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Effect of seasonal malaria chemoprevention in children between 5 and 9 years old in Kita and Bafoulabe districts, Mali

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ABSTRACT

Background: Seasonal malaria chemoprevention (SMC) has been widely expanded in Mali since its recommendation by the the World Health Organization in 2012. SMC guidelines currently target children between three months and five years of age. The SMC initiative has been largely successful. Children at least five years of age are not currently covered by current SMC guidelines but bear a considerable portion of the malaria burden. For this reason, this study sought to determine the feasibility and effectiveness for extending SMC to children aged 5–9 years.

Methods: A non-randomized, pre-post study was performed with an intervention district (Kita) and a comparison district (Bafoulabe). Children aged 3–59 months received SMC in both comparison districts, and children aged 60–120 months received SMC in the intervention district. SMC was delivered as sulfadoxine-pyriméthamine plus amodiaquine (SP-AQ) at monthly intervals from July to October in 2017 and 2018 during the historical transmission seasons. Baseline and endline cross-sectional surveys were conducted in both comparison districts. A total of 200 household surveys were conducted at each of the four monthly SMC cycles to determine adherence and tolerance to SMC in the intervention district.

Results: In July 2017, 633 children aged 60–120 months old were enrolled at the Kita and Bafoulabe study sites ($n = 310$ and $n = 323$, respectively). Parasitemia prevalence was similar in the intervention and comparison districts prior the SMC campaign (27.7% versus 21.7%, $p = 0.07$). Mild anemia was observed in 14.2% children in Kita and in 10.5% of children in Bafoulabé. At the Kita site, household surveys showed an SMC coverage rate of 89.1% with a response rate of

Abbreviations: AQ, Amodiaquine; CBD, Community based distributors; CHW, Community Health Workers; DHIS2, District Health Information System 2; DHS, Demographic Health Survey; EPI, Expended Program on Immunization; HMIS, Health Management and Information System; IPTi, Intermittent Preventive treatment in Infant; ITN, Insecticide Treat Net; LLIN, Long-lasting Insecticide Treated bed Net; SMC, Seasonal Malaria Chemoprevention; SP, Sulfadoxine-Pyriméthamine; WHO, World Health Organization.

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93.3% among child caregivers. The most common adverse event reported by parents was drowsiness (11.8%). One year following SMC implementation in the older age group in Kita, the coverage of three doses per round was 81.2%. Between the baseline and endline surveys, there was a reduction in parasitemia prevalence of 40% (OR = 0.60, CI: 0.41–0.89). Malaria molecular resistance was low in the intervention district following the intervention. A significant reduction in the prevalence of parasitemia in children 60 to 120 months was observed in the intervention district, but the prevalance of clinical malaria remained relatively constant.
Conclusion: This study shows that the prospect of extending SMC coverage to children between five and nine years old is encouraging. The reduction in the parasitemia could also warrant consideration for adapting SMC policy to account for extended malaria transmission seasons.

