role in increased susceptibility to AEs. Cairns *et al.*, found that malnutrition and micronutrient deficiencies, more common in rural areas, can exacerbate drug side effects [21]. Furthermore, Druetz *et al.*, noted that limited access to health services and medical care in rural areas could delay the detection and management of AEs, thereby increasing their prevalence and severity [22].

The fact that only 34.8% of children with AEs were referred to a health center may indicate various challenges in the healthcare system. Studies such as that by Druetz *et al.*, in 2015 highlighted that gaps in AEs monitoring and management are common in many parts of sub-Saharan Africa [22]. In rural areas, limited access to healthcare services and adequate infrastructure may explain low referral rates to health center. Families may be reluctant to seek care due to distance, cost or perceived severity of symptoms [21] [23].

The rate of children whom discontinued SMC due to AEs is relatively low, suggesting that most children and their parents are willing to continue treatment despite the occurrence of minor AEs. This was consistent with the findings of several studies, which have shown that the overall tolerability of SMC is acceptable, and that discontinuations are rare [1] [8] [13].

The absence of a significant association between the proportion of children discontinuing SMC after vomiting and the proportion discontinuing SMC for other reasons indicates that vomiting is not a primary reason for discontinuation. Studies such as that by Meremikwu *et al.* have also observed that vomiting, although a common side effect, does not often lead to treatment discontinuation, probably due to the effective management of this symptom by caregivers [19].

Children referred for treatment at a health center were less likely to discontinue treatment than those who were not treated at a health center. This underlines the importance of appropriate medical management in the management of AEs and the prevention of treatment discontinuation. Researchers have shown that early and appropriate interventions by healthcare professionals can improve adherence to treatment by reducing the perceived severity of AEs [20] [24]. The geographical variation in treatment discontinuation highlights the need for targeted awareness programs to inform communities about AEs management and the importance of treatment continuity. The implementation of continuous monitoring and follow-up systems is crucial to detect and manage AEs rapidly, in order to minimize treatment interruptions.

5. Conclusion

Although the prevalence of AEs is notable, most children continue SMC despite these effects, underscoring acceptable treatment tolerance. Adequate medical management plays a crucial role in managing AEs and reducing treatment discontinuation. Regional variations in treatment discontinuation highlight the need for targeted interventions to improve access to care and AEs management. By strengthening health systems and raising community awareness, it is possible to improve treatment adherence and maximize the benefits of SMC in children.

Conflicts of Interest

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

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