

Research Article

Factors Associated with Malaria in Children Aged 3 to 59 Months Under Seasonal Malaria Chemoprevention with Direct Observation Therapy in Two Districts in Burkina Faso, 2020: A Quasi-Experimental Trial

Yanogo Pauline Kiswendsida^{1,2,*} , **Sanou Estelle Nadine²** , **Yanogo Chantal²** ,
Ou édraogo Sma Ia¹ , **Meda Nicolas^{1,2}** , **Halidou Tinto³** 

¹Department of Public Health, Health Science Research and Training Unit, Joseph Ki-Zerbo University, Ouagadougou, Burkina Faso

²Burkina Field Epidemiology and Laboratory Training Program (BFELTP), Health Science Research and Training Unit, Joseph Ki-Zerbo University, Ouagadougou, Burkina Faso

³Clinical Research Unit of Nanoro, Institut de Recherche en Sciences de la Santé Nanoro, Burkina Faso

Abstract

The seasonal malaria chemoprevention (SMC) represents one of the key interventions for malaria elimination in seasonal malaria transmission settings. However, though the SMC was implemented in Burkina Faso since the last ten years, the incidence of malaria in children of 3 to 59 months under seasonal malaria chemoprevention (SMC) remains high in the country. To enhance the intervention's effectiveness in its routine system, strategies are being explored, including a new delivery approach in which community health workers directly supervise the administration of the three doses of SMC therapy (3DOT), compared to the standard delivery approach in which only the first dose is directly observed therapy (1DOT) and the remaining two doses are given to the child's guardians or parents, who must administer them to the child over the following two days. While the search for the most effective delivery strategy for SMC continues, our study aimed to identify factors associated with malaria under the 3DOT and 1DOT delivery of SMC in children aged 3 to 59 months in 2 districts in Burkina Faso. We identified factors associated with malaria in 2440 children included in a quasi-experimental cluster randomized trial, before-after with a control group design. Four health and social promotion centers were randomly selected in the Boromo health district (1DOT) and 3 in the Gaoua health district (3DOT) to receive a monthly four rounds of SMC with Sulfadoxine-pyrimethamine plus Amodiaquine. A survey logistic regression calculated the odds ratios of association between variables and malaria with significance threshold $\alpha = 0.05$. The results revealed, lack of optimal supervision (aOR = 2.466 [1.650–3.686], $p < 0.0001$), lack of optimal coverage (aOR = 4.881 [2.454–9.708], $p < 0.0001$), total vomiting/rejection (aOR = 14.016 [2.169–90.552], $p = 0.0055$), residence in the health district of Gaoua (3DOT) (aOR = 2.057 [1.425–2.970], $p = 0.0001$) and past history of fever (aOR = 3.045 [1.630–5.686], $p = 0.0005$) were significantly associated with malaria in children under five years of age under SMC. The factors associated with malaria under SMC identified in this study support the conclusion of the superiority of 3DOT compared to 1DOT to reduce the prevalence of malaria. Addressing these factors would make the strategy more relevant for the elimination of malaria by 2030.

*Corresponding author: yanogo.pauline@yahoo.fr (Yanogo Pauline Kiswendsida)

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Keywords

SMC, Factors Associated, Malaria, 3DOT, Burkina Faso

1. Introduction

Despite the implementation of Seasonal Malaria Chemoprevention (SMC) in Burkina Faso, the incidence of malaria remains high and then, the objective of reducing by at least 60% the morbidity of the disease in children under 5 years of age has not yet been achieved (data from National malaria control program 2015-2016). According to World Health Organization (WHO), SMC is defined as “intermittent administration of full treatment courses of an antimalarial medicine during the malaria season to prevent malarial illness with the objective of maintaining therapeutic antimalarial drug concentrations in the blood throughout the period of greatest malarial risk” [1].

The question of the effectiveness of the SMC does not arise much, but questions about what goes wrong in implementation remain. While some studies show suboptimal reductions of malaria with SMC [2, 3] and some affirm the good adherence of the population [4], others have not shown any difference in malaria prevalence between children with and without SMC intervention [5].

