

# WHO Guidelines for malaria

## Systematic reviews, background papers and other unpublished evidence considered in the development of recommendations

### Prevention/Preventive chemotherapies

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#### Section

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#### Title

Review of contextual factors related to seasonal malaria chemoprevention

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## Review of contextual factors related to Seasonal Malaria Chemoprevention

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## Executive summary

The extent to which systematic reviews and guidelines of complex interventions, like seasonal malaria chemoprevention (SMC), consider and report contextual factors that determine the direction and strength of recommendations in public health policy formulations is limited. We reviewed and abstracted data on contextual factors related to SMC, including its coverage and equity, acceptability, feasibility and health systems considerations, financial and economic considerations, and antimalarial drug resistance and safety, from 42 studies conducted in nine countries in the west and central Africa.

SMC coverage, with sulfadoxine-pyrimethamine plus amodiaquine (SP+AQ), was high in the seven countries (Burkina Faso, Chad, The Gambia, Guinea, Mali, Niger, and Nigeria) where the Achieving Catalytic Expansion of SMC in the Sahel (ACCESS-SMC) project was implemented. In 2015, the overall mean monthly SMC coverage was 76.4% (95% CI 74.0–78.8), with 54.5% children (95% CI 50.4–58.7) receiving all four treatments; in 2016, it was 74.8% (95% CI 72.2–77.3), and 53.0% (95% CI 48.5–57.4) respectively. However, SMC coverage varied among countries, with consistently low coverage in Chad to higher in Burkina Faso. In addition, SMC coverage rates in Senegal and Ghana were also high (>90%).

SMC coverage was equitable with similar levels of coverage across wealth quintiles in all countries. There was no significant difference in SMC coverage across age and gender, but in Senegal, coverage was higher amongst children aged 5–9 years (87%, 95% CI 84.5%–90.0%) than amongst children aged 3–59 months (82%, 95%CI 78.0%–85.0%).

SMC acceptability was generally high, with overall refusal rates <1% in five countries. However, in Kano, Nigeria, a higher proportion of urban residents were willing to accept SMC.

SMC delivery approaches and coverage varies across countries. For example, in Mali, SMC coverage was significantly higher in children who received SMC using door-to-door delivery (DDD) compared to fixed-point delivery (FPD) (76.1% versus 62.2%,  $p = 0.0028$ ), while in The Gambia, SMC delivery through village health workers achieved a substantially higher coverage level than delivery by reproductive and child health (RCH) teams (74% versus 48%, a difference of 27%, 95% CI 16%–38%).

The economic cost of administering four monthly SMC to one child across the seven countries where the ACCESS-SMC project was implemented was US\$3.63, ranging from US\$2.71 in Niger to US\$8.20 in The Gambia. Other studies have also shown variable SMC cost per course per child with US\$0.59 per course of SP+AQ in Senegal to US\$14.79 per course of artesunate plus amodiaquine (AS+AQ) in Ghana.

The estimated average total economic cost per malaria case averted ranged from US\$2.91 in Niger to US\$30.73 in The Gambia. In Ghana, AS+AQ monthly was the most cost-effective SMC drug regimen at US\$67.77 (95% CI 61.71–74.75), per malaria case averted based on intervention costs only, US\$64.93 (95% CI 58.92–71.92) per malaria case averted once the provider cost savings are included and US\$61.00 (95% CI 54.98, 67.99) when direct household cost savings are accounted. SP bimonthly was US\$105.35 (95% CI 75.01–157.31) and AS+AQ bimonthly US\$211.80 (95% CI 127.05–399.14 per malaria case averted based on intervention costs only.

The prevalence of molecular markers of resistance to sulfadoxine-pyrimethamine and amodiaquine was low in the general population before (2016) and two years after (2018) SMC

implementation in seven countries in the west and central Africa. In the general population (aged 10–30 years) not receiving SMC, the combined mutations associated with resistance to amodiaquine, *P falciparum* chloroquine resistance transporter (*pfcr*t)-CVIET haplotype, and *P falciparum* multidrug resistance 1 (*pfmdr*1) mutations (86Tyr and 184Tyr) prevalence was <1 % in 2016 and 2018; the quintuple mutation associated with resistance to sulfadoxine-pyrimethamine, triple mutation in *P falciparum* dihydrofolate reductase *pfdhfr* and *P falciparum* dihydropteroate synthase *pfdhps* mutations (437Gly and 540Glu), had a prevalence of 0·2% (95% CI 0·1–0·5) in 2016 and 1·0% (95% CI 0·6–1·6) in 2018. In Ghana, the prevalence of *pfdhfr*-N51I/C59R/S108N/*pfdhps*-A437G quadruple mutant associated with SP resistance was significantly higher in the northern savannah (45.5%) where SMC was implemented compared to other areas (3.7%).

Serious adverse drug reactions related to SMC treatment were rare, including fever, extrapyramidal syndrome, Quincke's oedema, and rash. Severe skin reactions such as Stevens-Johnson or Lyell syndrome were not reported. However, five deaths have been reported. The causes of death were suffocation from aspirating the SMC dissolved tablets after administration when the child was not fully awake, burns, dysentery, a febrile illness characterized by vomiting and diarrhoea and febrile illness and convulsions. Other more commonly reported adverse events were fever, vomiting, and abdominal pain.

## Introduction

The extent to which systematic reviews and guidelines of complex interventions, like seasonal malaria chemoprevention (SMC), consider and report contextual factors that determine the direction and strength of a recommendation in public health policy formulations (WHO 2014) is limited by inadequate information on the context in included primary studies (Booth, Moore et al. 2019). To facilitate a structured process of reflection and discussion in a problem-specific and context-specific manner, the WHO, in its new WHO-INTEGRATE (INTEGRATe Evidence) evidence to decision framework 1.0, recommends reporting and consideration of six substantive criteria—balance of health benefits and harms, human rights and socio-cultural acceptability, health equity, equality and non-discrimination, societal implications, financial and economic considerations, and feasibility and health system considerations—and the meta-criterion quality of evidence, applicable to all the six criteria. In our review, we have added drug resistance and its safety as additional factors that influence the success of SMC. The first criteria balance of health benefits and harms was the primary objective of our systematic reviews. The secondary objective was to review contextual factors relevant to the SMC guideline development process.

The systematic review methods and findings of primary study outcomes are reported elsewhere (Thwing et al. Seasonal malaria chemoprevention for malaria in children in areas with seasonal malaria.)

In this report, we report on contextual factors from a review of 42 studies from nine countries (Burkina Faso, Chad, The Gambia, Ghana, Guinea, Mali, Niger, Nigeria, and Senegal in the Sahel and sub-Saharan Africa. (Annex) Data was not available for values and preferences. We abstracted data for the other categories of contextual factors, which are discussed below.



### SMC coverage and equity

We abstracted SMC coverage and equity data from the Achieving Catalytic Expansion of SMC in the Sahel (ACCESS-SMC) project study (Partnership 2020) and five other studies (Kweku, Webster et al. 2009, Ndiop, Thwing et al. 2017, Ba, Pitt et al. 2018, Druetz 2018, Kaly, Ndiaye et al. 2018) from Ghana, Mali, and Senegal, which focused mainly on equity of SMC coverage among children of different ages, gender, their household's socioeconomic status (SES), and their mother's education type or level.

The ACCESS-SMC project implemented in Burkina Faso, Chad, The Gambia, Guinea, Mali, Niger, and Nigeria delivered sulfadoxine-pyrimethamine plus amodiaquine treatment (SP+AQ) to about 3.6 million children (aged 3–59 months) in 2015, and about 7.6 million children in 2016 (Partnership 2020) (Table 1). In 2015, 12,467,933 monthly SMC treatments were administered to a target population of 3,650,455 children achieving an overall mean monthly coverage of 76.4% (95% CI 74.0–78.8), with 54.5% children (95% CI 50.4–58.7) receiving all four treatments. In 2016, 25,117,480 SMC treatment were administered to a target population of 7,551,491, achieving an overall mean monthly coverage of 74.8% (95% CI 72.2–77.3), with 53.0% children (95% CI 48.5–57.4) receiving all four treatments. However, SMC coverage varied among countries, with consistently low coverage in Chad and higher coverage in Burkina Faso (Tables 1 and 2).

In Ghana, the proportion of eligible children receiving SMC was high, with SMC delivered through community health workers being higher (90.7%) compared to those receiving through health workers at health centres (86.6%) (Kweku, Webster et al. 2009). Following the introduction of SMC in Senegal in 2014, SMC coverage among 625,000 eligible children aged 3–120 months in the four high transmission regions was about 95% (Ndiop, Thwing et al. 2017).

### Age and gender

In Senegal (Ba, Pitt et al. 2018), SMC coverage in 2009 was higher amongst children aged 5–9 years (87%, 95% CI 84.5%–90.0%) than amongst children aged 3–59 months (82%, 95%CI 78.0%–85.0%). Coverage increased substantially in both age groups the following year, but remained higher in older children (96.3%, 95%CI 94.4–98.2 vs 90.4%, 95%CI 86.4– 94.3%). However, in Mali (Druetz 2018), SMC coverage was not statistically significantly different by the child's gender or age.