1. Introduction

Malaria remains a major global cause of morbidity and mortality, resulting in an estimated 229 million clinical cases and 409,000 deaths in 2019. Malaria occurrence has dispropriotnately impacted Africa, and it is estimated that the continent accounts for 94% of the overall malaria burden (WHO, 2020; WHO, 2019). Regular administration of antimalarial drugs during the transmission season continues to be effective for preventing malaria morbidity and mortality in children to alleviate the malaria burden (WHO, 2015). In 2012, the World Health Organization (WHO) endorsed seasonal malaria chemoprevention (SMC) for malaria prevention in those sub-Saharan African countries with highly seasonal malaria transmission and an absence of sulfadoxine-pyrimethamine (SP) resistance. Mali is among those countries recommended for SMC coverage, where malaria prevalence is 19% in children under 5 years old according its latest Demographic Health Survey (*Cellule de Planification et de Statistique, M.D.L.S., Direction Nationale de la Statistique et de l'Informatique, Ministère de l'Économie dIIedC, Bamako, Mali, Demographic Health Survey*, 2018). Despite substantial gains in addressing malaria prevalence in the young children (under five years of age), few recommendations exist for antimalarial prevention therapies in children at least five years old. Routine surveillance data showed an almost three times higher prevalence of malaria cases in children 5 to 14 years 58.1% versus 19% in children 3–59 months old (DGS-HP, M.O.H, 2018). Analysis of routine data in Kayes region found mortality due to malaria is 3.9% among children 5 to 14 years old, (DGS-HP, M.O.H, 2018). In neighboring Senegal, Ndiaye et al. found a substantial benefit of SMC among children 5–9 years of age for reducing the prevalence of parasitemia and anemia (Ndiaye et al., 2019). Several studies have shown the epidemiological impact of SMC in school-aged children in clinical trials (Ndiaye et al., 2019; Nankabirwa et al., 2014b; Barger et al., 2009). Touré et al. (2016) found that the proportion of children over 5 years of age carrying malaria parasites was higher in all seasons compared to 3–59 months in Sélingué, Mali due to malaria control policies focused on children under five years old and pregnant women (Toure et al., 2016). Elsewhere, in African school-aged children, malaria prevalence and incidence have also increased (Nankabirwa et al., 2014a). Children were found to use long-lasting insecticide-treated bed nets (LLINs) less frequently than other population groups may not have had access to free anti-malarial treatment, and were not protected by routine SMC to control malaria. The focus on children under 5 years of age may also delay the acquisition of natural immunity, causing older children to be increased a risk of acute infection once they have outgrown the age-specific control interventions targeted to children under 5 years old in malaria endemic areas (Pemberton-Ross et al., 2015; Ndiaye et al., 2015). Historically, school-aged children have received inadequate attention for malaria. Additional measures to protect children not currently covered by standard SMC policy is warranted by expanding current treatment and prevention campaigns targeting this age demographic. This study therefore aimed to assess the effect of seasonal malaria chemoprevention for preventing malaria in children aged 60–120 months through a controlled study in two Mali districts.

2. Methods

2.1. Study site

This study was conducted in two neighboring health districts, Kita, the intervention district, and Bafoulabe, the comparison district, with a total population of about 670,000 inhabitants (RGPH, 2009). Together, these two districts have 67 community health centers (CSCom) and two referral health centers (district). The study areas have the same geographic, demographic and epidemiological characteristics, including a Sahelian climate with a single rainy season from July to October. SMC implementation covering children 3–59 months has been implemented in the two districts since 2012 by the National Malaria Control Program.

2.2. Study design

A non-randomized, pre-post design study was conducted among children aged 60–120 months to compare the prevalence of parasitemia, clinical malaria and anemia in both intervention (Kita) and control (Bafoulabe) district. The intervention consisted of administration of SP–AQ to children aged from 60 to 120 months at monthly intervals during the high malaria transmission season from July to October 2017 and 2018 in Kita district (four rounds per year). Children aged up to 120 received 1.5 tablets of SP + 3 × 1.5 tablets of AQ. The comparison group of children in the same age range from the district of Bafoulabe where SMC was not given to these children. During that same period. In both districts, SMC was implemented to children under the age of 5 per national protocols. Two cross-sectional surveys were conducted in July 2017 and December 2018 to collect data on coverage and acceptability, as well as

biomarkers of parasitemia and anemia in the two districts.

Sample size: A Cochrane review of intermittent preventive treatment in children (the precursor to SMC) in 2011 (Wilson, 2011), estimated that chemoprevention could reduce parasitemia by 65%. For this study, we assumed a 50% reduction under programmatic conditions. To detect a 50% difference in parasitemia in older age group between the normal SMC and extended SMC districts at follow-up, with alpha = 0.05, power of 80% and assuming 12.5% and 25% parasitemia in the district at follow-up respectively, 304 children aged 5–10 years would be needed to be surveyed in each district. Assuming one child 5–10 years old per household, survey teams would need to visit 304 households in each of the two health areas at baseline and follow-up each year (total sample size = 608 household at baseline and 608 at endline. Data for 1216 children from 5 to 10 years were assessed).

