






Research Article

# Superiority of Three Directly Observed Treatment Compared to One Directly Observed Treatment in the Seasonal Malaria Chemoprevention in Children Aged Under Five in Burkina Faso: A Quasi-Experimental Trial

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## Abstract

The implementation of seasonal malaria chemoprevention (SMC) in Burkina Faso has not achieved its objective of reducing by at least 60% the morbidity associated with malaria in children under 5 years of age. We assessed a new approach of delivery consisting for the community health workers to directly supervise the three doses of the treatment compared to the standard of delivery (only the first dose directly observed treatment). The objective of the study was to compare the superiority of three doses supervised intake of SMC (3DOT) to the supervised intake of the first dose only. Three centers for health and social promotion were randomly selected in the Gaoua health district (3DOT) and 4 in the Boromo health district (1DOT) to receive a monthly four rounds of SMC with Sulfadoxine-pyrimethamine plus Amodiaquine (SP+AQ) in a quasi-experimental cluster randomized trial, before-after with a control group design which included in total 2440 children. The primary endpoint was the reduction in prevalence between each SMC round. The Khi-2 test was used to assess the superiority of 3DOT versus 1DOT. The reduction of malaria prevalence was significantly higher in 3DOT compared to the 1DOT, 68.60% vs 53.00% ( $p < .0001$ ). The coverage in the 3DOT was significantly lower than that in the 1DOT, 81.39% versus 95.72%;  $p < 0.0001$  for optimal coverage. The 3DOT delivery approach of SMC provides better reduction of malaria prevalence than the 1DOT. However, the lower coverage obtained with the 3DOT compared to the 1DOT is a concerning issue to overcome in the perspective of the scale-up of this strategy at large scale.

## Keywords

SMC, Method of Delivery, 3DOT, Burkina Faso

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## 1. Introduction

The implementation of Seasonal Malaria Chemoprevention (SMC) in Burkina Faso has not achieved its objective of reducing by at least 60% the morbidity of malaria in children under 5 years of age, (data from the National malaria control program). While the question of the effectiveness of the SMC does not arise much, that of the effectiveness of the strategy currently used in routine for its deployment in the country deserves several answers. SMC is defined as “intermittent administration of full treatment courses of an antimalarial medicine during the malaria high transmission season to prevent malaria with the objective of maintaining therapeutic antimalarial drug concentrations in the blood throughout the period of greatest malarial risk” [1].

Although a meta-analysis of clinical trial data showed 82% of decrease in clinical malaria cases with SMC compared to placebo and there is some evidence of its overall benefit in routine implementation [2], SMC is not barrier-free, and the impact of SMC on malaria morbidity in Burkina Faso remains far below the results of randomized trials [3, 4] having led to its recommendation by the World Health Organization (WHO) in 2013 [1].

Campaign reports in districts where SMC has been implemented in 2015 in the country showed a reduction of malaria incidence in the best cases at 49%, the lowest reduction being 9%, i.e. 25% average reduction (analysis made from morbidity data aggregated in district health information software, DHIS2). The administrative SMC coverage was almost 100% in all health districts. However, a study evaluating the fidelity of the implementation of the SMC in the district of Kaya, in the north center of Burkina Faso revealed that only 32.3% of children had received at least the first dose of each of the 4 rounds of SMC, 43.3% of children had received at least the first dose of each of 3 rounds of SMC. Although almost all of the parents claimed to have administered the other two doses of SMC, but this was not assessed because the SMC treatment cards were not checked and as only 44.7% of the SMC cards were available [5].

In the current method of delivery, community health workers (CHWs) are trained to administer the first dose in directly observed treatment (1DOT). The other two doses are given to the parents/guardians of children who are responsible for administering them to the child on the following two days. 1) If it appears that only 32.3% of children had received the first dose of 4 rounds (i.e. 32.3% overall 1DOT coverage), therefore, CHWs do not meet the SMC target. 2) The effectiveness of the administration of the other two doses of sulfadoxine-pyrimethamine and amodiaquine (SP-AQ) is not guaranteed and there is no way to verify it. As the SMC cards were not checked, the parents' statements alone do not allow an objective decision on the other two administrations. Getting a healthy child to take medication is not easy for parents; the drug is then forgotten or taken at the wrong time, not to mention voluntary abandonment due to side effects. Both of

these factors could limit the effectiveness of SMC. It is obvious that only good adherence to treatment could guarantee the expected effectiveness of SMC.

Compliance with this 3-day preventive treatment has not been fully documented and this may be difficult in real-life conditions though clinical trial data suggested high levels of adherence in populations over the 3 days required by SMC [6]. To date, there is little objective and quantitative data that assessing adherence to the SMC treatment, such as plasma drug concentrations in areas where SMC is routinely implemented. Poor compliance immediately results in a decrease of the protective efficacy of SMC and could also contribute to accelerate the spread of resistance mutations to SP and AQ. Therefore, it is essential to ensure a good adherence to the 3-day treatment in order to guarantee its long-term efficacy.