### Household socioeconomic status

In a multi-country study of SMC in west and central Africa (Partnership 2020), monthly SMC treatments received per child in 2015 and 2016 were equitable with similar levels of coverage across wealth quintiles in all countries (Figure 1).

In Senegal, there was no linear trend in the probability of receiving all three courses of SMC across SES quintiles in either 2008 (p-value for trend = 0.63) or in 2009 (p-value for trend = 0.36), the two years for which SES data were collected (Table 3; Ba, Pitt et al. 2018). In 2008, coverage of all three intended courses of SMC in the poorest SES quintile was 94.5%, which was higher than all but the highest SES quintile, which achieved 94.9% coverage. In 2009, coverage levels of all three courses dropped across all quintiles, but the 85.3% coverage achieved in the poorest quintile was slightly lower than the 87.5% coverage in the highest quintile.

### Mother's education level

In Mali (Druetz 2018), SMC coverage was equitable with respect to the mother's education type. In 2008 ( $p = 0.55$ ), 2009 ( $p = 0.77$ ), or 2010 ( $p = 0.33$ ) coverage levels were similar between groups where the mother had no education, only a Koranic education, or any French education (Table4). In both 2008 and 2010, children whose mothers had no education achieved the highest

levels of SMC coverage. In another study from south Senegal (Kaly, Ndiaye et al. 2018) adequate therapeutic coverage of children was higher among mothers with no formal education (30.5%) compared to mothers with primary (19.8%) or secondary education (18.8%) but was not statistically significantly different ( $p=0.08$ ).

In Mali (Druetz 2018), SMC coverage was statistically significantly associated with variables at higher levels: mother's education, household size, and socioeconomic status (Table 5).

**Table 1. Monthly treatments of sulfadoxine-pyrimethamine plus amodiaquine administered and estimates of SMC coverage from cluster-sample surveys, in children 3-59 months of age in the west and central Africa, 2015 and 2016**

	Overall		Burkina Faso		Chad		The Gambia		Guinea		Mali		Niger		Nigeria	
	2015	2016	2015	2016	2015	2016	2015	2016	2015	2016	2015	2016	2015	2016	2015	2016
Target population	3 650 455	7 551 491	707 317	2 056 169	268 956	514 042	88 748	90 925	253 252	438 123	875 330	1 492 137	596 355	1 050 932	860 497	1 909 163
Total treatments administered	12 467 933	25 117 480	2 721 731	5 780 062	1 061 417	2 511 371	308 830	297 453	805 131	1 750 224	2 752 912	4 667 224	1 668 015	3 810 088	3 149 897	6 301 058
Number surveyed who were eligible for four treatments	9376	13 063	786	874	707	1010	690	1138	1258	1743	740	799	4113	5646	1082	1853
Mean coverage per month	76.4% (74.0–78.8)	74.8% (72.2–77.3)	92.2% (87.9–96.4)	96.4% (94.5–98.2)	68.3% (63.5–73.1)	53.0% (47.1–58.8)	81.8% (77.8–85.8)	67.4% (61.6–73.2)	78.8% (74.6–83.0)	86.4% (84.0–88.9)	68.3% (57.4–79.2)	77.9% (66.6–89.2)	61.8% (58.1–65.4)	75.6% (70.7–80.5)	83.0% (78.3–87.6)	52.1% (44.9–59.4)
Percentage of children treated at least once	86.4% (83.4–89.3)	91.7% (89.3–94.2)	95.8% (91.1–98.0)	99.3% (97.1–99.8)	96.0% (91.6–98.2)	91.4% (85.0–95.3)	93.7% (90.4–95.9)	83.5% (73.1–86.3)	94.2% (90.1–96.7)	96.2% (94.7–97.3)	87.2% (74.9–94.0)	90.1% (79.7–95.5)	78.9% (75.4–81.9)	91.4% (88.2–93.8)	76.8% (68.2–83.4)	82.7% (74.1–88.9)
Percentage of children who received four treatments	54.5% (50.4–58.7)	53.0% (48.5–57.4)	86.4% (78.8–91.5)	91.2% (86.6–94.4)	24.0% (16.8–33.1)	12.4% (7.9–19.0)	56.1% (46.4–65.4)	43.7% (36.6–51.2)	56.8% (44.8–68.0)	73.0% (67.7–77.8)	45.2% (33.3–57.7)	56.9% (37.9–74.1)	43.0% (37.8–48.3)	50.2% (43.8–56.6)	54.6% (45.3–63.6)	19.5% (13.1–28.2)

Source: [ACCESS-SMC Partnership. Effectiveness of seasonal malaria chemoprevention at scale in the west and central Africa: an observational study Lancet, 396 \(2020\), pp. 1829-1840](#)

**Table 2 Estimates of the percentage of children 3-59 months of age treated with sulfadoxine-pyrimethamine plus amodiaquine, central and west Africa, 2015 and 2016**

Country	Year	Number of monthly treatment doses				
		0	1	2	3	4
Nigeria	2015	3.7	3.4	5.2	32.6	55.1
	2016	17.3	19.2	20.5	23.4	19.5
Niger	2015	20.4	12.2	9.6	14.8	43.0
	2016	7.9	5.2	14.4	22.3	50.2
Chad	2015	3.8	6.3	26.6	39.3	24.0
	2016	8.5	24.0	27.0	28.1	12.4
Mali	2015	11.7	10.7	15.6	16.8	45.2
	2016	8.6	5.0	9.6	19.9	56.9
Guinea	2015	4.9	7.6	11.8	19.0	56.8
	2016	3.3	3.2	11.0	9.5	73.0
Burkina Faso	2015	3.1	3.0	2.6	4.9	86.4
	2016	0.7	0.7	2.3	5.1	91.2
The Gambia	2015	5.8	2.1	7.2	28.8	56.1
	2016	16.6	6.4	11.6	21.7	43.7

Source: [Supplement to ACCESS-SMC Partnership. Effectiveness of seasonal malaria chemoprevention at scale in the west and central Africa: an observational study. \*Lancet\* 2020; \*\*396\*\*: 1892–40.](#)

**Table 3 Sulfadoxine-pyrimethamine plus amodiaquine coverage of in children 3–119 months by household socioeconomic quintile, Senegal, 2008 and 2009**

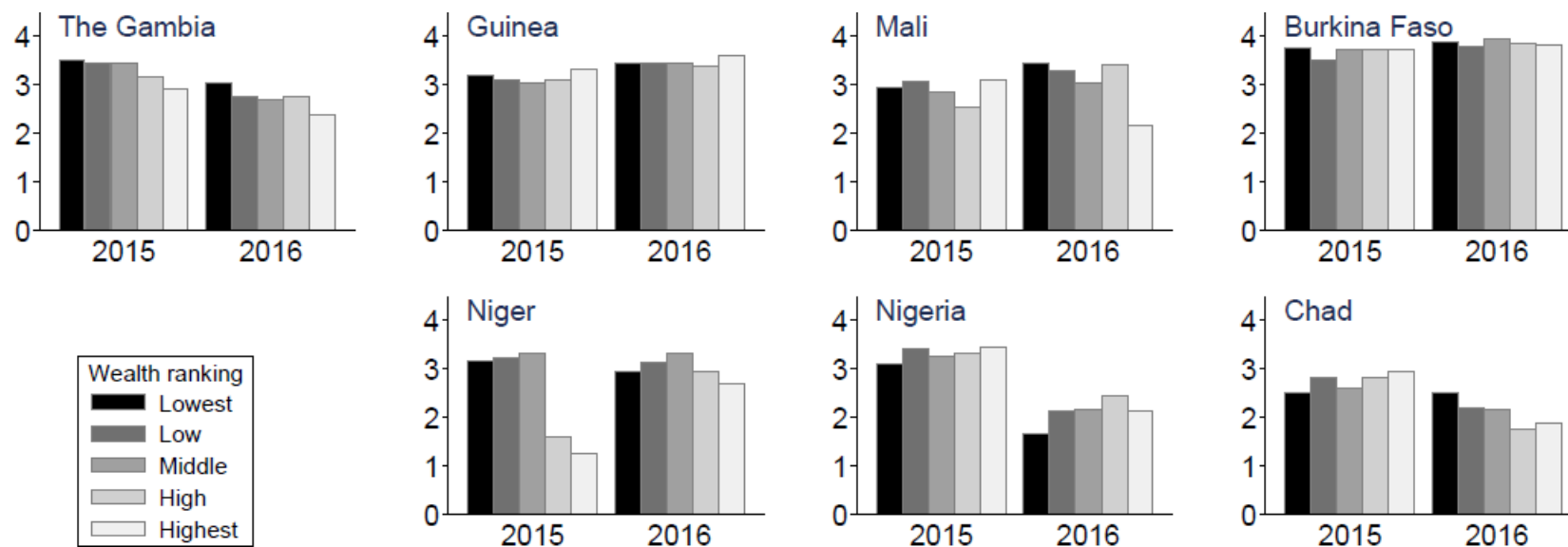
		Socio-economic status (SES) quintile					Odds ratio for one level increase in SES	P-value for trend
		Lower	Lower middle	Middle	Upper middle	Upper		
<b>2008</b>	N	253	154	171	190	251		
	Received all 3 SMC courses (%)	94.5	91.2	87.6	90.1	94.9	1.04 (0.88, 1.22)	0.63
<b>2009</b>	N	689	725	631	674	678		
	Received all 3 SMC courses (%)	85.3	80.0	86.4	83.4	87.5	1.07 (0.95, 1.20)	0.36