The SMC represents one of the key interventions for the malaria elimination. However, though the SMC was implemented in seasonal malaria seasonal transmission settings since the last ten years, the burden of the disease remains high in Africa. In Burkina Faso, the burden of malaria among children under five years old remains significant [6], reaching an annual incidence of 86.73% compared to 47.10 in the general population [7]. Prior to the implementation of SMC, the country conducted studies that showed the high effectiveness of this intervention in reducing the incidence of uncomplicated and severe malaria cases in children under five years of age [8, 9]. To enhance the intervention's effectiveness in its routine implementation, strategies are being explored, including a new delivery approach in which community health workers (CHW) directly supervise the three doses of SMC Therapy (3DOT), compared to the standard delivery approach in which only the first dose is directly observed Therapy (1DOT) and the remaining two doses are given to the child's guardians or parents, who must administer them to the child over the following two days.

While the research to propose the most effective delivery strategy for SMC continues, it is also important to seek the reasons of the persistence of malaria in children under SMC in order to address it efficiently.

Various reasons to explain this such persistence, including malnutrition, underdosing in the malnourished, weak adherence to SMC in the population, and mutations of drugs'

resistance markers though the mediation of SMC drugs' therapeutic efficacy remains uncertain [10-17].

The factors classically associated with malaria in children under five are known and are in particular, age, distance from residence to health facility, malnutrition, non-instruction of parents/guardian, having his parents who have a history of using traditional drugs, long-acting insecticide-treated nets use after 9pm, non-use of insecticides, number of seasonal malaria chemoprevention <3 doses [18-20]. The question arises as to whether the same factors are involved in the occurrence of malaria in children under SMC with 3DOT compared to 1DOT. To our knowledge, no study to date has investigated the factors associated with malaria in children under SMC with 3DOT.

We conducted a baseline study which identified the age range from 12 to 59 months, distance to health facilities beyond 5 km, past history of fever, and the non-use of long-lasting insecticide-treated nets (LLINs) as factors associated with malaria in children aged 3 to 59 months [21]. Following the implementation of 3DOT and 1DOT, which demonstrated the superiority of 3DOT to reduce the prevalence of malaria compared to 1DOT (68.60% vs. 53.00%; $p < .0001$) (article in press), it is useful to identify the factors that explain persistent malaria in children under SMC in these health districts. Identifying these factors and taking them into account in SMC campaign planning could improve the effectiveness of the SMC intervention. Therefore, our objective in this study was to identify factors associated with malaria in children aged 3 to 59 months under the seasonal malaria chemoprevention with 3DOT and 1DOT in 2 districts in Burkina Faso.

2. Materials and Methods

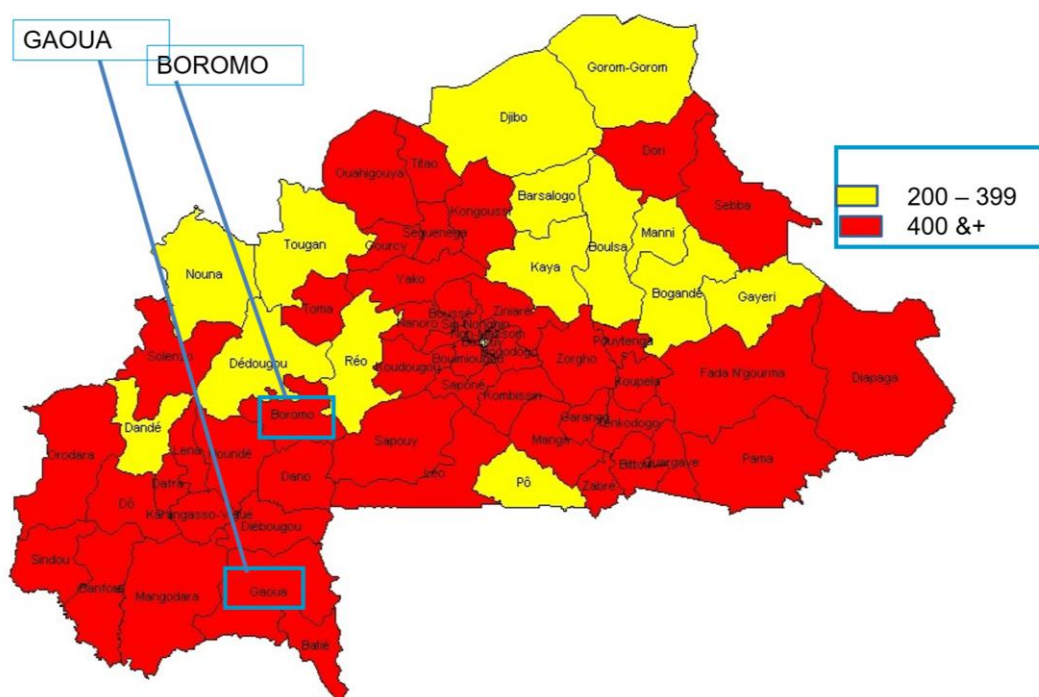
2.1. Study Area: Districts of Gaoua and Boromo

The study was carried out in the health districts of Gaoua and Boromo, which served for the baseline study as well as for the intervention phase [21]. Gaoua benefited from the 3DOT and Boromo from the 1DOT. These two health districts are located in the high-rainfall zone, where malaria transmission is hyper-endemic.