2.3. Recruitment of participants

The sampling covered eligible children in one health area by district, 304 households were randomly selected according to the census database. At baseline 323 children in Bafoulabé and 310 in Kita were selected for the survey. At endline, a total of 279 children in Bafoulabé district and 372 children in Kita district were selected for the survey. A questionnaire-based household interview survey was used to collect data on children from 5 to 10 years of age including locality, health status, insecticide treated nets use and adverse events.

To estimate parasitemia and anemia prevalence, two cross-sectional surveys were conducted in the districts at baseline (July 2017) and endline (one month after the 4th round of SMC in December 2018).

Written informed consent was obtained from all participants' mothers or guardians prior to inclusion and residing in Kita or Bafoulabe during the period study were inclusion criteria. Each participant known allergic to SP and AQ or having chronic disease were excluded. Each selected child gave a blood sample for hemoglobin measurement using a HemoCue device, and for malaria parasite detection using a blood smear and filter paper for molecular markers of the resistance to SP and AQ.

Drug adverse events were monitored by household visits 4–7 days after each of four rounds during the SMC campaign in the intervention district (Kita). Community based distributors (CBD) checked any reactions to treatment, documented them, and reported to health team manager. Laboratory investigation was conducted in cases of severe skin reactions and signs of liver disease.

2.4. Drug delivery

Community Health Workers (CHWs) and Community based distributors (CBDs) received 3 days of training on SMC administration, screening for fever, and inquiring about any intake of SP or AQ or sulfadoxine containing antibiotics in the preceding month. A therapeutic dose of the standard drug regimen per WHO, AQ (10 mg/kg/day for 3 days) combined with one dose of SP on the first day (25 mg Sulfadoxine and 1.25 mg pyrimethamine per kg) was administered once per month from July to October to all children 3–59 months old in both districts and to children from 5 to 10 years in Kita (1.5 tablets of SP + 3 × 1.5 tablets of AQ); the first dose of SMC was given by CHWs/CBDs by a 'door to door' strategy and the subsequent doses were given by the child's mother or guardian. For data monitoring, the first dose was recorded in registers maintained by the CHWs/CBDs. The administration at home was recorded on SMC cards maintained by the parents.

2.5. Laboratory methods

The stained thick and thin blood films were examined microscopically at a magnification of 1000× to identify the parasite species and to determine the parasite density. Parasite density was assessed by experienced certified microscopists unaware of the intervention and comparison groups, by counting the number of asexual parasites in a set number of white blood cells (typically 200) with a hand tally counter according to established standard operating procedures, assuming 8000 white blood cells (WBC)/μL. The parasite density (trophozoite per μl of blood sample) was calculated by using this formula (Bejon et al., 2006): $\frac{\text{number of parasites counted x 8,000}}{\text{number of leukocytes counted.}}$

Slides were read independently by two laboratory technicians, and, in case of discrepancy, slides were read by a third technician. Slides were labeled with the unique identification number of the child and the date. Slides were dried in the open air in slide boxes and then transferred at the end of day in slide boxes for safe storage.

A HemoCue device (Angelholm, Sweden) was used to measure hemoglobin levels in the field from finger prick samples. The samples were classified according to DeMaeyer framework (DeMaeyer, E.M.P.D.E.A, 1989): Children with hemoglobin level below 8.0 g / dl were classified as severely anemic; between 8.0 and 9.9 g / dL as moderately anemic and between 10.0 and 10.9 g / dl as mildly anemic.

Thick and thin smears were performed for each child participating in the study.

During cross sectional surveys, clinical malaria was defined as axillary temperature $\geq$ 37.5 °C and the presence of asexual malaria parasites in the blood smear. In addition to these criteria, prostration or convulsions or coma were considered as severe malaria and patients were triaged for appropriate management.