Studies in Burkina Faso have shown the effectiveness of SMC with a greater reduction of the incidence of uncomplicated and severe malaria cases prior to its large scale deployment in routine [3, 7]. Nevertheless, an intervention may have shown high efficacy in randomized controlled trials but the effectiveness of the same intervention following its implementation in real-life setting in the general population may be problematic due to operational reasons.

If SMC intervention in routine deployment achieved the efficacy demonstrated in randomized controlled trials, thanks to a good delivery strategy, it would allow the country to take the path to accelerate the agenda of malaria elimination which is the goal of the Global Technical Strategy for Malaria 2016-2030.

While the current strategy for administering SMC is intended to be more economical, failure to achieve maximum efficiency results in an unprecedented cost. Since SMC was recommended, research on innovative strategies for its delivery has continued, but the benefit of a directly observed treatment of the 3 doses of SMC (3DOT) compared to a directly observed treatment of only one of the 3 doses (1DOT) as it is done routinely has not yet been documented.

In such a context, we formulated the hypothesis that a change in the method of the SMC delivery in which the administration of the 3 doses of the treatment is fully supervised (3 directly observed treatment, 3DOT) would contribute to significantly improve its efficacy in Burkina Faso compared to the current routine strategy of delivery in which only the intake of the first dose of SMC (1DOT) is observed.

The objective of the study was to assess the superiority of a new approach of delivery consisting for the community health workers (CHWs) to directly supervise the three doses of the SMC treatment (3DOT) compared to the standard of delivery in which only the first dose directly observed treatment (1DOT) when the remaining two doses are given to the parents / guardians of children who are responsible for administering them to the child on the following two days.

