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Current strategies of Seasonal Malaria Chemoprevention, its challenges, and alternatives

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Summary

Malaria is a disease that occurs in tropical regions of the world, and particularly affects countries with a low and medium socioeconomic status. Malaria infection is caused by a single-celled blood parasite, a protozoan, named *Plasmodium spp.*, and humans are infected through the bites of female Anopheles mosquitoes. For many years, the control of malaria has been a global health priority and, because of international efforts, the incidence of malaria reduced from 81 cases per 1000 population at risk in 2000 to 56 in 2019. However, the burden of malaria remains very high. In 2020, an estimated 228 million cases occurred in Sub-Saharan Africa, which accounted for around 95% of worldwide cases. Children under the age of 5 years make up 80% of all malaria deaths in Sub-Saharan Africa.

Within Sub-Saharan Africa lays the Sahel region, where malaria transmission is moderate to high. This region is characterized by seasonal malaria transmission, that is, malaria cases increase during the rainy season, which occurs during some months of the year. Here, seasonal malaria chemoprevention (SMC) has been recommended in children aged three to 59 months by the WHO since 2012. It has been implemented in 13 countries so far, and continues to expand in higher capacities. The WHO recommendation for SMC consists of a monthly administration of a combination of two drugs named SP+AQ: sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ) for 4 consecutive months, providing therapeutic concentrations in the blood during the high transmission period. Clinical trials have shown good evidence on the efficacy of SMC leading to a reduction of clinical malaria cases in children under five years old. However, some questions and challenges remain for its application in large-scale settings.

The present review aims to give an overview of the current drug used for SMC, namely SP+AQ, and identify potential alternative drug combinations. For this purpose, three research databases were used. Articles were screened and selected through specific inclusion and exclusion criteria. Data were collected from each study, summarised, and compared. The results show that the protective efficacy of SP+AQ against clinical malaria ranged from around 60% to 85%. Vomiting was the most common adverse reaction, and only a low number serious adverse effects were observed. The presence of *P. falciparum* resistant genes that are associated with treatment failure was generally low. Among other three drug combinations, DHA+PQ (dihydroartemisinin-piperaquine) was identified as the second most studied and promising drug combination, and results show that it confers a protective efficacy of 74%, is well tolerated by children, and the frequency of resistant genes is even lower when compared to the currently used SP+AQ.

Overall, SMC with SP+AQ was found to be an effective tool for malaria control, when used in children younger than five years old in countries in the Sahel. This review identified some drawbacks, such as cases of low compliance, underreporting of adverse effects, and risk of resistance development, as well as the already existing resistance to antifolates (SP) in areas outside the Sahel region. Therefore, it will be important to continue monitoring the possible adverse effects, in combination with training health care workers to better recognise them, and to establish effective surveillance programs for monitoring the presence of resistance, in addition to finding new drug alternatives. Moreover, various studies showed that expanding SMC programmes to include a wider age-range in children and administering SMC during more than four months of the year could be beneficial in reducing malaria cases. As three

trials suggested, DHA+PQ seems to be an appropriate alternative combination, especially in locations where it might not be suitable to use SP+AQ due to increasing resistance. However, further studies are needed to assess DHA+PQ's efficacy and coverage when implemented at a larger scale, in order to fully evaluate its potential as an alternative treatment combination for SMC.

Abstract

Seasonal malaria chemoprevention (SMC) is a malaria control measure implemented in children aged between three and 59 months old, in countries of the Sahel region in Africa, which are characterised by highly seasonal transmission. A combination of sulfadoxine-pyrimethamine and amodiaquine (SP+AQ) is used monthly during four consecutive rounds. Clinical trials have shown suitable evidence on the efficacy of SMC.

This review aims to provide an overview of the effectiveness and pitfalls of SMC, focusing on SP+AQ, and explore potential SMC drug combination alternatives. For this purpose, three databases were used. Articles were identified and selected through a screening process with inclusion and exclusion criteria, based on the PRISMA statement. Data were extracted from each full text article included in the review. Parameters included were malaria prevalence, incidence, mortality, anaemia status, and gametocytaemia, depending on the measurements and outcomes of each study. Details on adverse reactions and resistance markers were also collected. A final total of 31 articles were included in the review.