2.6. Assessment of molecular markers of resistance to SP and AQ

Molecular analysis to investigate markers of drug resistance was performed on samples from children with whose blood smear showed *P. falciparum* parasitemia $\geq$160/uL (4 parasites/200 WBC). Blood samples on filter paper were analyzed by nested polymerase

chain reaction (PCR) and/or PCR-restriction fragment length polymorphism (RFLP) for mutations at codons 51, 59 and 108 of the dhfr gene, 437 and 540 of the dhps gene, mutations at codon 76 in the *P. falciparum* chloroquine transporter gene (pfcrt), and at codon 86 of the *P. falciparum* multidrug resistance gene one (pfmdr1) according to published methods (Plowe et al., 1995; Djimde et al., 2001). Cases of mixed infection (wild type and mutant) were categorized as mutant. Quintuple mutant was defined as the presence of the three dhfr mutations (N51I, C59R and S108N) and the two dhps mutations (A437G and K540E).

2.7. Ethical considerations

The study protocol was approved by the ethics committees of the Faculty of Medicine and Odonto- stomatology of Bamako and the US Centers for Disease Control and Prevention (CDC) in Atlanta. Written informed consent from parents/ guardians was obtained for all participants by explaining the aims and activities prior to seeking signed consent. The study objectives and data collection procedures were explained in detail to administrative, community and health authorities. Only ID numbers of participants were on the samples and CRFs to ensure anonymity and confidentiality.

2.8. Data management and analysis

Data on each participant were collected by the study team on case report forms (CRF) kept in place in accordance with good clinical practices. These data from household surveys and health facilities were double entered in ACCESS 2010 by two different operators. Data processing and statistical analysis were performed on Stata version 14.0 (https://www.stata.com/stata14/; StataCorp LLC, College Station, Texas, USA).

Bivariate analysis was performed to compare the prevalence of anemia and malaria parasitemia between intervention and control districts one month after the fourth round of SMC. Logistic regression model was used to estimate in intervention district a reduction in the prevalence of parasitemia, anemia and clinical malaria with the level of significance at 5%

3. Results

3.1. Coverage and adherence

The coverage of SMC, defined as 3 days of treatment for all four rounds, according to parent/guardian report was 89.1% and 81.2% in 2017 and 2018, respectively (Fig. 2). (See Fig. 1.)

3.2. Adverse events

The most frequently mentioned being drowsiness (11.8%), followed by vomiting (9.1%), diarrhea (8.8%), abdominal pain (5.1%) and itching in 2.1% (Fig. 3).

3.3. Parasitemia and anemia prevalence

There was no significant difference in the prevalence of parasitemia at baseline in the two districts (27.7% in Kita vs. 21.7% in Bafoulabe; $p = 0.07$) (Table 1).The parasitemia prevalence was 25.1.0% in Bafoulabe district compared to 16.9% in the intervention district (Kita) at endline. A reduction of 40% in parasitemia prevalence was observed in the intervention district (OR = 0.60, 95% CI 0.41–0.89, $p = 0.011$). Clinical malaria was also similar in the two districts, at baseline (4.0% in Bafoulabe vs 5.8% in Kita, $p = 0.29$)

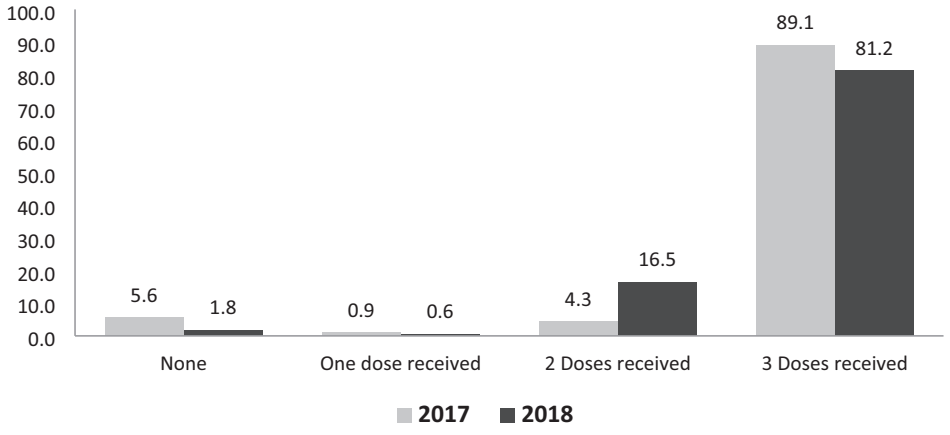

Fig. 2. Coverage of SMC with four monthly rounds of 3 days of treatment according parents/guardian report.