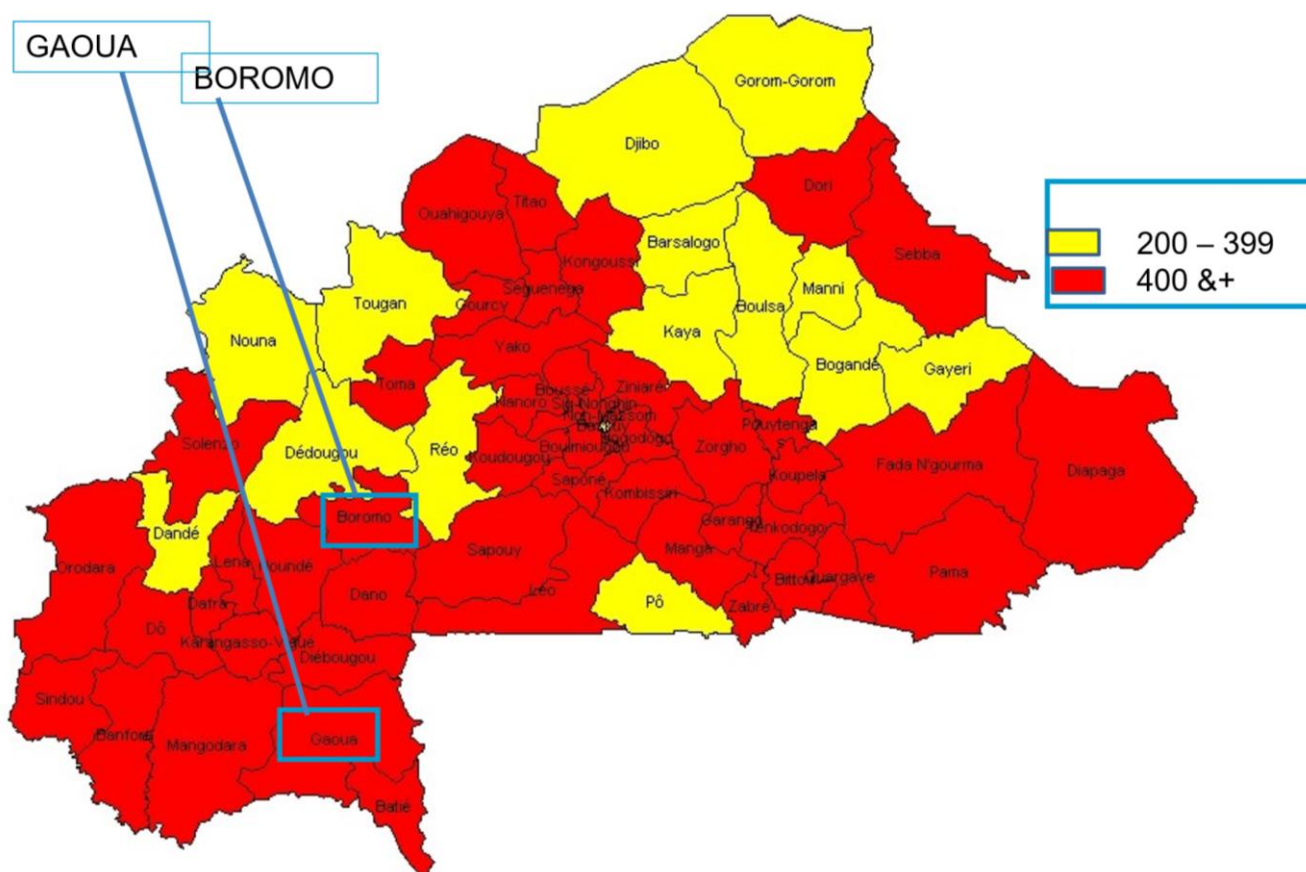
## 2. Materials and Methods

### 2.1. Study Area: Districts of Gaoua and Boromo (Figure 1)

Boromo covers an area of 4 539 km<sup>2</sup> and is located in the Boucle-du-Mouhoun region of Burkina Faso. Its population was estimated in 2020 at 313 839 inhabitants; 64.4% were rural and 18.78% were children under 5 years. The annual rainfall in the district was about 935 mm, with a hyper-endemic malaria transmission representing 39.92% of the total consultations in 2020. About 42.18% of malaria cases and 70.58% of malaria deaths in the district were recorded in children under five [8]. There were 38 centers of health and social promotion (CHSP), 1 medical center and a medical center with surgical unit in the district in 2020, with 53,472 target children for SMC [8]. SMC distribution uses the

1DOT delivery method.

Gaoua covers an area of 5 098 km<sup>2</sup> and is located in the southwest region. Its population was estimated at 275,274 inhabitants in 2020 and 17.2% represented children below five years of age. The district had one medical center, 31 centers for health and social promotion (CHSP), and the regional hospital [8]. In 2020, the south-west region recorded 4 949 health attendance for malaria of which 935 visits were from the district of Gaoua. Children under 5 represented 42.18% of malaria cases and 70.58% of death due to malaria. The type of climate is south soudanian and the region receives the highest rainfalls with an annual mean rainfall of 1205 mm. The district of Gaoua started to implement the SMC on February 12th 2015. The 1DOT method was the strategy of SMC delivery until 2020 when the 3 directly observed treatment (3DOT) method of delivery was introduced in a few districts including the district of Gaoua.



Data source: National Malaria Control Programme malaria surveillance, 2019

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

These 2 districts were selected because they have the same climate and malaria epidemiological pattern characterized by a incidence rate. Between the district of Gaoua and Boromo there is the district of Dano (next to Boromo) and Diébougou (next to Gaoua) where the 1DOT and the 3DOT were respec-

tively implemented. in 2020. The latter served as a buffer zone, facilitating concealment. Among the districts using the the strategy of 3DOT, Gaoua district was the only one surrounded by districts implementing the 3DOT. It was then the typical example of a district for the comparison with a dis-

strict implementing the 1DOT. Indeed, Gaoua is surrounded by the districts of Bati é Magodara and Di ðougou which all implemented SMC with a supervised administration of the 3 doses in 2020 when Boromo district is surrounded by districts using the 1DOT delivery method.

## 2.2. Type of Study

This is a quasi-experimental cluster trial, before-after with a control group design to test the superiority of the method of a supervised delivery of the three doses of SMC (3DOT) compared to the 1DOT.

Children were followed-up by the local health workers from the 3<sup>rd</sup> dose of each SMC round until the next round., from July to November. The parents/guardian were encouraged to take their children to the health facility whenever the child had a fever or history of fever. The health worker recorded the data of the reason of the health facility attendance in the register, whether it was for malaria or another pathology.

## 2.3. Study Phases

The study had two major phases: an initial assessment phase (non-intervention phase) and an intervention phase. The first phase assessed the baseline malaria situation outside the SMC period in both groups of children [9]. In the second phase, the effectiveness of SMC was assessed and compared between the two methods of delivery (3DOT versus 1DOT).