**Table 4. Sulfadoxine-pyrimethamine plus amodiaquine coverage in children 3–119 months by mother's education, Senegal, 2008 and 2009**

	Year	2008			2009			2010		
	Level/ Type of education	None (N=58 6)	Koranic only (N=152)	French (N=235)	None (N = 1916)	Koranic only (N = 608)	French (N = 699)	None (N = 502)	Koranic only (N = 141)	French (N = 195)
<b>Number of courses</b>	0	2.9	2.5	5.2	11.1	9.3	8.6	5.6	4.5	5.5
	1	0.4	1.2	0.6	1.4	1.4	1.7	0.12	0	0.34
	2	3.3	3.9	3.0	3.0	2.2	3.5	0.24	1.65	0.34
	3	93.4	92.4	91.2	84.5	87.1	86.2	94.0	93.8	93.9
<b>Design-based p-value for test of difference between groups</b>		0.55			0.77			0.33		

Tables 3 and 4 sources: [Supplementary Information Implementation, coverage and equity of large-scale door-to-door delivery of Seasonal Malaria](#)

[Chemoprevention \(SMC\) to children under 10 in Senegal https://doi.org/10.1038/s41598-018-23878-2](#)



**Figure 1. The mean number of monthly sulfadoxine-pyrimethamine plus amodiaquine treatments received per child across wealth ranking of the household (determined by ownership of household assets), in children 3-59 months of age in the west and central Afr Africa, 2015 and 2016**

[Source: Supplement to ACCESS-SMC Partnership. Effectiveness of seasonal malaria chemoprevention at scale in the west and central Africa: an observational study. Lancet 2020; 396: 1892–40](#)



**Table 5. Characteristics of children aged 6–59 months who received sulfadoxine-pyrimethamine plus amodiaquine (SMC), Mali, 2015<sup>1</sup>**

	Received SMC	Test statistic (p-value)
<b>Number</b>	2,666	
<b>Female</b>	48%	$\chi^2 = 2.83$ (0.092)
<b>Mean age in months (SD)</b>	32 (16)	$t = -1.52$ (0.127)
<b>Slept under a bed net the night before</b>	74%	$\chi^2 = 1.47$ (0.225)
<b>Mothers' education</b>		$\chi^2 = 46.75$ (<0.001)
• None	80%	
• Primary	13%	
• Secondary or higher	7%	
<b>Ethnic group</b>		$\chi^2 = 3.76$ (0.152)
• Bambara	32%	
• Peulh/Toucouleur	15%	
• Other	53%	
<b>SES</b>		$\chi^2 = 355.21$ (<0.001)
• Poorest	22%	
• Poorer	26%	
• Medium	26%	
• Richer	20%	
• Richest	6%	
<b>Size of the household</b>		$\chi^2 = 20.57$ (<0.001)
• 1–5	11%	
• 6–10	33%	
• $\geq 10$	56%	

<sup>1</sup>Druetz, T. Evaluation of direct and indirect effects of seasonal malaria chemoprevention in Mali. Sci Rep 8, 8104 (2018). <https://doi.org/10.1038/s41598-018-26474-6>

## Acceptability

Qualitative and quantitative data on SMC acceptability were abstracted from eight studies (Pitt, Diawara et al. 2012, Kpormegbe and Ahorlu 2014, Ansah, Malm et al. 2016, Antwi, Bates et al. 2016, Compaore, Yameogo et al. 2017, Shehu 2017, Ba, Pitt et al. 2018, Chatio, Ansah et al. 2019) from five countries (Burkina Faso, Ghana, Mali, Nigeria, and Senegal).

## Community acceptability

Quantitative data on SMC acceptability was available from two studies conducted in Burkina Faso (Compaore, Yameogo et al. 2017) and Senegal (Ba, Pitt et al. 2018). In both studies, acceptability was generally high, with overall refusal rates <1%. In Burkina Faso, almost all the parents (99.7%) provided consent for their child to receive SP+AQ, and the medication was administered at home in 96% of the cases (Compaore, Yameogo et al. 2017). In addition, nearly all parents reported administering the remaining two doses of AQ in the two days following the first directly observed treatment (DOT). However, due to under-reporting or low availability of the SMC cards, these data could not be cross-verified. SMC administration card was available in 44.7% of the cases, and approximately 7.4% of parents reported that they had not received a card during the last campaign.

A qualitative study in Burkina Faso and Mali (Pitt, Diawara et al. 2012) conducted parallel to a cluster-randomized study reported widespread perceptions of health benefits for children, which led to acceptability and enthusiasm for the SMC study. Trust in and respect for those providing the tablets and a sense of obligation to the community to participate in activities favoured initial adoption. Participants did not express concerns about the specific drugs used for SMC or about providing tablets to children without symptoms of malaria.

In Kano, Nigeria, a cross-sectional survey that assessed malaria preventive practices and

acceptability of SMC found a higher proportion of urban residents (85.7%) willing to accept SMC. Age (aOR 7.6, 95% CI 1.1–54.7) and awareness of SMC (aOR 6.6, 95% CI 1.9–23.5) significantly predicted SMC acceptability in the urban community while higher literacy status (aOR 0.3, 95% CI 0.09–0.79) significantly predicted SMC acceptability in the rural community (Shehu 2017). Distribution of SMC drugs free, use of incentives, and involvement of traditional/religious leaders would enhance SMC acceptability in both communities.

Several qualitative studies from Ghana (Kpormegbe and Ahorlu 2014, Ansah, Malm et al. 2016, Antwi, Bates et al. 2016, Chatio, Ansah et al. 2019) have also reported high acceptability of SMC with AQ+SP at monthly intervals by parents and other community members. In the Upper West Region, participants perceived that the introduction of the SMC intervention in the area had helped reduce the prevalence of malaria among children less than five years of age. Parents held the view that the drug was very good in preventing malaria. Parents reported that they were willing to allow their children to receive the drug and wished the intervention could continue in the district for children to benefit. Another study from the Ashanti Region of Ghana (Antwi, Bates et al. 2016) assessed the acceptability of the extended SMC programme (5 monthly cycles). The study found that caregivers of children who took four or more monthly doses of SMC reported positive health effects (including no malaria, reduced headaches, and no sickness, ceased diarrhoea, and no high body temperature). They were motivated by these benefits to continue taking medicine. However, the fact that some caregivers were found to have not administered some tablets to their children highlights the need for community health workers (CHWs) to check and encourage caregivers to administer the total dose. The CHWs believed they were more suitable administrators of the programme than the child welfare clinics (CWC),

given their extensive knowledge of caregivers in the community and flexible working hours and outreach capabilities. CHWs preferred full responsibility for distributing the medicine to reach all households in a 'systematic way.'

In the Keta district of Ghana (Kpormegbe and Ahorlu 2014), where SMC was delivered at community health posts and facility-based delivery, most interviewed leaders maintained that the project was well introduced into the community as the project team had observed the necessary community protocols and allowed the local people to participate in the project activities fully. Findings indicated that the people were aware of the project in their communities. Community participation was high, and they accepted the intervention as their own. In addition, the people preferred that community members deliver the drugs because they are more approachable, caring, and sensitive to their health needs than the nurses (Kpormegbe and Ahorlu 2014).

#### Healthcare workers and policy maker's acceptability

Our review found no studies reporting healthcare workers' or policy makers' acceptability of SMC.

#### Feasibility and health systems consideration

We abstracted feasibility and health systems considerations data from ten studies (Kweku, Webster et al. 2009, Bojang, Akor et al. 2011, Pitt, Diawara et al. 2012, Kpormegbe and Ahorlu 2014, Issiaka, Barry et al. 2015, Antwi, Bates et al. 2016, Ceesay, Hubbard et al. 2016, Barry, Issiaka et al. 2018, Kombate, Guiella et al. 2019, Oresanya, Ahmadu et al. 2019) from five countries (Burkina Faso, The Gambia, Ghana, Mali, and Nigeria).

Key barriers and facilitators for SMC in Burkina Faso, Mali, and Ghana are presented in Tables 6 and 7 (Pitt, Diawara et al. 2012, Antwi, Bates et al. 2016).

## SMC delivery methods

In Mali (Issiaka, Barry et al. 2015), SMC coverage was significantly higher in children who received SMC using door-to-door delivery (DDD) compared to fixed-point delivery (FPD) (76.1% versus 62.2%,  $p = 0.0028$ ). However, SMC coverage was similar in children who received SMC using DOT or non-DOT (NDOT) (68.2% versus 68.6%;  $p = 0.95$ ). Across the four study arms, coverage was highest in DDD+NDOT (77.7%), followed by DDD+DOT (74.5%), FPD+DOT (64.2%) and FPD+NDOT (60.0%)  $p = 0.038$ .