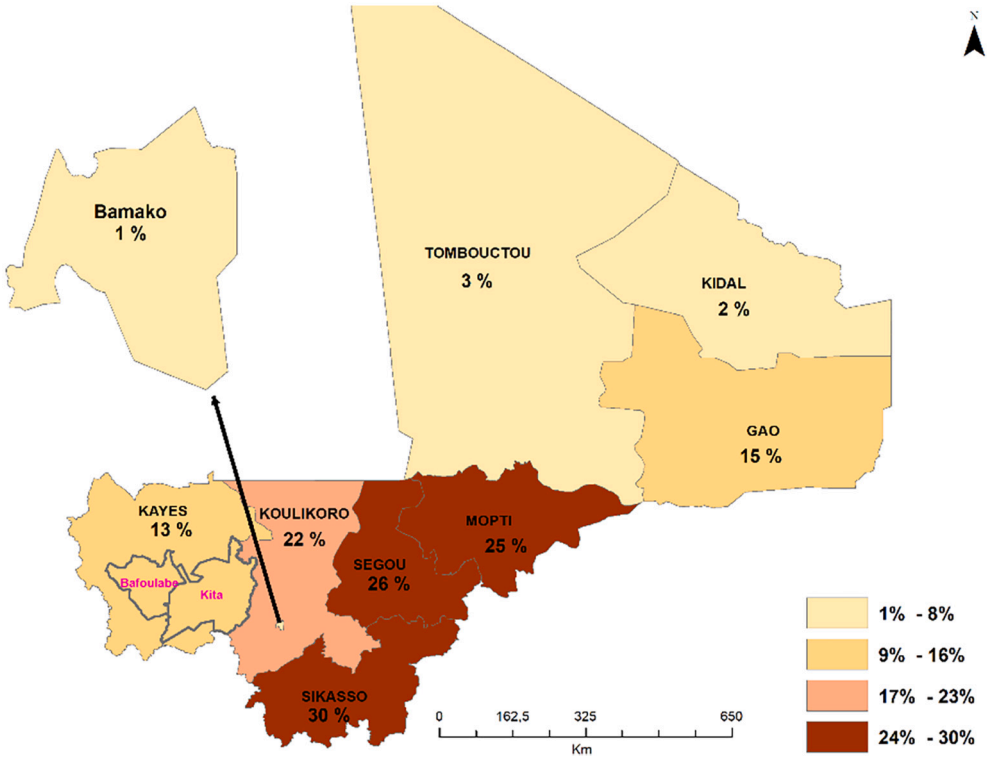

Fig. 1. Malaria prevalence by region among children 6–59 months with a positive malaria rapid diagnostic test

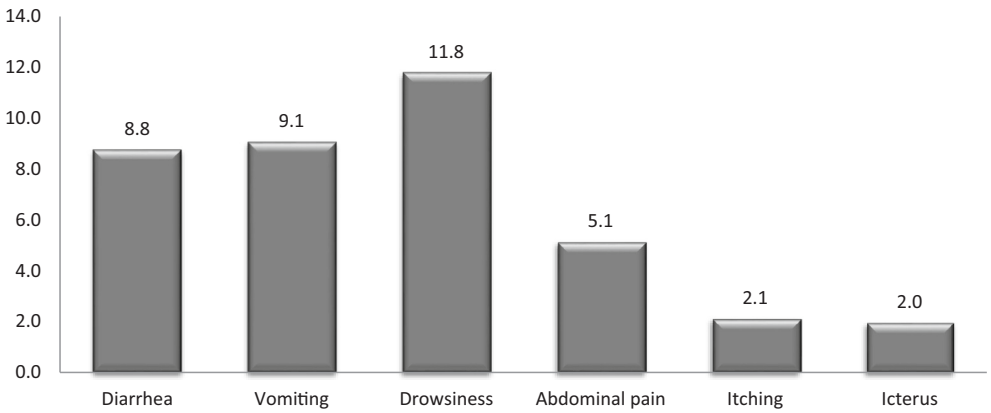

Fig. 3. Average of reported adverse events after four rounds of SMC in children 5 to 10 years at endline in Kita.