## 2.4. Eligibility Criteria

### *Inclusion Criteria*

A child was eligible to receive SMC drugs if he meets the following conditions:

- 1) Does not suffer from confirmed malaria (on the day of the visit)
- 2) Aged 3 to 59 months
- 3) Residing in the 2 selected districts
- 4) Whose parents / guardians' consent to participate in the study

### *Criteria of non-inclusion*

A child was not eligible to receive SMC if:

- 1) A child presenting a severe acute illness or unable to take oral medication
- 2) An HIV-positive child receiving co-trimoxazole
- 3) A child who has received a dose of either AQ or SP drug during the past month
- 4) A child who was allergic to either drug (AQ or SP)

## 2.5. Description of the Intervention

### *Treatment under Study*

Seasonal malaria chemoprevention is defined as “intermittent administration of full treatment courses of an anti-malarial medicine during the malaria high transmission sea-

son 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 deployment of this intervention began in 2014 in Burkina Faso with a gradual scale-up. In our study, the SMC strategy was administered a maximum of four cycles (July-November) of complete treatment of sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ) at monthly intervals to children aged from 3 to 59 months living in the health districts of Boromo and Gaoua in Burkina Faso, the full treatment lasting 3 days. The treatment for SMC was a combination of the antimalarial drug, sulfadoxine-pyrimethamine and amodiaquine. The form used for the study was the dispersible drug of SP (500/25 mg) and AQ (153 mg). The distribution was done door-to-door.

### *The two Methods of Delivery Compared*

The 3DOT method of delivery: (the intervention): it consisted, in each round of SMC, of a supervised intake by the CHWs of the three doses of SP-AQ. At the same time each morning, the CHW went door to door to supervise the child's administration of the remaining doses. The CHW was also asked to deliver malaria prevention messages to the child's guardian the first day.

The 1DOT method of delivery (the control): This was the method currently used routinely in Burkina Faso for which, only the first dose of SP-AQ was supervised by the CHW when the remaining two doses being given by the parent / guardian of the child without any supervision. In addition to malaria prevention messages, the CHW gives guidance to the parent/guardian for the administration of the two remaining doses on the following two days.

In both methods of delivery, CHWs are supervised by the head nurse and his team, but also by the health district, regional and central level supervisors in the routine implementation, and by investigators of this study.

*Definitions (from SMC implementation documents of Burkina national malaria control program)*

- 1) SMC campaign: corresponds to a season of high malaria transmission consisting of 4 monthly cycles of SMC, July to August, August to September, September to October and October to November.
- 2) SMC round: 1-month interval between two passages of SMC treatment.
- 3) Passage: this is the 3-days period during which the drugs (SP + AQ) are administered to eligible children. The passage constitutes the first 3 days of the round.

*Treatment administration: guidelines for giving dispersible SP + AQ via DOT*

- 1) If the child was eligible, choose the right dose of dispersible SP + AQ based on the child's age: children of 3-11 months of age received a half tablet of 153 mg AQ once daily for three days and a single dose of half a 500/25 mg tablet of SP on the first day; and children of 12-59 months old, one whole tablet of 153 mg AQ once a day for three days and a single dose of one whole tablet of 500/25 mg of SP on the first day.



- 2) Place 1 dispersible tablet of SP and 1 dispersible tablet of AQ in a clean cup
- 3) Explain to the caregiver that the tablets are already sweet and taste like orange.
- 4) Make sure the child drinks all of the medicine by rinsing the cup or spoon with a little water and then having him swallow again.
- 5) Ask the caregiver to wait 30 minutes to make sure that the child does not vomit or spit out the medicine in which case (If the child vomits all the medicines during the 30 minutes, the CHW or that person must give again a dose of the rejected medicine).

#### Concealment

Though challenging the blind in this study was important because the rationale behind our main hypothesis was indeed the lack of compliance to the treatment which could explain why the current method of delivery does not allow to achieve the expected results. In order to avoid contamination throughout the study, concealment was ensured by several workarounds:

- 1) The choice of districts: by choosing districts separated by a buffer district so that there was no contamination. In a selected district, all children were subject to the same method of delivery.
- 2) Training: investigators / treatment administrators from the two delivery strategies areas were trained separately and were unaware (the reference ones) of the presence of the other method of delivery.
- 3) Information:
- 4) The child and his legal guardian were informed of the study;
- 5) Treatment administrators were informed of the study;
- 6) The child and his / her legal guardian should not have been aware of the existence of one or the other method of delivery;
- 7) Treatment administrators, CHWs should not have been aware of the existence of one or the other method of delivery.

## 2.6. Criteria for Judgment

#### Primary Endpoint:

The reduction of malaria prevalence between each SMC round (month) and the baseline level

#### Secondary Endpoints:

The coverage rate of SMC, calculated for each round as the proportion of children who received all the 3 doses of treatment in the passage;

The optimal coverage rate of SMC, calculated globally for the SMC campaign (4 months) as the proportion of children having received the 3 doses of treatment in each of the four SMC round.

## 2.7. Sampling

This was a quasi-experimental cluster trial, before-after with a control group design comparing two methods of delivery in which the unit of randomization was the centers for health and social promotion (CHSP). The number of clusters and person-months required in each group was estimated by Hayes Randomized Controlled Trials Size Calculation Method [10]. The number of clusters estimated on the basis of the incidence rate (to have an optimal size), was used to estimate the number of subjects needed for the estimate of the other study parameters.