Another study from Mali (Barry, Issiaka et al. 2018) also reports significantly higher coverage in children who received SMC using DDD 74% (95% CI 69%–80%) compared to FPD 60% (95% CI 50%–70%;  $p = 0.009$ ). It was similar in children who received SMC using DOT or NDOT 65%, (95% CI 55%–76%) versus 68% (95% CI 57%–79%;  $p = 0.72$ ). In this study, in villages assigned to DDD, CHWs visited each compound to administer SMC drugs. In the villages assigned to FPD, children received SMC at a central fixed point in the village. CHWs administered three days treatments doses at each round for children assigned to DOT, while for children assigned to NDOT, the first-day treatment was given by CHWs and treatments for second and third days were given by the caregiver at home for each round (Barry, Issiaka et al. 2018).

In The Gambia (Bojang, Akor et al. 2011), SMC delivery through village health workers (VHWs) achieved a substantially higher coverage level of three courses of SMC than delivery by reproductive and child health (RCH) teams (74% versus 48%, a difference of 27%, 95% CI 16%–38%). However, another study from The Gambia shows DDD achieved high coverage of SMC (Ceesay, Hubbard et al. 2016); 84% of children received at least three months of SMC.

In Nigeria (Oresanya, Ahmadu et al. 2019), although CHWs' coverage of SMC eligible children in Nigeria is high, the quality of their delivery could be better.

In Ghana (Kweku, Webster et al. 2009), SMC delivered through community-based or facility-based systems can achieve a high coverage rate with the support and supervision of the district health management team. However, to maximize the impact of SMC, both delivery systems may be needed in some settings. The people preferred that community members deliver the drugs because they are more approachable, caring, and sensitive to their health needs than the nurses (Kpormegbe and Ahorlu 2014).

### Training and supervision of SMC implementation

Several studies have emphasized the importance of supervision during SMC implementation (Kweku, Webster et al. 2009, Kombate, Guiella et al. 2019). For example, in Burkina, supervision for the monitoring and evaluation component of SMC, particularly to overcome the difficulty of completing the household surveys on the days following DOT administration, has been suggested by designing an activity specifically to check if the remaining doses are given has not been done (Kombate, Guiella et al. 2019). In Ghana, good supervision and support from a District Health Management Team and the study team were needed to achieve high SMC coverage (Kweku, Webster et al. 2009).

**Table 6 Key facilitators and barriers to IPTc<sup>2</sup> uptake in the trial, in Burkina Faso and Mali, 2009**

Facilitators	Barriers
<ul style="list-style-type: none"> <li>• Perception of the dramatic decrease in child morbidity and mortality</li> <li>• Association of IPTc with free LLINs and free curative care (which were highly valued) as part of a single package</li> <li>• Trust in and respect for authorities (including health workers), who were seen to sanction and implement IPTc</li> <li>• Compatibility with previous positive experience of chloroquine chemoprophylaxis and mass distribution of Vitamin A and antihelminthic tablets</li> <li>• A syncretic approach to health favouring multiple prevention strategies</li> <li>• Acceptance of perceived side effects as not concerning or even a positive sign</li> <li>• Observation of other community members participating</li> <li>• Lack of concerns about the specific drug combination</li> <li>• Perceiving attendance at health centre for IPTc as opportunity to see a health worker</li> <li>• Proximity to health centre</li> <li>• Presence of other women in the household to cook while children are brought to the health centre</li> <li>• Male family members supporting participation</li> </ul>	<ul style="list-style-type: none"> <li>• Rumours associated with the trial</li> <li>• Concerns over finger-prick blood samples</li> <li>• Concerns amongst some parents who perceived side effects</li> <li>• Distance to the health centre</li> <li>• Time and effort of travelling to and waiting at health centre repeatedly, especially if nobody else in household available to cook</li> <li>• Male family members forbidding participation</li> <li>• Travel of child or female caregiver during the administration days</li> </ul>

Source: Pitt C, Diawara H, Ouédraogo DJ, Diarra S, Kaboré H, et al. (2012) Intermittent Preventive Treatment of Malaria in Children: A Qualitative Study of Community Perceptions and Recommendations in Burkina Faso and Mali. PLOS ONE 7(3): e32900. <https://doi.org/10.1371/journal.pone.0032900>  
<https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0032900>

<sup>2</sup> IPTc were considered as SMC for the purpose of this review

**Table 7 Facilitators and barriers to SMC uptake amongst caregiver respondents, collected during a qualitative study in Ghana in January 2013**

<b>Facilitators of SMC uptake</b>	<b>Barriers to SMC uptake</b>
• Trust in and respect for authorities who were seen to sanction and implement the SMC	• SMC programme was incompatible with some caregivers perceived needs, who believed there was no need to medicate children who were not sick and their time was better spent at work
• Proximity to and communication of fixed point delivery (community gatherings)	• Large distances to travel, restricted timings of, and poor communication of fixed point delivery (community gatherings)
• Flexible door-to-door (household) delivery	• Delivery of medication only to primary caregiver during door-to-door visits
• Beliefs that any perceived side-effects of SMC were attributable to the SMC medication treating undiagnosed malaria in the child	• Beliefs that any perceived side-effects of SMC were attributable to the SMC medication harming the child
• CHW supervision and administration of medication directly to the child at home.	• Need to consume all SMC medication over 3 consecutive days within a month.
• Reference to IPTp to explain the difference between malaria treatment medication and malaria prevention medication	• Caregivers found the concept of preventive medication difficult to understand despite experience of IPTp and the SMC programme
• Observation of other caregivers' participation and their perceived positive health responses	• Belief the intervention was for research only and not routine care
• Reassurance from CHWs and senior family members on perceived side-effects (the basis for a supportive community-based network)	

doi:10.1371/journal.pone.0166951.t003

Source: Antwi GD, Bates LA, King R, Mahama PR, Tagbor H, et al. (2016) Facilitators and Barriers to Uptake of an Extended Seasonal Malaria Chemoprevention Programme in Ghana: A Qualitative Study of Caregivers and Community Health Workers. PLOS ONE 11(11): e0166951.

<https://doi.org/10.1371/journal.pone.0166951>

<https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0166951>



## Financial and economic considerations

Financial and economic data on SMC were abstracted from eight studies (Conteh, Patouillard et al. 2010, Bojang, Akor et al. 2011, Patouillard, Conteh et al. 2011, Pitt, Ndiaye et al. 2015, Nonvignon, Aryeetey et al. 2016, Pitt, Ndiaye et al. 2017, Dieng, Gonzalez et al. 2019, Partnership 2020) from eight countries (Burkina Faso, Chad, The Gambia, Guinea, Mali, Niger, Nigeria, and Senegal).

### Economic cost

The total recurrent economic cost of SMC in seven countries in west and central Africa in 2016 (for all ages) was US\$22.8 million (Table 8), comprising US\$20.6 million in financial costs and US\$2.2 million in volunteer opportunity costs (Partnership 2020). The weighted average economic cost of administering four monthly SMC cycles to a single child across the seven countries where the ACCESS-SMC project was implemented was US\$3.63, ranging from US\$2.71 in Niger to US\$8.20 in The Gambia (Partnership 2020).

Other studies have also shown variable economic cost of SMC per course per child with US\$0.59 per SP+AQ course in Senegal (Pitt, Ndiaye et al. 2017) to US\$14.79 per course of artesunate plus amodiaquine (AS+AQ) in Ghana (Conteh, Patouillard et al. 2010).

In Ghana (Conteh, Patouillard et al. 2010), the economic costs per child receiving at least the first dose of each course of bimonthly SP was US\$8.19, followed by AS+AQ bimonthly at US\$10.67 and then by AS+AQ monthly at US\$14.79. In another study from the Upper West Region of Ghana (Nonvignon, Aryeetey et al. 2016), the economic cost per child dosed was US\$67.35 from a societal perspective and US\$22.53 from the provider perspective.

In the Jasikan District of Ghana (Patouillard, Conteh et al. 2011), the economic cost per child receiving at least the first dose of all four courses was US\$4.58 when SMC was delivered by

VHWs, US\$4.93 by outpatient department nurses, and US\$ 5.65 by the expanded program on immunization nurses. The unit economic cost of receiving all three doses of all four courses was US\$7.56 and US\$8.51 when SMC was delivered by VHWs or facility-based nurses, respectively (Patouillard, Conteh et al. 2011). The unit economic cost of receiving all three doses of all four courses was US\$7.56 and US\$8.51 when SMC was delivered by VHWs or facility- based nurses, respectively.

In Senegal (Pitt, Ndiaye et al. 2017), the economic cost per SP+AQ course administered widely varied between health posts, from US\$0.38 to US\$2.74, with an average of US\$0.59.