and endline (4.0% and 3.6% respectively in Kita and Bafoulabe ($p = 0.77$; Table 1). The prevalence of anemia was similar at baseline (14.2% in Kita vs 10.5% in Bafoulabe, $p = 0.16$) and endline (20.2% in Kita vs 17.2% in Bafoulabe; $p = 0.34$) in the two districts (Table 1). In Bafoulabe district (control), anemia prevalence increased from 10.5% at baseline to 17.2% at endline (OR = 1.76, 95% IC:1.10–2.86) (Table 2). In the intervention district (Kita), parasitemia prevalence decreased from 27.7% at baseline to 16.9% at endline (OR = 0.53, 95% IC 0.36–0.76), while anemia prevalence increased from 14.2% at baseline to 20.2% at endline (OR = 1.52, 95% IC 1.01–2.29 (Table 2).

At endline, parasitemia prevalence fell to 20% in the intervention district compared to control district [difference-in-differences (DD) OR = 0.20; 95% CI 0.07–0.33]. No difference was observed in anemia and clinical malaria prevalence $p = 0.63$ (Table 3).

3.4. Resistance to SMC drugs

The prevalence of quadruple mutants (dhfrtriple+dhps437) and quintuple mutants (dhfr triple +dhps437 + dhps540) remained

Table 1
Parasitemia and anemia prevalence in children 5 to 10 years between the two districts at baseline and endline (after SMC implementation).

Baseline (Jul. 2017)	**Kita (N = 310)**		**Bafoulabé (*N* = 323)**		**OR**	**p**
	n	%	n	%		
Parasitemia	86	27.7	70	21.7	0.72 [0.50–1.03]	0.07
Anemia	44	14.2	34	10.5	1.40 [0.87–2.26]	0.16
Clinical malaria	18	5.8	13	4.0	1.47 [0.70–3.05]	0.29
Endline (Dec. 2018)	**Kita (*N* = 372)**		**Bafoulabé (*N* = 279)**			
Parasitemia	**63**	**16.9**	**70**	**25.1**	**0.60 [0.41–0.89]**	**0.011**
Anemia	75	20.2	48	17.2	1.21 [0.81–1.81]	0.34
Clinical malaria	15	4.0	10	3.6	1.13 [0.50–2.55]	0.77

Table 2
Parasitemia and anemia prevalence in children 5 to 10 years at baseline and endline inside each district (Kita and Bafoulabé).

Bafoulabe	**Parasitemia**		**Anemia**		**Clinical malaria**	
	n	**%**	**n**	**%**	**n**	**%**
Base line (N = 323)	70	21.7	34	10.5	13	4.0
Endline (N = 279)	70	25.1	48	17.2	10	3.6
P	0.32		**0.017**		0.78	
OR, CI95%	OR = 1.21 [0.82–1.76]		**OR = 1.76 [1.10–2.86]**		OR = 1.12 [0.48–2.61]	

Kita	**Parasitemia**		**Anemia**		**Clinical malaria**	
	n	**%**	**n**	**%**	**n**	**%**
Base line (N = 310)	86	27.7	44	14.2	18	5.8
Endline (N = 372)	63	16.9	75	20.2	15	4.0
P	**10^{-4}**		**0.041**		0.28	
OR, CI95%	**OR = 0.53 [0.36–0.76]**		**OR = 1.52 [1.01–2.29]**		OR = 1.46 [0.72–2.96]	

Table 3
SMC effect on parasitemia, clinical malaria and anemia risk in children 60–120 months at endline in Kita compared to Bafoulabe.