According to the National Malaria Control Program, the two districts receive the same anti-malaria interventions over the study period, these include, indoor insecticide spraying,

the national campaign for the distribution of long-lasting, multi-product insecticide-treated nets with the introduction of new generation nets, integrated community case management of children (diarrhea, uncomplicated malaria, malnutrition, and pneumonia in children under 5), and management

of simple malaria (>5 years), information, education, communication/behavior change communication activities, monitoring of LLIN use, and intermittent preventive treatment during pregnancy (IPTp-SP) [22]. Both districts benefit from nutrition interventions as well.



Data source: National Malaria Control Programme malaria surveillance, 2019

Figure 1. Incidence of malaria per 1000 inhabitants by health district in 2019 in Burkina.

2.2. Study Type

This was a quasi-experimental cluster trial, before-after with a control group design in which factors associated with malaria in the context of SMC were identified in both delivery methods 3DOT and 1DOT from July to October 2020.

2.3. Eligibility Criteria

Inclusion Criteria

- 1) Eligible children were all to those who met the following conditions:
- 2) Aged from 3 to 59 months of age
- 3) Residing in the 2 selected districts

Whose guardians/parents consented the participation to the study

Criteria of Non-Inclusion

- 1) Children who were not eligible for SMC were not included in this etiological analysis; these are:
- 2) Children younger than 3 months are not eligible to get SPAQ
- 3) Children older than 5 years are not eligible to get SPAQ

- 4) Children with positive RDT will not get SPAQ in the first Cycle however should be treated with an ACT
- 5) Children who are sick and not able to swallow should not get SPAQ
- 6) Children that have Malaria should not get SPAQ rather refer to health facility
- 7) Children allergy to SP or AQ or Cotrimoxazole or Septrin or Bactrim
- 8) Children taken SP or AQ or Cotrimoxazole or Septrin or Bactrim in last 4 months

2.4. The Two Methods of Delivery Compared

This is a secondary analysis of data from a randomized study comparing the SMC 3DOT delivery approach (intervention arm) versus 1DOT delivery method (control arm). Both delivery methods were described in detail elsewhere (article in press). Briefly, the 3DOT delivery method consisted, of a supervised intake by the community health workers, of the three doses of Sulfadoxine-pyrimethamine plus Amodiaquine (SP-AQ) in each round of SMC. Every morning, at the same time, the CHW went door to door to supervise the administration of the medicine to the child. The first day, the

the CHW delivered malaria prevention messages to the care giver of the child.

The 1DOT delivery method of delivery or the control: The country currently uses this method. Only the administration of the first dose of SP-AQ was supervised by the CHW. In this method, the other two doses being given by the child's care giver. In addition to malaria prevention messages were given by the CHW. The CHW also gave guidance to the child's care giver for the administration of the two doses on the following two days.

In both methods of delivery, CHWs were supervised by the center of health and social promotion (CHSP) team, members of the health district, regional and central level team in the routine implementation, and by investigators of this study.

2.5. Sampling

The sample size used for testing the superiority of 3DOT (n=924) compared to 1DOT (n= 1516) were used in this secondary analysis (to have an optimal size).

The number of clusters and person-months required in each group was estimated by Hayes' randomized controlled trial size calculation method [23]. The incidence rate estimated from DHIS2 data for 15 CHSP that had benefited from the SMC in 2015 was 24 cases per 100 person-months, corresponding to the incidence rate of the 1DOT group. Considering the assumptions of relative reduction of the incidence rate as shown in the table below, a power of 80% and an alpha risk of 0.05, for an equal number of subjects between 3DOT and 1DOT, the following scenarios were considered (table 1).

Table 1. Estimate of the number of subjects required for the comparison of incidence rate between the two groups in the month following the round of SMC.