SP+AQ conferred a protective efficacy against clinical malaria ranging from around 60% to 85% over 28 days, in five- to 59-month-olds. The drug combination was found to be well tolerated with low number of serious adverse effects, and vomiting was the most commonly reported reaction identified in this review. The presence of *P. falciparum* resistant genes (*Pfmdr1*, *Pfdhps* and *Pfdhfr*) was generally low throughout all studies. Dihydroartemisinin-piperaquine (DHA+PQ), which is already approved for treatment of uncomplicated malaria, was the second most studied drug combination. It conferred a protective efficacy against clinical malaria cases of 74% within 4 weeks post drug administration. It was also well tolerated, with no serious adverse effects reported, and the frequency of resistance genes was lower compared to that of SP+AQ.

Overall, SP+AQ is a drug combination that is effective at reducing malaria prevalence and incidence in children under five years of age, in areas of seasonal malaria transmission. It is however important to maintain efficient surveillance systems to continuously monitor the presence of resistance and drug safety. Extending SMC implementation to include older children and more numbers of rounds proved to be beneficial based on various trials. In areas where SP+AQ might not be suitable due to development of resistance, DHA+PQ appears to be an appropriate alternative. Additional studies would be valuable to further assess DHA+PQ's efficacy and coverage when implemented at a larger scale, in order to evaluate its potential usage for SMC.

1. Introduction

Malaria is a parasitic and vector-borne disease that mostly affects countries with low and medium socioeconomic status in the tropical areas of the world. The disease is caused by a protozoan, *Plasmodium spp.*, which is transmitted to humans through an *Anopheles spp.* mosquito bite. There are four known species of *Plasmodium spp.* that infect humans, *Plasmodium falciparum* being the most severe. Additionally, one species of zoonotic malaria transmitted from monkeys to humans, *P. knowlesi*, occurs in regions of South East Asia. The disease can manifest asymptotically, as well as present nonspecific general symptoms in its uncomplicated form, such as fever, sweating, vomiting and diarrhoea. The symptoms of the most severe form of disease, also known as complicated malaria, include severe anaemia and organ failure, which can culminate in coma (cerebral malaria) and death (1,2).

The highest burden of malaria, and subsequently *P. falciparum*, is present in Sub-Saharan Africa (1–3). In this region, in 2020, an estimated 228 million cases occurred, which accounted for around 95% of global cases. An increase in case incidence from 222 cases per 1000 population at risk in 2019 to 233 in 2020 has been reported due to service disruptions related to the SARS-CoV-2 pandemic (3). Children under five years old are particularly affected (1–3) and represented 80% of malaria deaths on the African continent (3). Furthermore, children older than six months of age are at higher risk due to the loss of maternal antibodies. If infection is overcome at a young age, older children and adults will acquire partial immunity due to repeated exposure to malaria (2).

Among several control methods for malaria, and to reduce the risk of *P. falciparum* infection and disease in young children, the World Health Organisation (WHO), in October 2021, recommended the usage of the RTS,S vaccine in children from 5 months of age, in areas of moderate to high transmission (3). Since 2010, chemoprevention approaches have been endorsed for the same purpose. The word chemoprevention is an umbrella definition that includes both seasonal malaria chemoprevention (SMC) in children aged three to 59 months (previously known as intermittent preventive treatment – IPTc) (4) and intermittent preventive treatment in infants aged up to 12 months (IPTi) (3,5). Intermittent preventive treatment (IPT) can be defined as “the administration of a full curative dose of an antimalarial or antimalarial combination to a selected, target population at specified times without determining whether or not the subject is infected” (6). Other approaches that could fall under the chemoprevention umbrella, such as intermittent preventive treatment in school children ranging from five to 18 years old (IPTsc) and intermittent preventive treatment post-discharge (IPTpd) are still under consideration for malaria prevention in children by the WHO (5). The present review will focus on SMC (or IPTc) in children between three and 59 months old.