**Table 8 Estimated SMC costs and costs savings (2016, US \$) in seven countries in west and central Africa**

	<b>Totaleconomic costs of administering SMC</b>	<b>Diagnosis and treatment economiccostssaved<sup>3</sup></b>	<b>Net economic costs saved<sup>2</sup></b>
<b>Burkina Faso</b>	\$5,464,604	\$12,310,252	\$6,845,648
<b>Chad</b>	\$2,422,920	\$3,288,511	\$865,591
<b>Guinea</b>	\$1,557,622	\$3,755,813	\$2,198,191
<b>Mali</b>	\$3,827,362	\$14,469,046	\$10,641,683
<b>Niger</b>	\$2,578,453	\$11,767,661	\$9,189,209
<b>Nigeria</b>	\$6,321,460	\$20,071,640	\$13,750,180
<b>The Gambia</b>	\$609,889	\$291,966	\$317,923
<b>Total</b>	\$22,782,310	\$65,954,888	\$43,172,578

Source: [Source: Supplement to ACCESS-SMC Partnership. Effectiveness of seasonal malaria chemoprevention at scale in the west and central Africa: an observational study. \*Lancet\* 2020; \*\*396\*\*: 1892–40.](#)

<sup>3</sup> Potential cost savings from a provider perspective were calculated from the diagnostic and treatment costs for non-severe and severe malaria cases averted, and assumed 60% of malaria cases were diagnosed and treated.

### Financial cost

In Ghana, the average financial cost per fully dosed child (four rounds of SMC) for the Region was US\$9.66 (95 % CI 7.46–14.21), ranging from US\$4.61 in Wa East to US\$26.14 in Sissala West (although the district's record seems to be an outlier) (Nonvignon, Aryeetey et al. 2016).

In Senegal, the door-to-door SMC (AQ and SP tablets each month to children aged 3–119 months) to 180 000 children over one malaria season, reaching ~93% of children with all three intended courses of SMC was US\$234,462 (constant 2010 USD) or US\$0.50 per monthly course administered. Excluding research–participation incentives, the financial cost was US\$0.32 per resident (all ages) in the catchment area, which is 1.2% of Senegal's general government expenditure on health per capita (Pitt, Ndiaye et al. 2015).

### Cases and deaths averted

In countries where the ACCESS-SMC project was implemented, the estimate of the average total economic cost per malaria case averted, based on modelled estimates of the incidence of malaria in the absence of SMC, ranged from US\$2·91 in Niger to US\$30·73 in The Gambia (Partnership 2020). The average total cost per severe malaria case averted ranged from US\$119·63 in Niger to US\$506·00 in The Gambia, and the average cost per death averted ranged from US\$533·56 in Niger to US\$2256·92 in The Gambia. Potential cost savings were estimated to be US\$66·0 million in total, ranging from US\$291 966 in The Gambia to US\$20·1 million in Nigeria. The net economic cost savings (deducting the costs of administering SMC) were US\$43·2 million across the seven countries.

In the Hohoe district of Ghana, AS+AQ monthly was the most cost-effective SMC drug regimen at US\$67.77 (95% CI 61.71–74.75), per malaria case averted based on intervention costs only, US\$64.93 (95% CI 58.92–71.92) per malaria case averted once the provider cost savings are

included and US\$61.00 (95% CI 54.98, 67.99) when direct household cost savings are also taken into account. SP bimonthly was US\$105.35 (95% CI 75.01–157.31), and AS and AQ bimonthly US\$211.80 (95% CI 127.05–399.14 per malaria case averted based on intervention costs only (Conteh, Patouillard et al. 2010).

In the Upper West Region of Ghana (Nonvignon, Aryeetey et al. 2016), the total financial cost of the intervention was US\$1,142,040.80. The total economic cost was estimated to be US\$7.96 million and US\$2.66 million from the societal and provider perspectives, respectively.

Additional cases estimated to be averted by the intervention were 24,881 and 808, respectively.

The economic cost per child dosed was US\$67.35 from a societal perspective and US\$22.53 from the provider perspective. The economic cost per additional case averted was US\$107.06 from the provider perspective and US\$319.96 from the societal perspective. The economic cost per additional child death averted by the intervention was US\$3298.36 from the provider perspective and US\$9858.02 from the societal perspective. The financial cost per the SMC intervention delivered to a child under five years of age was US\$9.66. The incremental cost-effectiveness ratios were sensitive to the mortality rate used (Nonvignon, Aryeetey et al. 2016).

In The Gambia (Bojang, Akor et al. 2011), delivery of SMC by VHWs was less costly in both economic and financial terms than delivery through RCH teams, resulting in incremental savings of US\$872 and US\$1,244, respectively. The annual economic cost of delivering at least the first dose of each course of SMC was US\$3.47 and US\$1.63 per child using trekking team and VHWs, respectively.

## Molecular markers of resistance to sulfadoxine-pyrimethamine and amodiaquine

The prevalence of molecular markers of resistance to sulfadoxine-pyrimethamine and amodiaquine was found to be low in the general population before (2016) and two years after (2018) SMC implementation in 7 countries in west and central Africa (Partnership 2020) (Table 9).

In children, 3–5 months of age, the prevalence of the combination of the *pfcr*t-CVIET (amino acid positions 72–76), *pfmdr*1-86Tyr, and *pfmdr*1-184Tyr variants, associated with resistance to amodiaquine, was 1·3% in 2016 and 0·5% in 2018 (Table 10). The prevalence of the quintuple mutation associated with resistance to sulfadoxine-pyrimethamine (triple mutation in *pf**dhfr* with *pf**dhps*-437Gly and *pf**dhps*-540Glu) was 0·4% (0·2–0·8) in 2016 and 0·7% (0·3–1·5) in 2018 (prevalence ratio 1·8, 95%CI 0·7–5·0). In the 10–30 age group, the prevalence of *pfcr*t-CVIET, *pfmdr*1-86Tyr, and *pfmdr*1-184Tyr variants were 0·7% in 2016, and 0·4% in 2018; and the prevalence of quintuple mutation were 0·2% in 2016 and 1·0% in 2018. In 2016, only two samples (one in each age group) carried the quintuple mutation and *pfcr*t-CVIET, *pfmdr*1-86Tyr, and *pfmdr*1-184Tyr, the combination associated with resistance to sulfadoxine-pyrimethamine and amodiaquine (prevalence of 0·05%). In 2018, no samples carried genotypes associated with resistance to both sulfadoxine-pyrimethamine and amodiaquine (Partnership 2020).

Other studies conducted in countries where the ACCESS-SMC project was implemented and Ghana and Senegal have also reported an increase in selection for resistance to sulfadoxine-pyrimethamine in parasites (Sokhna, Cisse et al. 2008, Cisse, Cairns et al. 2009, Fabrice, Zongo et al. 2011, Ndiaye, Alifrangis et al. 2011, Ndiaye, Tine et al. 2013, Some, Zongo et al. 2014,

Grais, Laminou et al. 2018, Maiga, Bamadio et al. 2018, Diarra, Doumbia et al. 2019, Dieng, Gonzalez et al. 2019, Mahamar, Sumner et al. 2019, Cairns, Sagara et al. 2020).

In a study conducted in three ecological zones of Ghana in 2017 (two years following implementation of SMC in northern Ghana), only 1% of genotyped samples for *pfcr*t codon K76T were found to contain the mutant allele 76T (Dieng, Gonzalez et al. 2019). No significant difference was detected in the *pfcr*t K76T mutation frequency among the three ecological zones. However, the *pfdhfr* N51I, C59R, S108N triple mutant prevalence was significantly higher in the north and central regions. Likewise, a significant difference was observed in the prevalence of the *pfdhfr* N51I, C59R, S108N and *pfdhps* A437G quadruple mutants between the north and other regions ( $p < 0.001$ ). No quintuple mutants were observed in all samples. The prevalence of *pfdhfr*-N51I/C59R/S108N/*pfdhps*-A437G quadruple mutant associated with SP resistance was significantly higher in the north (45.5%) where SMC was implemented compared to other areas (3.7%).

Table 9 Prevalence estimates for molecular markers to amodiaquine and sulfadoxine-pyrimethamine, in two age groups, in seven countries<sup>4</sup> west and central Africa, 2016 and 2018

	10-30 years			3-59 months		
	2016	2018	ratio	2016	2018	ratio
	prevalence	prevalence	2018:2016	prevalence	prevalence	2018:2016
	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)
<b>pfprt-CVIET</b>	0.428	0.364	0.85	0.422	0.685	1.62
	(0.385,0.471)	(0.326,0.403)	(0.73,0.99)	(0.378,0.467)	(0.643,0.725)	(1.43,1.84)
<b>pfmdr1-86Y</b>	0.108	0.088	0.82	0.118	0.066	0.56
	(0.093,0.124)	(0.072,0.108)	(0.65,1.04)	(0.102,0.136)	(0.050,0.087)	(0.41,0.76)
<b>pfmdr1-184Y</b>	0.348	0.246	0.71	0.342	0.263	0.77
	(0.322,0.374)	(0.216,0.278)	(0.61,0.82)	(0.317,0.368)	(0.228,0.302)	(0.66,0.90)
<b>pfdhfr-51I</b>	0.890	0.922	1.04	0.888	0.914	1.03
	(0.870,0.907)	(0.902,0.939)	(1.01,1.07)	(0.872,0.903)	(0.891,0.932)	(1.00,1.06)
<b>pfdhfr-59R</b>	0.886	0.954	1.08	0.891	0.905	1.02
	(0.859,0.908)	(0.941,0.965)	(1.05,1.11)	(0.873,0.907)	(0.876,0.928)	(0.98,1.05)