Assumption	Expected relative reduction	Incidence rate 1DOT (case in person-months)	Incidence rate 3DOT (case in person-months)	m (Cluster size)	K (the coefficient of variation of	Assumption	Expected relative reduction
1	75%	0,24	0,06	300	0,39	4	1200
2	67%	0,24	0,0792	300	0,39	6	1800
3	50%	0,24	0,12	300	0,39	12	3600
4	34%	0,24	0,1584	300	0,39	30	9000
5	30%	0,24	0,168	300	0,39	36	10800

Considering the budget constraints, and the fact that the district of the 3DOT (Gaoua) counted 45 958 children and that of the 1DOT (Boromo) counted 57 426 children in 2020, hypothesis 2 was used to include least 1980 children were included in at least 6 clusters. Proportionally, 3.33 CHSP (0,56%) of the participants were drawn from Boromo and 2.67 CHSP (0,44%) from Gaoua. The smallest health facility, the CHSP was used as sampling unit. From the above, three CHSP were randomly selected in Gaoua (3DOT) and four from Boromo (1DOT). All the children of a selected HSPC were included in the study.

2.6. Data Collection

For each round, the children were followed-up passively from the last dose of the three days treatment to the next round, i.e. one month by. Health workers and community health workers (CHWs). The guardian was encouraged to see a health worker whenever the child had a fever.

Data were collected during the SMC delivery period in the 2020 transmission season from July to October. Thus, as part of their usual work, the health center staff and the community

health worker were asked to record all consultation data in the consultation register as well as in the SMC record book.

At the end of each month, the investigators checked all collected data or completeness, and collected the data of children who consulted for fever during the SMC period, from the CHW record book, the child's health book, and the consultation register. Data, including sociodemographic characteristics (age, sex, number of children under five in the household, etc.), SMC and clinical characteristics (having received the 3 doses of SMC at all the four rounds or optimal coverage, having been supervised at the 3 doses of SMC at all the four rounds or optimal supervision, having rejected/vomited the 3 doses of SMC at all the four rounds or total rejection/vomiting, fever, date of consultation, diagnosis, malaria, form of malaria, treatment prescribed for malaria and duration of treatment, etc.), as well as knowledge and malaria prevention practices, were collected at baseline and during each round of SMC.

These data were collected through interviews and document reviews in the aforementioned documents.

The dependent variable was malaria confirmed by rapid diagnostic tests (RDT) or microscopy or suspected and treated

as such. Data collection was done by the interviewers, made up of a bônoma made up of a 6th year medical student and a community health worker (serving as an interpreter when required), who presented the study (information notice and consent form) and who obtained parent's consent, and under the supervision of an investigator.

2.7. Data Analysis

The data were analyzed with SAS (SAS, Institute, Inc., Cary, North Carolina, USA and R 4.1.0).

Descriptive analysis

The sociodemographic and clinical characteristics of the population as well as practices and knowledge of malaria and its prevention at inclusion were described. Qualitative and categorized variables were expressed as proportions and ratios (95% CI) which were compared by Khi-2 test, using surveyfreq commands in SAS, to consider the cluster effect.

Etiological analysis

In the set of the two methods of delivery, factors associated with malaria in children within the months following the 3rd dose of each round of SMC were identified in univariate and multivariate survey logistic regression. Age, not sleeping under LLINs, and distance between home and health facility which were associated with malaria in our baseline study were

forced into the multivariate analysis. Odds ratio (OR) of association with malaria and their 95% confidence intervals (95%CI) as well as the *p*-values were estimated for each variable. The significance threshold considered $\alpha = 0,005$.

2.8. Ethical Considerations

The study protocol has been approved by the national ethic committee of the Ministry of health and public hygiene of Burkina Faso (reference N° 2016-9-103) prior to the survey. Parents/guardians, after being informed about the study and asking clarifying questions, gave their signed consent before inclusion of their children.

3. Results

3.1. Characteristics of the Study Participants

A total of 2,240 children from seven centers for health and social promotion were included in the study, including 924 children from three CHSP in the 3DOT arm (Gaoua), and 1,516 children from four CHSP in the 1DOT arm (Boromo), (Table 2).

Table 2. Characteristics of the study participants.