Taking into account data from the DHIS2 2015, the estimated overall incidence rate for all 15 CHSP having implemented SMC was 24 cases per 100 person-months, corresponding in our hypothesis to the incidence rate in the 1DOT group. Considering the hypotheses of relative reduction of malaria incidence rate as shown in the Table 1 below, a risk alpha equal to 0.05 and a power of 80%, for the optimum case of an equal number of subjects between the two groups, the scenari of the following sample size as shown in the Table 1 below was considered.

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

Finally, the hypothesis 2 was used due to budget constraints. At least 1980 children were included in at least 6 clusters considering an increase of 10% in prevision of the non-responses.

As the CHSP is the smallest health area, it was used as sampling units. As the district of Boromo has 57 426 children and the district of Gaoua has 45 958 children, proportionally 0.56% (3.33 CHSP) of the participants were drawn from Boromo and 0.44% (2.67 CHSP) from Gaoua.

From the above, at 7 health facilities were randomly selected, 4 from the health districts of Boromo (KOKO, Madou, Ourobounon and Yano) and 3 from Gaoua (Dapola, Niampira and Tako), to receive the 3DOT or 1DOT method of delivery. For a chosen CHSP, all children were included in the study.

## 2.8. Informed Consent and Recruitment Procedures

Recruitment was carried out in the catchment area of the centers for health and social promotion selected at the same time as the survey. Investigators, supervisors and town criers received training one week before children enrollment. Community information about the study and the intervention was provided in the health centers selected for the study the two days prior to the enrollment.

During a visit to a household, under the supervision of an investigator, the interviewers, made up of a bônoma of a 6th year medical student plus a community health worker (serving as an interpreter if necessary), presented the study (information notice and consent form). The parents / guardians of the child were given the opportunity to ask questions about the study before giving their consent. If she/he was illiterate, she/he was assisted by an impartial witness. If consenting to participate, the parent and investigator wrote their names, date and sign the consent form. The interviewer could then assign the child an anonymous number and complete the data collection form.

## 2.9. Data Collection

The implementation of SMC in the selected health center took place during the 2020 transmission season (July-November). Data collection took place during this period, each month and at the end of the month. Monitoring was passive, and followed national standards.

During this phase, morbidity and safety data were also collected prospectively during all the four months of the SMC campaign. As part of his usual work, the health center agent took care of the child according to the standard of care. He had to make sure to note all the information of the consultation in the consultation register and the SMC notebook as requested. At the end of each month, the investigators went out and collect the data recorded, which were checked for completeness. This verification also included all other health documents of the

child or the CHW register if there was a need to check the data.

Socio-demographic data was collected on the child and his parents/guardians and health events including malaria during the month following the last dose of SMC. These data included the date of consultation, the reason for consultation, diagnostic tool, the diagnosis, the treatment prescribed if malaria, the duration of the treatment, having received the doses, having been supervised, malaria. These data were sought in the children's health records and in the health center consultation registers and also by interview.

### *Data Analysis*

Data were analyzed with the statistical analysis software Epi-Info and SAS (SAS, Institute, Inc., Cary, North Carolina, USA and R 4.1.0).

### *Descriptive Analysis*

The prevalence of malaria was calculated for each method of delivery and by round, and globally for the 4 rounds of SMC. It was the ratio between the number of children who had malaria between the last dose of the round and the last dose of the following round, i.e. in the month following the last dose of treatment of a round, and the number of children aged 3 to 59 months in the district. The coverage and the supervision rate were also estimated for each method of delivery and by round and globally for the 4 rounds of SMC. These prevalence, coverage and supervision rates were estimated with 95% confidence intervals (CI) and compared by an Khi2-test using surveyfreq commands in SAS, to take into account the cluster effect. The significance threshold was 5%.

### *Etiological Analysis*

The identification of the most effective method of delivery was done by comparing the effect of the SMC in the 2 methods of delivery. The SMC is expected to have an effect on the frequency of malaria. The 3DOT was also expected to be more effective than 1DOT. Since the 2 districts had different baseline prevalences due to several parameters, the evaluation of the superiority of 3DOT was a comparison between the two methods of delivery (3DOT and 1DOT), of the reduction in prevalence of the SMC round and the baseline level using a Khi-2 test.

### *Ethical Considerations*

The study protocol was approved by the national ethic committee of the Ministry of health and public hygiene of Burkina Faso (reference No 2016-9-103) prior to the study start. This approval was shared with the regional directors of the south-west and the Mouhoun buckle and then transmitted through the health pyramid to the doctors in charge of the health districts of Boromo and Gaoua, the nurses in charge of the selected centers, the community-based health workers, as well as the local authorities. informed consent was obtained from the children's representatives.