<sup>4</sup> Burkina Faso, Chad, The Gambia, Guinea, Mali, Niger, and Nigeria Source: [Supplement to: ACCESS-SMC Partnership. Effectiveness of seasonal malaria chemoprevention at scale in west and central Africa: an observational study. Lancet 2020; 396: 1892–40.](#)



<b>pfdhfr-108N</b>	0.920	0.973	1.06	0.915	0.991	1.08
	(0.900,0.937)	(0.963,0.980)	(1.03,1.08)	(0.888,0.936)	(0.982,0.995)	(1.05,1.11)
<b>pfdhps-431V</b>	0.022	0.079	3.66	0.030	0.064	2.09
	(0.016,0.030)	(0.062,0.101)	(2.44,5.50)	(0.023,0.040)	(0.043,0.093)	(1.30,3.39)
<b>pfdhps_436A</b>	0.531	0.712	1.34	0.591	0.581	0.98
	(0.483,0.579)	(0.675,0.746)	(1.21,1.48)	(0.551,0.630)	(0.537,0.623)	(0.89,1.09)
<b>pfdhps-437G</b>	0.747	0.852	1.14	0.780	0.928	1.19
	(0.704,0.785)	(0.824,0.876)	(1.07,1.22)	(0.741,0.815)	(0.907,0.945)	(1.13,1.25)
<b>pfdhps-540E</b>	0.002	0.010	4.01	0.005	0.007	1.42
	(0.001,0.006)	(0.006,0.016)	(1.63,9.83)	(0.003,0.008)	(0.003,0.015)	(0.58,3.46)
<b>pfdhps-581G</b>	0.023	0.067	2.96	0.025	0.056	2.26
	(0.017,0.031)	(0.052,0.085)	(2.03,4.33)	(0.019,0.032)	(0.039,0.079)	(1.43,3.58)
<b>pfdhps_613S/T</b>	0.082	0.183	2.23	0.091	0.109	1.19
	(0.067,0.100)	(0.158,0.210)	(1.76,2.83)	(0.078,0.106)	(0.078,0.150)	(0.82,1.75)

Table 10 Prevalence estimates for combinations of molecular markers associated with resistance to amodiaquine and sulfadoxine-pyrimethamine, in two age groups, in seven countries<sup>5</sup> in west and central Africa, 2016 and 2018

Combination	10-30 years			3-59 months		
	2016 Prevalence (95%CI)	2018 Prevalence (95%CI)	Ratio 2018:2016	2016 Prevalence (95%CI)	2018 Prevalence (95%CI)	Ratio 2018:2016
<b>pfmdr1-86Y + pfmdr1-184Y</b>	0.013 (0.009,0.020)	0.015 (0.009,0.023)	1.11 (0.62,1.98)	0.023 (0.016,0.033)	0.007 (0.003,0.016)	0.29 (0.12,0.72)
<b>pfert-CVIET + pfmdr1-86Y + pfmdr1-184Y (a)</b>	0.007 (0.004,0.012)	0.003 (0.001,0.008)	0.50 (0.20,1.21)	0.013 (0.009,0.020)	0.005 (0.002,0.014)	0.41 (0.15,1.14)
<b>pfdhfr-51I+59R+108N</b>	0.752 (0.713,0.788)	0.908 (0.885,0.926)	1.21 (1.14,1.27)	0.754 (0.721,0.785)	0.849 (0.818,0.875)	1.12 (1.07,1.18)
<b>pfdhps-437G+pfdhps-540E</b>	0.002 (0.001,0.005)	0.009 (0.005,0.014)	3.73 (1.50,9.24)	0.005 (0.003,0.008)	0.007 (0.003,0.015)	1.47 (0.60,3.58)
<b>pfdhfr-51I+59R+108N + pfdhps- 437G + pfdhps-540E (b)</b>	<b>0.002</b> <b>(0.001,0.005)</b>	<b>0.010</b> <b>(0.006,0.016)</b>	<b>4.78</b> <b>(1.67,13.73)</b>	0.004 (0.002,0.008)	0.007 (0.003,0.015)	1.84 (0.68,4.97)
<b>(a)+(b)</b>	0.001 (0.000,0.004)	0.000 (0.000,0.001)		0.000 (0.000,0.003)	0.000 (0.000,0.001)	
<b>pfdhps-VAGKGS haplotype</b>	0.006 (0.003,0.011)	0.027 (0.015,0.047)	4.86 (2.07,11.44)	0.008 (0.005,0.012)	0.003 (0.001,0.012)	0.39 (0.09,1.57)

<sup>5</sup> Burkina Faso, Chad, The Gambia, Guinea, Mali, Niger, and Nigeria Source: [Supplement to: ACCESS-SMC Partnership. Effectiveness of seasonal malaria chemoprevention at scale in west and central Africa: an observational study. Lancet 2020; 396: 1892–40.](#)

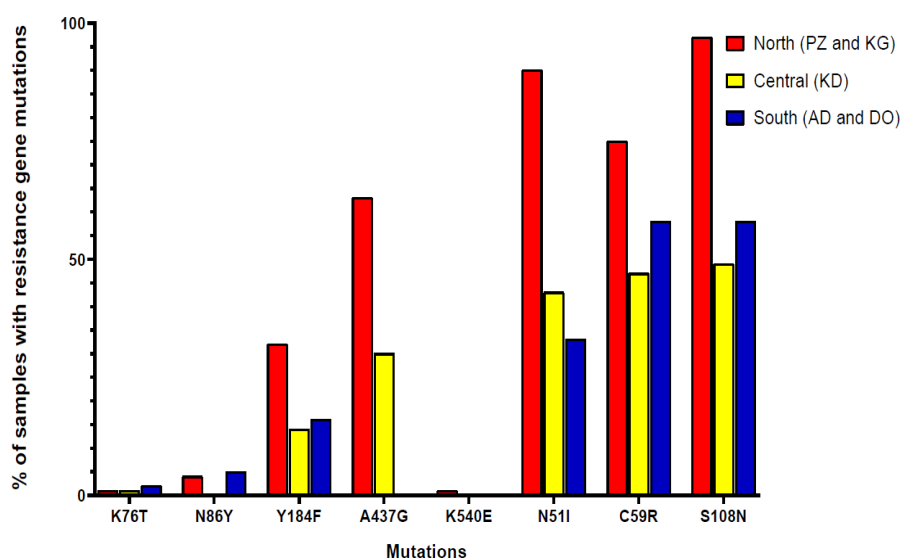
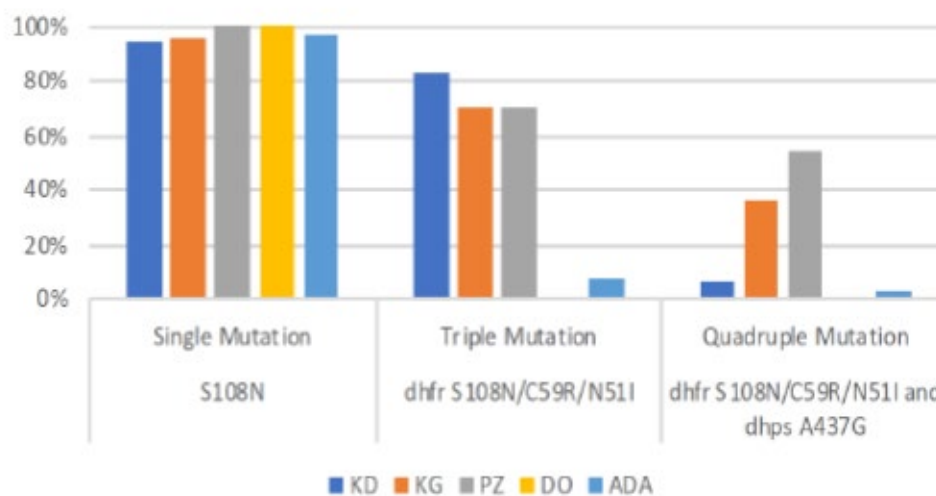


Figure 2 Percentage of *P. falciparum* samples with mutations obtained from children 5 to 14 years, across there ecological zones of Ghana<sup>5</sup>, June-September, 2017. Top panel: Percentage of single, triple and quadruple mutations. Bottom panel. Percentage of samples with resistance gene codons.

<sup>6</sup> **Northern Savannah Region** Pagaza (PZ) in Tamale Municipality and Kpalsogou (KG) in Kumbungu district; **Central Forest Region** Duase (KD) in Konongo district; **Southern Coastal Region** Ada (AD) and Dodowa (DO). Source: Dieng CC, Gonzalez L, Pestana K, Dhikrullahi SB, Amoah LE, Afrane YA, Lo E. Contrasting Asymptomatic and Drug Resistance Gene Prevalence of *Plasmodium falciparum* in Ghana: Implications on Seasonal Malaria Chemoprevention. *Genes*. 2019; 10(7):538. <https://doi.org/10.3390/genes10070538> [Supplementary materials](#)

## Safety

Seven hundred seventy-nine individual case safety reports related to SMC treatment were available for 2015 and 2016 from the seven countries (Burkina Faso, Chad, The Gambia, Guinea, Mali, Niger, and Nigeria) where ACCESS-SMC project was implemented (Partnership 2020). Thirty-six reports were classified as serious, including one child with rash, two with fever, 31 with gastrointestinal disorders, one with extrapyramidal syndrome, and one with Quincke's oedema. All children recovered from these serious adverse events. No cases of severe skin reactions (Stevens-Johnson syndrome or Lyell syndrome) were reported. One death was reported due to suffocation from aspirating the SMC dissolved tablets after administration when the child was not fully awake. In the cohort of 10,445 children in Nigeria, the most commonly reported symptoms were fever, vomiting and diarrhoea.