Features	1DOT		3DOT		<i>P</i>
	(n)	(%)	(n)	(%)	
Age					0.0004
[3 months -1 year]	307	23.35	140	16.51	
[1year - 2 years [200	15.21	127	14.98	
[2years – 5 years [808	61.44	581	68.51	
Sex					0.7688
Male	767	50.73	466	51.38	
Female	745	49.27	441	48.62	
Possession of a bed net					<0.0001
Yes	1329	87.66	719	77.81	
No	187	12.34	205	22.19	
Sleep under a LLIN last night					<0.0001
Yes	1316	89.04	584	65.40	
No	162	10.96	309	34.60	
Past history of fever					0.0005
Yes	50	3.30	59	6.39	
No	1466	96.70	865	93.61	

Features	1DOT		3DOT		P
	(n)	(%)	(n)	(%)	
Children under 5 years of age with a tutor					<0.0001
1 child	349	30.56	306	36.17	
[2-6[750	65.67	538	63.59	
≥6	43	3.77	2	0.24	
Number of persons in the family					<0.0001
[0-6[676	60.52	309	36.40	
[6-11[280	25.07	317	37.34	
[11-21[123	11.01	188	22.14	
>21	38	3.40	35	4.12	
Distance from CHSP					<0.0001
< 5km	944	97.42	100	28.90	
≥5km	25	2.58	246	71.10	
Tutors					0.0002
Legal Guardian	332	22.68	270	30.13	
Mother	981	67.01	531	59.26	
Father	151	10.31	95	10.60	
Level of education of parent/guardian					0.9354
Not schooled	1019	91.14	731	91.03	
Schooled	99	8.86	72	8.97	
Gender of parent/guardian					
Male	151	10.31	95	10.60	
Female	1313	89.69	801	89.40	
Marital status					<.0001
Single	48	3.23	97	10.60	
In a couple	1437	96.77	818	89.40	
Age of parent/guardian					<0.0001
<18 years	5	0.40	31	3.63	
[18-25[264	21.17	136	15.94	
[25-60[961	77.06	636	74.56	
[60-79[17	1.36	50	5.86	

3.2. Features of Children and Their Caregivers Associated with Malaria in Children from 3 to 59 Months Old Under SMC with 3DOT and 1DOT in Burkina Faso in Univariate Analysis

In univariate analysis (Table 3), 3DOT district (OR = 1.605 [1.268–2.031], $p < 0.0001$), fever (OR = 1.910 [1.192–3.061], $p = 0.0071$) and the number of dependent children under 5 years of old were associated with malaria (OR = 0.743 [0.566–0.976], $p = 0.0330$).

Table 3. Features of children and their caregivers associated with malaria in children from 3 to 59 months old under SMC with 3DOT and 1DOT in Burkina Faso in univariate analysis.

Features	n ^{+/} N	OR;95%IC	P
Age			0.7695
[3 months -1 year]	58/438	1	
[1year - 2 years [48/318	1.165 [0.771 1.760]	
[2years – 5 years [190/1350	1.073 [0.782 1.472]	
Sex			0.5497
Male	166/1160	1	
Female	160/1189	0.931 [0.737 1.177]	
Health district			<0.0001
1DOT	171/1461	1	
3DOT	155/887	1.605 [1.268 2.031]	
Possession of a bed net			0.4341
Oui	272/1998	1	
Non	54/356	1.135 [0.827 1.557]	
Past history of fever			0.0071
No	302/2249	1	
Yes	24/105	1.910 [1.192 3.061]	
Distance from CHSP			<0.0001
< 5km	109/1013	1	
≥5 km	56/259	2.288 [1.602 3.268]	
Sleep under a LLIN last night			0.3425
Yes	239/1779	1	
No	86/573	1.138 [0.872 1.486]	
Children below 5 years of age with a tutor			0.0330
1	98/636	1	
≥2	155/1300	0.743 [0.566 0.976]	
Persons in the family			0.3945
[0-6[123/960	1	
[6-11[81/584	1.096 [0.811 1.481]	
≥11	122/810	1.207 [0.921 1.581]	
Parent/guardian			0.0555
Legal Guardian	190/1469	1	
Mother	96/579	1.338 [1.025 1.747]	
Father	28/244	0.873 [0.572 1.331]	
Level of education of parent/guardian			0.1493
Schooled	28/169	1	
Not schooled	215/1700	0.729 [0.474 1.120]	
Gender of parent/guardian			0.2861

Features	n ⁺ /N	OR;95%IC	P
Male	28/244	1	0.5577
Female	286/2048	1.252 [0.828 1.892]	
Marital status			
In a couple	302/2183	1	0.8440
Single	16/133	0.852 [0.498 1.456]	
Age of tutors			0.8440
< 25ans	59/425	1	
≥ 25 ans	230/1613	0.970 [0.712 1.320]	

3.3. Malaria Prevention Knowledge and Practices and SMC Status Associated with Malaria in Children from 3 to 59 Months Old under SMC in Burkina Faso in Univariate Analysis

In univariate analysis (table 4) the lack of awareness of malaria symptoms (OR = 1.929 [1.351–2.754], $p = 0.0003$), lack of optimal coverage (OR = 3.428 [2.491–4.717], $p < 0.0001$), lack of optimal supervision (OR = 1.695 [1.263–2.275], $p = 0.0004$), and total rejection/vomiting (OR = 16.585 [4.262–64.536], $p < 0.0001$) were significantly associated with malaria.