### 3. Results

#### 3.1. Main Characteristics of Study Participants

The characteristics of the study participants are summa-

rized in Table 2. 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.** Socio-demographic and clinical characteristics of study participants.

Variables	1DOT		3DOT		P
	(n)	(%)	(n)	(%)	
Age					0.0004
[3 months -1 year]	307	23.35	140	16.51	
[1 years- 2 years ]	200	15.21	127	14.98	
[2 years - 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	
Past history of fever					0.0005
Yes	50	3.30	59	6.39	
No	1466	96.70	865	93.61	
Children below 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	
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	
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 tutors					0.9354
Not schooled	1019	91.14	731	91.03	
Schooled	99	8.86	72	8.97	
Gender of tutors					
Male	151	10.31	95	10.60	

Variables	1DOT		3DOT		P
	(n)	(%)	(n)	(%)	
Female	1313	89.69	801	89.40	<.0001
Marital status					
Single	48	3.23	97	10.60	
In a couple	1437	96.77	818	89.40	<0.0001
Age of tutors					
<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. Comparison of the Proportions of Supervised Children in 3DOT and 1DOT

The proportions of children who received supervision in

taking the three daily doses of each SMC round were statistically higher in the 3DOT than in the 1DOT. This was also the case for optimal supervision, i.e., the proportion of children who received supervision in taking all doses of all four SMC rounds (50.11 vs. 20.79,  $p = <0.0001$ ). (Table 3)

**Table 3.** Proportions of children supervised in 3DOT and 1DOT.

Supervision per round	1DOT		3DOT		P
	n/N	% (95%CI)	n/N	% (95%CI)	
Round 1	320/1450	22.07 [19.96 - 24.29]	512/818	62.59 [59.17 - 65.92]	<0.0001
Round 2	321/1459	22.00 [19.90 - 24.22]	532/843	63.11 [59.75 - 66.37]	<0.0001
Round 3	319/1461	21.83 [19.74 - 24.04]	521/830	62.77 [59.38 - 66.07]	<0.0001
Round 4	327/1463	22.35 [20.24 - 24.57]	718/851	84.37 [81.75 - 86.75]	<0.0001
Optimal Supervision	307/1477	20.79 [18.74 - 22.95]	438/874	50.11 [47.30 - 94.61]	<0.0001

### 3.3. Seasonal Malaria Chemoprevention Coverage and Rejections/Vomiting in the Study Population

SMC coverage was statistically higher in the 1DOOT arm than in the 3DOT arm, at each of the 4 rounds (96.56 versus 89.66,  $p < 0.0001$ ; 98.58 versus 94.30,  $p < 0.0001$ ; 98.58 versus 92.21,  $p < 0.0001$ ; 99.19 versus 96.34,  $p < 0.0001$ ) as well as

overall for all 4 rounds where optimal coverage was estimated (95.72 versus 81.39,  $p < 0.0001$ ) (Table 4). The study could not demonstrate a statistically significant difference between rejections/vomiting between the 1DOT arm and the 3DOT arm. 3DOT and 1DOT, i.e. 3.69% versus 4.44%,  $p = 0.25$ ; 0.96% versus 0.48%,  $p = 0.18$ ; 1.46% versus 1.59%,  $p = 0.85$ ; 1.19% versus 2.63%,  $p = 0.061$  1st, 2nd, 3rd and 4th pass respectively.



**Table 4.** Seasonal malaria chemoprevention coverage and rejections/vomiting in the study population.

Round	1DOT		3DOT		p
	n/N	% (95%CI)	n/N	% (95%CI)	
Coverage 1	1431 /1482	96.56[95.50 - 97.43]	798/890	89.66 [87.47 - 91.59]	<.0001
Coverage 2	1456/1477	98.58[97.83 - 99.12]	827/877	94.30[92.55 - 95.74]	<0.0001
Coverage 3	1460/1481	98.58[97.84 - 99.12]	805/873	92.21[90.23 - 93.90]	<.0001
Coverage 4	1465/1477	99.19[98.59 - 99.58]	842/874	96.34[94.37 - 97.48]	<0.0001
Optimal coverage	1388/1450	95.72[94.55 - 96.71]	678/833	81.39[78.58 - 83.98]	<0.0001

### 3.4. Comparison of the Reduction in Malaria Prevalence Between Each SMC Cycle and the Baseline Prevalence Between the 3DOT and 1DOT

The reduction in malaria prevalence was significantly higher in the 3DOT than in the 1DOT, i.e. 78.71% vs. 60.06%,

$p<.0001$ ; 75.38% vs. 52.75%,  $p<.0001$ ; 58.41% vs. 54.55%,  $p=0.0025$  and 61.89% vs. 44.63%,  $p=0.0004$ , in the 1<sup>st</sup> (July 15-August 14), the 2<sup>nd</sup> (August 15-September 14), the 3<sup>rd</sup> (September 15-end of October 14), and the 4<sup>th</sup> (October 15-November 14) rounds, respectively. This corresponded to an average reduction of 68.60% in the 3DOT and of 53.00% in the 1DOT,  $p<.0001$  over the 4 cycles.