Other studies (Sokhna, Cisse et al. 2008, Cisse, Cairns et al. 2009, Bojang, Akor et al. 2010, Bojang, Akor et al. 2011, Ndiaye, Cisse et al. 2011, Diallo, Diouf et al. 2014, Bonkougou, Badolo et al. 2018, Diallo, Diouf et al. 2018, Cairns, Sagara et al. 2019, Cairns, Sagara et al. 2020) conducted previously in countries where the ACCESS-SMC project was implemented similar adverse events, commonly among persons who received SP+AQ, most frequently fever, vomiting, abdominal pain. Rash and itching were less commonly reported, with no reports of Stevens-Johnson syndrome or Lyell syndrome.

In Senegal, severe adverse reactions were rare, but four deaths were reported (Sokhna, Cisse et al. 2008, Cisse, Cairns et al. 2009) due to burns, dysentery, a febrile illness characterized by vomiting and diarrhoea, a febrile illness and convulsions. The mortality rate of 2 per 1000 (4/2020) among the study children was lower than the rate of 6 per 1000 in the same age group in the rest of the

population in the demographic surveillance area during the same period (Sokhna, Cisse et al. 2008).

**Disclaimer**

The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the U.S. Centers for Disease Control and Prevention.

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## Annex: Studies included for seasonal malaria chemoprevention contextual factors data abstraction

Lead author/ Publication year	Objective(s)	Study population and age	SMC age group	Study Site(s)	Study/Data collection period	SMC drug regimen(s)	Contextual factors abstracted
<a href="#">Ansah, N.A., et al., 2016</a>	To assess the community acceptability of this intervention in addition to other malaria control measures in reducing the burden of malaria	Parents and guardians of children who received SMC and CHWs	Under five years (age not specified)	Lawra District, Upper West Region, <b>Ghana</b>	Not specified	SP+AQ 4 monthly treatment courses	Acceptability
<a href="#">Antwi, G.D., et al., 2016</a>	To assess the acceptability of the extended SMC programme and identify its facilitators and barriers	Female caregivers of who received SMC community health workers	3–59 months	Ejisu-Juaben Municipality, Ashanti Region, <b>Ghana</b>	Jan– Feb, 2013	SP+AQ five monthly treatment courses	Acceptability, Feasibility and health systems consideration
<a href="#">Ba, E.H., et al., 2018</a>	To describe findings from the pilot study, and the results on SMC delivery from the large-scale study	Children 3–59	Children 3–59 months (pilot and first year of SMC); expanded to aged 3–119 months in 2009–2010	Tivaouane (pilot), Mbour, Bambey, and Fatick Districts, <b>Senegal</b>	Sep-Oct 2006 (pilot). Sep 2008-Dec 2010	SP+AQ 3 monthly treatment courses	Coverage and equity, Acceptability
<a href="#">Barry, A., et al., 2018</a>	To determine the optimal mode of SMC delivery	Children 3–59 month	Children 3–59 months	Ouesselbouougou sub-district, Koulikoro Region, <b>Mali</b>	Jun–Oct, 2015	SP+AQ 4 monthly treatment courses	Feasibility and health systems consideration

Lead author/ Publication year	Objective(s)	Study population and age	SMC age group	Study Site(s)	Study/Data collection period	SMC drug regimen(s)	Contextual factors abstracted
<a href="#">Bojang, K. et al.2011</a>	To compare the effectiveness SMC delivery VHWs or by RCH trekking teams	3 months–6 years	3 months–6 years	Upper River Region (URR), <b>The Gambia</b>	Sept 2006 and June 2007	SP+AQ 3 monthly treatment courses	Feasibility and health systems considerations, Financial and economic costs, Safety
<a href="#">Bojang, K., et al., 2010</a>	To investigate the safety, tolerability and efficacy of SP plus AQ, SP plus piperaquine (PQ) and dihydroartemisinin (DHA) plus (PQ) for SMC	Children 6–59 months	Children 6–59 months	Basse, Upper River Region, <b>The Gambia</b>	May 2007 and Dec 2008	SP+AQ, SP+ PQ and DHA+PQ 3 monthly treatment courses	Safety
<a href="#">Bonkougou, M., et al., 2018</a>	To describe malaria morbidity and mortality following SMC implementation	General population and Children under-five years	Children 3–59 months	Boromo and Dano Health districts, <b>Burkina Faso</b>	2016 and 2017	SP+AQ	Safety
<a href="#">Cairns, M., et al., 2019</a>	To study effectiveness of SMC in two areas of intense, seasonal malaria transmission in Burkina Faso and Mali	Children 3–59 months	Children 3–59 months	<b>Burkina Faso and Mali</b>	Aug 2014 and Dec 2016	along with either azithromycin or placebo, 4 monthly treatment courses	Safety

Lead author/ Publication year	Objective(s)	Study population and age	SMC age group	Study Site(s)	Study/Data collection period	SMC drug regimen(s)	Contextual factors abstracted
<a href="#">Cairns, M.E., et al., 2020</a>	To determine the prevalence of molecular markers of parasite resistance to SP and AQ	Children 3–59 months	Children 3–59 months	Houndé, Burkina Faso and Bougouni, <b>Mali</b>	Aug 2014 and Dec, 2016	SP + AQ with either AZ or a matching AZ or placebo, 4 monthly treatment courses	Drug resistance, Safety
<a href="#">Ceesay, S., et al., 2016</a>	To measure SMC coverage at the end of transmission season	Children 0–7years	Children 3–59 months	Upper River and Central Rivers, <b>The Gambia</b>	Aug–Nov, 2015	SP+AQ 4 monthly treatment courses	Feasibility and health systems consideration
<a href="#">Chatio, S., et al., 2019</a>	This study assessed community acceptability of the SMC intervention in the Lawra district of Northern Ghana.	Parents of children who received SMC and community health volunteers who delivered SMC	Under five years (age not specified)	Lawra District, Upper West Region, <b>Ghana</b>	Not specified	SP+AQ 4 monthly treatment courses	Acceptability
<a href="#">Cisse, B., et al., 2009</a>	To compare the acceptability, efficacy and safety of combining PQ with SP and compared this combination with DHA+PQ and sulfalene-pyrimethamine plus AQ	Children 3–59 months	Children 3–59 months	Ndoffane district, <b>Senegal</b>		SP+AQ, DHA+PQ or SP+PQ three monthly courses	Drug resistance, Safety

Lead author/ Publication year	Objective(s)	Study population and age	SMC age group	Study Site(s)	Study/Data collection period	SMC drug regimen(s)	Contextual factors abstracted
<a href="#">Compaore, R., et al., 2017</a>	To assess the implementation fidelity of the seasonal malaria chemoprevention strategy in one of the districts, Kaya Health District	Children 3–59 months	Children 3–59 months	Kaya Health District, <b>Burkina Faso</b>	2014 and 2015	SP+AQ 4 monthly treatment courses (three in 2014)	Acceptability
<a href="#">Conteh, L., et al., 2010</a>	To determine the costs associated with SMC delivery via community-based volunteers and potential savings to health care providers and caretakers due to malaria episodes averted	3–59 months	3–59 months	Hohoe district, <b>Ghana</b>	April to September 2005	(i) SP every two months, (ii) AS+AQ every two months (iii) AS+AQ every month	Financial and economic costs
<a href="#">Diallo, I., et al., 2014</a>	To describe adverse events recorded by pharmacovigilance system implemented during SMC campaign in 2013	Under 10 years	Not specified	<b>Senegal</b> (sites not specified)	2013	SP+AQ	Drug resistance, Safety
<a href="#">Diallo, I., et al., 2018</a>	To describe adverse events recorded by pharmacovigilance system implemented during SMC campaign in 2013	Under 10 years	Children 3 months–10 years	<b>Senegal</b> (sites not specified)	2013–2017	SP+AQ	Safety

Lead author/ Publication year	Objective(s)	Study population and age	SMC age group	Study Site(s)	Study/Data collection period	SMC drug regimen(s)	Contextual factors abstracted
<a href="#">Diarra, Y., et al., 2010</a>	To examine the frequency of quintuple mutants in the <i>Pf dhfr</i> and <i>Pf dhps</i> genes and to identify potential new mutations	Children and pregnant women	Children 3–59 months	Mali	2018	Not specified	Drug resistance
<a href="#">Dieng, C.C., et al., 2019</a>	To estimate the prevalence of asymptomatic <i>P. falciparum</i> and different molecular methods in identifying asymptomatic infections	Children 5–14 years	Children 5–14 years	Three ecological zones of Ghana.	Jun–Sep of 2017	Not specified	Financial and economic costs
<a href="#">Druetz, T., 2018</a>	To assess the effectiveness of SMC at reducing the prevalence of malaria and anemia in 6–59 months, using data from the 2015 malaria indicator surveys (MIS) in Mali	Children 3–59 months	Children 3–59 months	Mali	Sept-Nov, 2015	SP+AQ 3 monthly treatment courses	Coverage and equity
<a href="#">Fabrice, S.A., et al., 2011</a>	To assess the baseline prevalence and selection of common SNPs associated with AQ and SP resistance	Children 3–59 months	Children 3–59 months	Bobo-Dioulasso, Burkina Faso	Nov 2009 (one month after the third treatment course)	SP+AQ 3 monthly treatment courses or monthly dihydroartemisinin-piperaquine (DP)	Drug resistance