Table 4. Malaria prevention knowledge and practices and SMC status associated with malaria in children from 3 to 59 months old under SMC with 3DOT and 1DOT in Burkina Faso in univariate analysis.

Features	n ⁺ /N	OR;95%IC	P
knowledge of malaria prevention			0.1213
Yes	231/1750	1	0.1213
No	95/604	1.227 [0.947 1.590]	
knowledge of malaria symptoms			0.0003
Yes	258/1994	1	0.0003
No	45/202	1.929 [1.351 2.754]	
Optimal coverage			<0.0001
Yes	243/2033	1	<0.0001
No	67/211	3.428 [2.491 4.717]	
Optimal supervision			0.0004
Yes	66/739	1	0.0004
No	199/1396	1.695 [1.263 2.275]	
Total rejection/vomiting			<0.0001
No	259/2100	1	<0.0001
Yes	7/10	16.585 [4.262 64.536]	

3.4. Factors Associated with Malaria in Children from 3 to 59 Months Old Under SMC with 3DOT and 1DOT on a Multivariate Analysis

In multivariate analysis (table 5), lack of optimal supervi-

sion (aOR = 2.466 [1.650–3.686], $p < 0.0001$), lack of optimal coverage (aOR=4.881 [2.454–9.708], $p < 0.0001$), vomiting/rejection (aOR = 14.016 [2.169–90.552], $p = 0.0055$), residence in the health district of Gaoua (3DOT) (aOR = 2.057 [1.425–2.970], $p = 0.0001$) and past history of fever (aOR = 3.045 [1.630–5.686] $p = 0.0005$) were significantly associated with malaria.

Table 5. Factors associated with malaria in children from 3 to 59 months old under SMC with 3DOT and 1DOT in Burkina Faso in multivariate analysis.

Features	aOR; 95%CI	P
Health district		0.0001
1DOT	1	
3DOT	2.057 [1.425 2.970]	
Past history of fever		0.0005
Yes	1	
No	3.045 [1.630 5.686]	
Distance from CHSP		0.0641
< 5km	1	
≥ km	.492 [0.948 6.552]	
Age		0.7020
[3 months -1 year]	1	
[1year - 2 years [1.471 [0.599 3.613]	
[2years – 5 years [1.223 [0.590 2.534]	
Sleep under a LLIN last night		0.0256
Yes	1	
No	1.459 [0.232 1.909]	
Children below 5 years of age with a tutor		0.1291
1	1	
≥2	1.504 [0.888 2.547]	
Tutors		0.8279
Legal Guardian	1	
Mother	0.912 [0.484 1.719]	
Father	0.853 [0.499 1.456]	
Level of education of tutors		0.3715
Schooled	1	
Not schooled	0.777 [0.446 1.352]	
knowledge of malaria prevention		0.1125
Yes	1	
No	0.611 [0.333 1.123]	
knowledge of malaria symptoms		0.0658

Features	aOR; 95%CI	P
Yes	1	
No	1.149 [0.819 3.785]	
Optimal coverage		<0.0001
Yes	1	
No	4.881 [2.454 9.708]	
Optimal supervision		<0.0001
Yes	1	
No	2.466 [1.650 3.686]	
Total rejection/vomiting		0.0055
No	1	
Yes	14.016 [2.169 90.552]	

4. Discussion

Our study identified the lack of optimal coverage, the lack of optimal supervision, the total vomiting/rejection, the residence in the health district of Gaoua (3DOT) and the past history of fever as factors associated with malaria among children under five in children receiving SMC under the 3DOT or 1DOT method of delivery in Burkina Faso in 2020.

Age of the child, distance to health facilities beyond 5 km, and the non-use of long-lasting insecticide-treated nets (LLINs) which were associated with malaria in children under 5 years of age in the baseline study [21] were no longer associated with malaria in children under SMC with 3DOT or 1DOT. Only past history of fever remained associated with malaria in children under 5 years of age under SMC with 3DOT or 1DOT.