**Table 5.** Comparison of the variation in malaria prevalence between the 3DOT and 1DOT arms between each SMC cycle and the baseline prevalence.

Round	Baseline prevalence de (%)		Round Prevalence (%)		Reduction in prevalence (%)		p
	1DOT	3DOT	1DOT	3DOT	1DOT	3DOT	
Round 1	7.26	13.2	2.9	2.81	60.06	78.71	<.0001
Round 2	7.26	13.2	3.43	3.25	52.75	75.38	<.0001
Round 3	7.26	13.2	3.3	5.49	54.55	58.41	0.0025
Round 4	7.26	13.2	4.02	5.03	44.63	61.89	0.0004
Rounds 1, 2, 3, 4					53.00	68.60	<.0001

## 4. Discussion

This study showed superiority of supervised administration of the 3 daily doses of SMC treatments (3DOT) compared to the supervised administration of only one of the 3 doses (1DOT). Similarly, the reduction of malaria prevalence at each cycle of SMC was significantly higher in 3DOT than in 1DOT. This corresponds to an average reduction of 68.60% and 53.00% in the 3DOT and 1DOT arms respectively. This is further evidence for the use of the SMC intervention for malaria control as already demonstrated by previous studies [11-13].

The new evidence provided by this study is the superiority of 3DOT compared to 1DOT. This study is the first of its kind to compare the two methods of delivery. Previous studies have evaluated different strategies of SMC delivery in Ghana and Gambia [14, 15], including 3DOT and 1DOT [16] in Mali. However, differently from the present study, the primary endpoint of these studies was the SMC coverage. Ended, Kweku et al. in Ghana searched the options for the delivery of intermittent preventive treatment for malaria to children (IPTc) in a community randomized trial. In the latter the coverage of IPTc that can be achieved by two different delivery systems in Ghana, through community-based or facility-based systems was compared [14]. In the Gambian study, children were

randomly allocated to receive IPT from an reproductive and child health (RCH) trekking teams or from a village health workers (VHWs) [15]. The malian study assessed the optimal mode for delivery of seasonal malaria chemoprevention in a cluster randomized trial with the aim to determine the optimal mode of delivery (fixed-point delivery (FPD) vs door-to-door delivery (DDD); directly observed treatment (DOT) vs. non-directly observed treatment (NDOT)) [16]. If the Gambian and Malian authors have shown that delivery through VHWs achieved a substantially higher coverage level of three courses of SMC than delivery by RCH trekking teams (74% versus 48%, a difference of 27% [95% CI 16%-38%]) [15] or when it was door-to-door than from a fixed point [16], the Ghanaian study showed similar SMC coverage when distributed by CHWs or health facility staff (69% vs 66%;  $p > 0.05$ ) [14]. In Mali, the authors were unable to identify a difference in coverage between the supervised (DOT) and unsupervised (NDOT) administration of SMC (65%, (95% CI 55% - 76%) versus 68% (95% CI 57% - 79%);  $p = 0.72$ ).

The significant reduction of malaria prevalence reported in the four rounds in our study could be explained by several factors including i) a problem of comparability between the 3DOT arm (the intervention) and the 1DOT arm (control). A difference in rainfall could explain this difference in malaria reduction between the two districts. Indeed, the two regions receive one of the highest rainfalls in the country with an annual rainfall of 1205 mm and 935 mm, in Gaoua and Boromo respectively. Considering other risk level indicators, both arms are in the high malaria incidence zone. However the malaria incidence was higher in the 3DOT (204.6 cases per 100 person-years) than in the 1DOT (79 cases per 100 person-years) according to the 2020 statistical yearbook of the Ministry of Health [8].

All these considerations would poorly explain the superiority of 3DOT over 1DOT, since they all favor Boromo (1DOT) over Gaoua (3DOT). Conversely, they may have led to a reduction in superiority of the 3DOT. To make the results comparable between the two arms, the quasi-experimental before-after study with a control group design was used. Thus, in each arm, the baseline indicator of malaria prevalence was calculated, and the variation in this indicator after the intervention was compared between the two arms.