Lead author/ Publication year	Objective(s)	Study population and age	SMC age group	Study Site(s)	Study/Data collection period	SMC drug regimen(s)	Contextual factors abstracted
<a href="#">Grais, R.F., 2018</a>	To study the prevalence of <i>pfdhfr</i> , <i>pfdhps</i> and <i>pfmdr1</i> genes mutations associated with resistance to SP and AQ	Children 6–59 months	Not specified	Gabi, Madaroun fa district, Maradi Region, <b>Niger</b>	2011–2012	Not specified	Drug resistance
<a href="#">Issiaka, D., et al., 2015</a>	To determine the optimal mode of SMC delivery	Children 3–59 months	Children 3–59 months	Ouelessebougou sub-district, Koulikoro Region, <b>Mali</b>	Jun–Oct, 2014	SP+AQ 4 monthly treatment courses (three in 2014)	Feasibility and health systems consideration
<a href="#">Kaly, J.S., et al., 2018</a>	To assess knowledge, attitudes and practices of mothers or guardians	Parents of children aged 3–120 months who participated in the SMC	3–120 months	Bounkilin g Health District, <b>Senegal</b>	Dec 2015 (SMC conducted Sep–Nov, 2015)	SP+AQ 3 monthly treatment courses	Coverage and equity
<a href="#">Kombate, G., et al., 2019</a>	To assess the quality of SMC provided by community health care provider	CHWs providing SMC	Children 3–59 months	Boulsa health district, <b>Burkina Faso</b>	Jul, 2017	SP+AQ 4 monthly treatment courses	Feasibility and health systems considerations
<a href="#">Kpormegbe, S.K. and C.K. Ahorlu, 2014</a>	This study investigated the role community participation play towards the success of SMC	Caregivers of under five years old, community assistants (who delivered SMC) and opinion leaders	6–60 months	Shime sub-District, Keta District, <b>Ghana</b>	Not specified.	AQ+AS, 4 monthly treatment courses	Acceptability, Feasibility and health systems considerations



Lead author/ Publication year	Objective(s)	Study population and age	SMC age group	Study Site(s)	Study/Data collection period	SMC drug regimen(s)	Contextual factors abstracted
<a href="#">Kweku, M., et al., 2009</a>	Evaluation of approaches to the deliver SMC in Ghana. (community- and facility-based)	Children 3–59 months	Children 3–59 months	Jasikan district, <b>Ghana</b>	May to October 2006	SP+AQ 4 monthly treatment courses	Coverage and equity; Feasibility and health systems considerations
<a href="#">Mahamar, A., et al., 2019</a>	To genotype the frequencies of molecular markers of resistance to SP and AQ before and after SMC implementation	Under 5 years of age	Children 3–59 months	Ouelessebougou, <b>Mali</b>	2014 and 2016	SP+AQ	Drug resistance
<a href="#">Maiga, H.I., et al., 2018</a>	To monitor the prevalence of Pfdhfr+Pfdhps+pfcrt+pfmdr1 mutations	Children 3–59 months (before and after SMC): non-SMC population aged 7 years or above (after SMC implementation)	Children 3–59 months	Koutiala District, <b>Mali</b>	Aug 2012 and Jun 2014	SP+AQ 3 monthly treatment courses	Drug resistance, Safety
<a href="#">Ndiaye, J.L.A., et al., 2011</a>	To evaluate the safety and effectiveness of SMC when delivered by district health staff on a large scale in three rural districts in Senegal	Not specified	Not specified	<b>Senegal</b>	2008-2010	SP+AQ	Safety

Lead author/ Publication year	Objective(s)	Study population and age	SMC age group	Study Site(s)	Study/Data collection period	SMC drug regimen(s)	Contextual factors abstracted
<a href="#">Ndiaye, M., et al., 2011</a>	To examine the frequency of SP-resistant related haplotypes in the Plasmodium falciparum genes, <i>Pfdhfr</i> and <i>Pfdhps</i>	Under five years	Not specified	Southern Senegal	2010	Not specified	Drug resistance
<a href="#">Ndiaye, M., et al., 2013</a>	To examine the frequency of SP-resistant related haplotypes in the Plasmodium falciparum genes, <i>Pfdhfr</i> and <i>Pfdhps</i>	Under 5 years of age	Not specified	Southern Senegal	2010 and 2011	Not specified	Drug resistance
<a href="#">Ndiop, M., et al., 2017</a>	To analyze routine malaria information system data, in three regions that received SMC		Children 3–59 months	Senegal	2013 to 2016	SP+AQ 4 monthly treatment courses	Coverage and equity
<a href="#">Nonvignon, J., et al., 2016</a>	To estimate the cost-effectiveness of seasonal malaria chemoprevention	Under-5 years	Under-5 years	Upper West Region, Ghana	Jun–Sep, 2015	SP+AQ 4 monthly treatment courses	Financial and economic costs
<a href="#">Oresanya, O.B., et al., 2019</a>	To ascertain the quality and effectiveness of CHWs' performance and SMC messaging	Caregivers of under-fives	Children 3–59 months	Northern, Nigeria (site not specified)	2018	SP+AQ 3 monthly treatment courses	Feasibility and health systems consideration

Lead author/ Publication year	Objective(s)	Study population and age	SMC age group	Study Site(s)	Study/Data collection period	SMC drug regimen(s)	Contextual factors abstracted
<a href="#">Partnership, A.-S, 2020</a>	Evaluation of SMC coverage, effectiveness of the intervention, safety, feasibility, drug resistance, and cost-effectiveness.	Children 3–59 months, Individuals aged 10–30 years not receiving SMC	Children 3–59 months	<b>Burkina Faso, Chad, The Gambia, Guinea, Mali, Niger, and Nigeria</b>	2015 and 2016	SP+AQ 4 monthly treatment courses	Coverage and equity, Financial and economic costs, Drug resistance, Safety
<a href="#">Patouillard, E., et al., 2011</a>	To determine the costs of delivering SMC by OPD or EPI nurses or by VHWs	Children 3–59 month	Children 3–59 month	Jasikan district, Volta region, <b>Ghana</b>	Jun 2005-Dec 2006	SP+AQ 3 monthly treatment courses	Financial and economic costs
<a href="#">Pitt, C., et al., 2012</a>	To assess community perceptions of and recommendations for SMC.	Caregivers of under five years old and Community Health Workers (CHWs)	3–59 months	<b>Burkina Faso and Mali</b>	Mali: May to July 2009. Burkina Faso: June to August 2009 (six to nine months following implementation )	SP+AQ 3 monthly treatment courses	Acceptability, Feasibility and health systems consideration
<a href="#">Pitt, C., et al., 2015</a>	To ascertain the incremental financial and economic costs of delivering	3–119 months	3–119 months	Bambey, Mbour, Fatick and Niakhar Districts, <b>Senegal</b>	2010		Financial and economic costs
<a href="#">Pitt, C., et al., 2017</a>	To assess costs of door-to-door SMC delivery to up to 10 years by CHWs.	Children 3–119 months	Children 3–119 months	Bambey, Mbour, Fatick and Niakhar Districts, <b>Senegal</b>	2008–2010.	SP+AQ 4 monthly treatment courses	Financial and economic costs

Lead author/ Publication year	Objective(s)	Study population and age	SMC age group	Study Site(s)	Study/Data collection period	SMC drug regimen(s)	Contextual factors abstracted
<a href="#">Shehu, U.L., 2012</a>	To assess and compare malaria preventive practices and acceptability of seasonal malaria chemoprevention	Caregivers of under five years old or head of households	Under-five (age not specified)	Gwale and Gezawa districts of Kano state, <b>Nigeria</b>	2017	SP+AQ	Acceptability
<a href="#">Sokhna, C., 2008</a>	To compare four SMC treatment regimens	Children 6–59 months	Children 6–59 months	Niakhar District, <b>Senegal</b>	Jul and Aug, 2004	<sup>7</sup> See footnote	Drug resistance, Safety
<a href="#">Some, A.F., et al., 2014</a>	To compare SNP prevalence before the onset of SMC and 1 month after the third treatment in <i>P. falciparum</i> PCR-positive samples	Children 3–59 months who received SMC and who did not receive SMC (controls)	Children 3–59 months	Lena District, <b>Burkina Faso</b>	Aug 2009 and Nov, 2009	SP+AQ or DP, 3 monthly treatment courses	Drug resistance

<sup>7</sup> SP+AS for 1 day, 1 treatment course; SP+ AS for 3 days, 1 treatment course; SP+AQ given for 3 days, one treatment course; AQ+AS for 3 days (3AQ+3AS) one treatment course