This study is the first of its kind to investigate factors that could explain the persistence of malaria in children under SMC with 3DOT or 1DOT. Our study findings show that the effectiveness of SMC is intimately depend on the conditions of its delivery. Indeed, having been supervised during the taking of the three doses of all four rounds of SMC, having taken all these doses (optimal coverage) and not having vomited/rejected these doses can efficiently protect children under SMC while sleeping under a LLINs with 1DOT does not prevent children under SMC against malaria..

Previous studies have identified the absence of a LLINs and a previous infection in the month preceding the survey as determinants of asymptomatic carriage of *Plasmodium falciparum* in the context of seasonal malaria chemoprevention. [24]. Our study was unable to collect data on past infection. Nevertheless, adjusting in our study for variables specific to 3DOT and 1DOT SMC such as optimal supervision, optimal coverage, and total vomiting/rejection would have eliminated

a possible confound in the association between the absence of LLINs in this study. This would also be the case in the disappearance of the association between not sleeping under LLINs, age, and distance between home and health facility that was shown in our baseline study. [21].

Lack of optimal supervision was associated with malaria in our study. This could be explained by the fact that supervision would ensure that SMC doses are actually correctly taken which is a necessary condition for its effectiveness. This association supports the conclusion of our previous study (article in press), which showed the superiority of 3DOT over 1DOT.

Further studies on the effectiveness of 3DOT could help to inform decisions about scaling up this delivery method. Studies have recommended the effectiveness of SMC in combination with other prevention methods [25, 26]. In a context of limited resources and where the spectrum of child health needs is also affected by the epidemiological transition, it would be more efficient to adopt and provide resources for a method of delivering SMC that gives it optimal efficacy and to save resources that would have been allocated to other malaria prevention interventions for other diseases.

Failure to achieve optimal SMC coverage or have vomited/rejected the medication were linked to malaria in children under 5 years of age receiving SMC in our study. This makes sense since by definition SMC is intermittent administration of full treatment courses of an antimalarial medicine the goal being to maintain therapeutic antimalarial drug concentrations in the blood throughout the period of greatest malarial risk [1]. In addition, in the national guidelines for giving Sulfadoxine-pyrimethamine plus Amodiaquine the caregiver is asked to wait 30 minutes to make sure that the child does not vomit or spit out the medicine in which case the CHW or that person must give again a dose of the rejected medicine if the rejection occurs within 30 minutes. Vomiting or rejection are unfortu-

nately and negatively associated with caregiver adherence to SMC administration; and it has been reported that over half of the children experiencing a vomiting or rejection episode don't receive a replacement dose from SMC distributor [27].

Therefore, not being fully covered by this treatment could not guarantee protection against malaria. In a study conducted in Burkina Faso in 2017 of the fidelity of implementation of SMC, only 32% of children had optimal coverage [28], the reduction in the annual incidence of malaria was only 9.25% in this region compared to the previous year [29, 30]. Other studies have shown a lack of adherence to the second and third doses of amodiaquine by mothers or guardians of children under 5 years old which could be explained by several reasons including the perceived side effects of the medication [26, 31]. In this context, 3DOT seems to be the best alternative to guarantee the necessary adherence the effectiveness of such an expensive but nevertheless effective intervention, the risk of rejection or vomiting has been shown to be lower in children receiving SMC under DOT [27] and 3DOT being a possible option according to the World health organization (WHO) [32].

Residing in the health district of Gaoua (3DOT) was associated with malaria in children under SMC compared to residing in the health district of Boromo (1DOT). This is logical, given that the annual rainfall is higher in Gaoua than in Boromo which makes the annual incidence of malaria in Gaoua significantly higher than that of Boromo (1DOT), 204.6% versus 79,0% in 2020 [21, 33] as malaria transmission is indeed highly dependent on rainfall [34, 35]. This supports the conclusion that 3DOT is superior to 1DOT since it may have resulted in a greater reduction in an area with a very high risk of malaria.

The role of SP/AQ resistance mutations molecular markers in malaria incidence cannot be excluded. Previous studies have identified mutations associated with clinical resistance to sulfadoxine-pyrimethamine. In children who developed malaria during their study, the frequency of pfmdr1 86Y and 184Y mutations in *Plasmodium falciparum*, associated with AQ resistance, was higher than in other children [36-39]; and Implementation of SMC over 2 to 3 years was associated with an increased frequency of the Pfmdr1 N86Y mutation [17]. Studies conducted before and since the beginning of SCM have not revealed differences in resistance mutations in Mali and in other parts in africa. After one year of intermittent preventive treatment of malaria, the prevalence of quadruple mutants associated with in vivo resistance to sulfadoxine-pyrimethamine (dhfr + dhps-437G triple mutants) was similar between the control and intervention groups [14, 40, 41]. These studies, including a literature review, concluded that malaria chemoprevention interventions did not inevitably lead to a significant increase in resistance, and that the efficacy of chemoprevention was not compromised even at high rates of resistance. However, while continuing the research to find out what are factors that could explain the persistence of clinical malaria in children under SMC and the propositions to prevent these factors, research on the mutation/resistance genes must remain the guardian of the effectiveness of this strategy.