Parasitemia	**Coef.**	**Std. Err.**	**t**	**P > t**	**[95% Conf. Interval]**	
Baseline	0	(base)				
Endline	0.127	0.031	4.03	0	0.065	0.189
Negative	0	(base)				
Positive	0.082	0.046	1.78	0.075	−0.008	0.171
Endline#Positive	**−0.205**	**0.067**	**−3.08**	**0.002**	**−0.335**	**−0.074**
_cons	0.470	0.023	20.67	0	0.425	0.514
Anemia						
Baseline	0	(base)				
Endline	**0.083**	**0.030**	**2.75**	**0.006**	**0.024**	**0.143**
No	0	(base)				
Yes	0.085	0.060	1.41	0.159	−0.033	0.203
Endline#Anemia	−0.038	0.078	−0.48	0.631	−0.191	0.116
_cons	0.479	0.021	22.69	0	0.438	0.521
Clinical malaria						
Baseline	0	(base)				
Endline	**0.085**	**0.028**	**3**	**0.003**	**0.029**	**0.141**
No	0	(base)				
Yes	0.096	0.092	1.04	0.297	−0.084	0.275
Endline# Clinical malaria	−0.066	0.137	−0.48	0.63	−0.334	0.203
_cons	0.485	0.020	23.9	0	0.445	0.525

low (<50% and < 5% respectively) at endline in Kita district (Fig. 4).

4. Discussion

This study in Malian school-aged children shows the potential of SMC to reduce parasitemia prevalence but no apparent effect on anemia and clinical malaria similar to the Thera et al. study of SMC using artesunate-amodiaquine in school-aged children in Mali (Thera et al., 2018). The prevalence of parasitemia was similar in intervention and control districts at baseline (Table 1). A reduction of 40% in the prevalence of parasitemia (OR = 0.60 95% CI [0.41–0.89]) was found in the intervention district compared to control district one month after the last round of SMC campaign in children 60–120 months. In 2017, following the initiation of SMC in the same two districts, Diawara et al. found a reduction of 65% in the prevalence of malaria infection in the intervention district (Kita) compared to Bafoulabe district in children aged 3–59 months (Diawara et al., 2017). Similar findings were observed by other authors in the children under 5 years age group (Nankabirwa et al., 2014a; Kweku et al., 2008). Same observations regarding the introduction of chemoprevention in the older age group were reported by Ndiaye and colleagues; Barger et al. (Ndiaye et al., 2019; Barger et al., 2009). Maiga et al. in 2020 observed a significant reduction of malaria infection, clinical malaria and anemia in children aged 3–59 months two years after SMC scale-up in Koutiala district in Mali (Maiga et al., 2020). Similar findings were obtained by Ambe et al. in Borno state, Nigeria in 2020 (Ambe et al., 2020). There was no significant difference in the prevalence of anemia at baseline in the two districts among children 60–120 months and this remained the case at endline after SMC implementation). Bojang, et al.; Diawara et al. and others reported a difference in anemia prevalence at the end of transmission season in children under 5 years (Ndiaye et al., 2019; Diawara et al., 2017; Kweku et al., 2008; Bojang et al., 2011). In this study, SMC did not appear to have a significant impact on anemia in both Bafoulabe and Kita as prevalence increased from baseline to endline in both districts (Table 3). Anemia was assessed at different time points during the malaria transmission period, which explains the high anemia rate at the end of the study. In sub-Saharan Africa, the same cohorts of school-aged children are also frequently infected by soil-transmitted helminth infections and parasitic diseases which are also risk factors for anemia (Oliveira et al., 2015).

During SMC implementation (Fig. 3), reported adverse events were drowsiness, vomiting and diarrhea. In previous studies Dicko et al. in 2011 in Mali (Dicko et al., 2011); Bojang et al. in 2010 in Gambia (Bojang et al., 2010), and Ndiaye, J. et al. (Ndiaye et al., 2018), found a frequency of adverse events similar in those reported in our study for vomiting and a slightly higher incidence of diarrhea, among children under 5. School age children are able to articulate reactions to SMC medications and are better able to promptly report any reaction. These adverse events were resolved spontaneously without any other medication. In Senegal, Ndiaye et al. (Ndiaye et al., 2018) found vomiting as the most frequently reported adverse event in children 5 to 9 years of age who have received SMC treatment and attributed this reaction to amodiaquine.