The same is true for the level of insecticide resistance as both sites present similar trends [17, 18], with sometimes a reported decrease in sensitivity, which could constitute a limiting factor in the use of insecticides in vector control. Moreover, data from the National Malaria Control Program shows that all other malaria interventions implemented in the two districts are similar over the study period including the national campaign for the distribution of long-lasting, multi-product insecticide-treated nets (LLINs) with the introduction of new generation nets (IG2, PBO), indoor insecticide spraying, information, education, communication/behavior change communication activities, integrated community case management in the child (iCCM) and

management of uncomplicated malaria in children >5 years (Burkina national malaria strategic plan). Similarly, nutrition interventions were implemented primarily in both the 3DOTs (Gaoua) and 1DOT (Boromo) arms.

To interpret our study findings, the question of the implementation of the intervention must also be addressed. Regarding the intervention implementation indicator, the proportions of children who received supervision while taking the three daily doses of each SMC round were statistically higher in the 3DOT than in the 1DOT. This was also the case for optimal supervision, i.e., the proportion of children who received supervision while taking all doses of all four MC rounds. This suggests that the intervention was implemented in the 3DOT arm. However, it is noted that there were shortcomings in its application, with this indicator being only 62.59%, 63.11%, 62.77%, and 84.37% in the 1st, 2nd, 3rd, and 4th rounds, respectively. This shortcoming in the application of the intervention could explain the coverage in the 3DOT, which is significantly lower than that in the 1DOT. Assuming no shortcomings in the checking of children's SMC booklets by agents, greater rigor in supervision of the implementation of the 3DOT is strongly recommended for optimal impact.

The difference in SMC coverage could explain this difference in effect between the 3DOT and the 1DOT. These coverages were calculated for each round as the proportion of children who received all 3 doses of medications. Therefore, receiving all 3 doses is the condition for a child to be protected from malaria for one month. These coverages which were better in Boromo than in Gaoua ( $p < 0.0001$ ), could therefore not explain very well the superiority of 3DOT over 1DOT. On the contrary, they could be the cause of a reduction in the superiority of 3DOT over 1DOT.

Rejection or vomiting of medications could have explained this difference in coverage, but these rejections/vomiting were not statistically different between 3DOT and 1DOT.

Our results were different from those of Barry in Mali who had not found a difference in coverage in children who received SMC using DOT or NDOT 65%, (95% CI 55% - 76%) versus 68% (95% CI 57% - 79%);  $p = 0.72$ . This led the authors to recommend the continuation of 1DOT in the country. In this study as in our study, the calculation of the coverage of SMC was based on the information collected by interview, and from the SMC notebooks in our study. We believe that the impact indicators (morbidity and mortality) more than the coverage should better respond to the evidence for decision-making, especially if the methods guaranteeing the internal validity of the study are met. Indeed, the estimation of the coverage has always posed difficulties in the interventions in the countries of the region [5, 19] and could not reflect reality; conversely the diagnosis of malaria based on rapid diagnostic tests (RDT) or thick drop is more objective. Thus, in our study, higher coverage in 1DOT does not translate into a higher reduction in malaria prevalence than in 3DOT.

This study demonstrated the superiority of 3DOT over 1DOT in reducing the prevalence of malaria. Under the assumption that the reductions of malaria prevalence were solely due to the interventions, at the national level in 2020, 576,193 cases of malaria in children under five years of age would be avoided with 1DOT. With 3DOT, these are 779,863 additional cases which could have been avoided among children under five years of age in Burkina Faso under the assumption that the superiority of 3DOT is solely due to the intervention. About 42.18% of malaria cases and 70.58% of deaths due to malaria have occurred among children below five years of age [8]. Economic studies could confirm whether the intervention will be relevant from a public health perspective, knowing that a life is priceless.

#### *Limitations and Strengths*

Due to time and financial constraints, and due to the fact that the SMC was implemented throughout the country, it was not possible to collect baseline data during the peak of the malaria transmission season. Baseline data were collected in December, a season of lower incidence in both study arms. While this may have caused measurement bias by reducing the effectiveness of the SMC or even the superiority of 3DOT, this bias is non-differential and its effect on the comparison would be minimized by the study design. The main strength of this study lies in its design, which makes the two arms of the study comparable. Furthermore, the very large sample size could guarantee sufficient power to demonstrate the difference in efficacy between the two groups.

## 5. Conclusion

This study, which was conducted under the conditions of routine implementation of SMC, showed superiority of 3DOT over 1DOT, despite poor implementation of the 3DOT intervention. At the national level, the deployment of this strategy could contribute to reducing the incidence of malaria and enable the country to move towards the elimination of the disease. This will only be possible through effective involvement of agents supervising the administration of drugs in the intervention. Their training and supervision of these supervisors could improve the implementation of 3DOT.

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## Abbreviations

BFELTP	Burkina Field Epidemiology and Laboratory Training Program
CHSP	Center of Health and Social Promotion

1DOT	One Directly Observed Treatment
3DOT	Three Directly Observed Treatment
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

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## 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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