Fever or past history of fever was significantly associated with malaria in children under SMC in our study. Fever, a symptom of malaria, occurs when infected red blood cells rupture and release parasites; this usually manifests as chills, followed by fever [42]. This symptom known as major indicator of clinical malaria [43-46] was permanent in children under SMC. This association supports the public health actions carried out by the CHW during the SMC campaign, in particular that of carrying out the rapid screening test on all children presenting Fever or past history of fever.

5. Limitations and Strengths

Our study had some limitations. First, fever history was based only on caregiver/parent reporting; this could potentially introduce a classification bias, particularly among children with little or no fever, even though this bias was non-differential between districts. However, this non-differential classification bias may have resulted in a loss of power that could have led to a decrease in the strength of the ORs towards 1. Second, malaria cases data collection also relied on medication prescriptions or child health records and could therefore be biased as this could underestimate the prevalence of the disease, particularly for children who did not attend any health center and then, did not undergo a rapid diagnostic test. This could have led to a differential classification bias that is also non-differential because it concerns both arms of the study. Thirdly, we were unable to collect the nutritional status of children which is known to be a factor associated with malaria. The food program implemented in these regions of the country by the Ministry of Health and its partners, namely the integrated community management of acute malnutrition, the use of the advanced strategy, the prevention and treatment of acutely malnourished children and mobile clinics, was the main reason why we did not collect this information. Moreover, it was not possible to adjust on the socio-economic status of the child's parent/guardian which is a variable identified as a factor associated with malaria. In fact, this variable was collected through the "Tutor's occupation" variable. However, 98.4% of the children's guardians in the selected villages had replied that they were farmers, making adjustment on this variable impossible. All these biases may have underestimated the existence of malaria, and could have led to an underestimation of the ORs of association. Nevertheless, the results of our study could be generalized to a large part of the country and even to other countries implementing SMC as these areas are predominantly rural.

The strength of this study lies in its size and design. Being the first of its kind, this study, with its large size, provided sufficient power to identify factors specific to 3DOT and 1DOT delivery methods associated with malaria under SMC, in a quasi-experimental cluster randomized trial.

6. Conclusion

The factors associated with malaria in children under SMC identified in this study support the conclusion of our previous report on the superiority of 3DOT compared to 1DOT to reduce the prevalence of malaria. This study is the first of its kind to investigate factors associated with malaria in children under SMC in 3DOT and 1DOT delivery methods. Our results support the most recent recommendations of the WHO second edition of the 2023 Seasonal malaria chemoprevention guidelines) suggesting the 3DOT as an option for an efficient deployment of the SMC in seasonal malaria transmission settings. Addressing the factors identified in our study would make the strategy more relevant for the elimination of malaria by 2030.

Abbreviations

CHSP	Center of Health and Social Promotion
OR	Odds Ratio
1DOT	One Directly Observed Therapy
3DOT	Three Directly Observed Therapy
CHWs	Community Health Workers
CI	Confidence Interval
iCCM	Integrated Community Case Management in the Child
LLINs	Long-lasting Insecticide-treated Nets
RDT	Rapid Diagnostic Tests
SMC	Seasonal Malaria Chemoprevention
SP-AQ	Sulfadoxine-pyrimethamine Plus Amodiaquine
WHO	World Health Organization

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Author Contributions

Yanogo Pauline Kiswendsida: Conceptualization, Formal Analysis, Methodology, Supervision, Writing – review & editing

Sanou Estelle Nadine: Data curation, Formal Analysis, Investigation, Writing – original draft

Yanogo Chantal: Data curation, Formal Analysis, Investigation, Writing – original draft

Ouédraogo Smaïa: Validation, Writing – review & editing

Meda Nicolas: Validation, Writing – review & editing

Halidou Tinto: Conceptualization, Methodology, Validation, Writing – review & editing

Data Availability Statement

The data is available from the corresponding author upon reasonable request.

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Conflicts of Interest

The authors declare no conflicts of interest.

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