Coverage of SMC among eligible children was higher in 2017 and 2018 for the full 3 doses, according to caregiver interviews and SMC cards (Fig. 2). The main reason reported for missing SMC rounds was travel. The lack of information about SMC rounds was the most common reason reported by parents for missing SMC rounds.

Our study showed no increase in the frequency of molecular markers of SP and AQ resistance in SMC areas where SP/AQ was used (Fig. 4). The frequency of quadruple mutants and quintuple mutants was still low (<50% and < 5% respectively) after the fourth year of SMC implementation in Mali and others neighboring countries. Based on these results, it appears the preventive effects of SP remain steady after multiple years of wide-spread SP use. This finding has also been established by other authors. (Grais et al., 2018; WHO, 2010; Dicko et al., 2010; Lo et al., 2013).

4.1. Limits

In the national HMIS system, age groups did not correspond to those of our study (< 5 years and ≥ 5 years vs 3–59 months and 60–120 months) which limited the use of this database for comparison. In addition, we lacked data on other causes of anemia (such as other parasitic infections) to explain the high prevalence in the areas. The prevalence of clinical malaria is similar in both districts due to assessment period, after transmission season.

5. Conclusion

This study shows high coverage and adherence to SMC and a significant reduction in the prevalence of malaria parasitemia among children 60–120 month in the intervention district. The drugs were well tolerated and the prevalence of molecular markers associated with resistance to SP and AQ was still low.

Ethics approval and consent to participate

Ethical clearance for this study was provided by the Ethics Committee of the Faculty of Medicine, Pharmacy, and Odontostomatology, University of Bamako (Study number 2017/67/CE/FMPOS). Written informed consent was obtained from parents or guardians of participants between 5 and 9 years of age.

Consent for publication

Yes

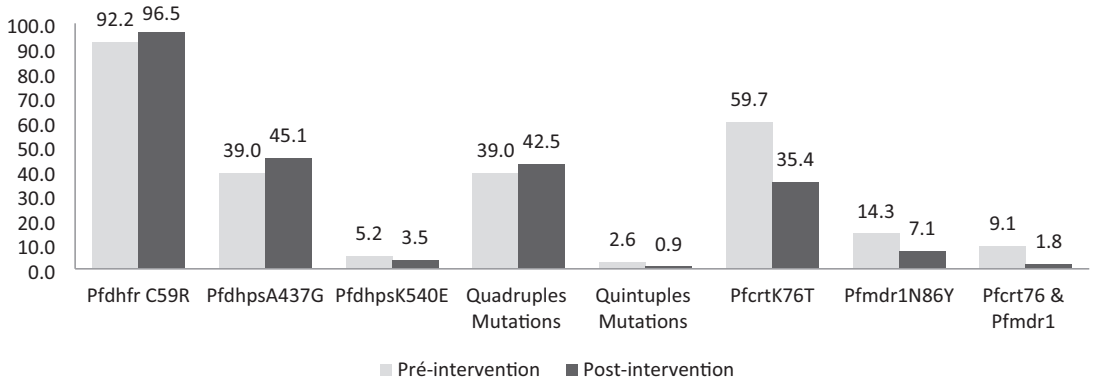

Fig. 4. Frequencies of individual and multiple mutations in dhfr, dhps, Pfcrt-76 T and Pfmdr1-86Y baseline and endline (after the intervention) in Kita.

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Authors' contributions

EE, SID, JM designed the study. DK, MT, BK, OD, MT, ES, CS, SID and DK coordinated and carried out field activities. KK, DK, SID, MT performed data analyses. KK, SID, DK, NP, DM, DS prepared initial draft of the manuscript; MS, NG, NP, EE and LS performed critical review and revision of the manuscript. All authors read and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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