IPTi was first endorsed by the WHO in 2010 (7). IPTi is administered in sub-Saharan African countries where transmission is moderate to high. Sulfadoxine-pyrimethamine (SP) is the drug of choice and is given three times in the first year of life with routine vaccination programmes, in areas in which increased parasite resistance to the drug does not occur (7,8).

In 2012, the WHO recommended SMC/IPTc in the Sahel sub-region (4), an area where malaria transmission is moderate to high. The Sahel is a semi-arid region in Sub-Saharan Africa, between the Sahara Desert in the north and the Savanna plains in the south, extending from west to east across the continent (9). This region is characterised by highly seasonal

malaria transmission dynamics (1,2,6). Normally, an increase in malaria cases starts a few weeks after the start of rainy season (1,2). Of the 11 countries with the highest worldwide burden of malaria (3), six of them are situated within this region, experiencing seasonal malaria. Following WHO's recommendation, several countries established delivery programmes. By 2020, 13¹ countries in the Sahel region were included, with about 35 million children receiving at least one round of SMC (compared to 0.2 million in 2012) (3).

The drug recommended for SMC is a combination of sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ) (SP+AQ). The WHO's advice is to implement SMC at the start of the transmission season in areas where 60% of malaria cases occur within four months of the year, and where the combination drug should have at least more than 90% therapeutic efficacy (4,10). Therefore, SP+AQ is given once monthly for those consecutive months in the year, until children reach five years (59 months) of age, with the goal of providing therapeutic concentrations in the blood during the high transmission period (4,10).

Prior to WHO endorsement, clinical trials were conducted (11–22) to study the efficacy of SMC/IPTc on incidence of malaria, as well as the safety of SMC and additional protection to other control measures in several countries in the Sahel in children under five years of age. The main drug studied in these trials was SP+AQ, with a small number of studies including 3 other drug combinations. SMC has been found to be an effective measure for control of malaria in highly seasonal transmission settings in this age group (23,24). Wilson (2011) and Meremikwu *et al.* (2012) carried out a systematic review and meta-analysis for these clinical trials, and found robust evidence that administration of SMC decreased clinical seasonal malaria cases when compared to placebo, in children under five years old (23,24). Differences were found in SMC efficacy between clinical trials (23,24), which could be related to the administration of different drugs, as well as to differences in transmission patterns between countries and regions (24). Additionally, no serious adverse effects were documented (23,24).

Despite clinical trials showing evidence on the efficacy of SMC, various challenges have been encountered. SMC is currently administered with monthly doses of treatment, which not only needs good resources and infrastructures, but can also potentially lead to a lack of compliance to complete the treatment course, which consists of one dose of SP and three consecutive daily doses of AQ. This reduced compliance to the three day treatment, could lead to sub-optimal drug concentration. Thus, contributing to a fast-tracked development of resistance, which is a great concern as the protective effect of SMC could potentially decline (25). Furthermore, apart from the Sahel region, areas of southern Africa were identified as candidates where SMC could be appropriate for malarial control. However, there is known resistance to antifolates, such as SP, in these areas (26). Effectiveness of SMC could potentially be reduced due to issues that might arise with the delivery, administration of the drugs, and adherence to the complete treatment, when SMC is implemented as an antimalarial programme at a larger scale. Therefore, it is of importance that additional research is conducted to identify potential alternative drug combinations, as well as to evaluate and monitor effectiveness of SMC programmes over time.

¹ The 13 countries are: Benin, Burkina Faso, Cameroon, Chad, Gambia, Ghana, Guinea, Guinea-Bissau, Mali, Niger, Nigeria, Senegal, Togo.

Through a systematic literature review, the aim of this study is to first provide an overview of the effectiveness and pitfalls of SMC, focusing on SP+AQ, which is the main drug combination used and recommended by the WHO. The identified literature will particularly be analysed for the effectiveness and pitfalls for different geographical settings, treatment intervals, dosing strategies, delivery strategies, adverse events, and resistance markers. Furthermore, an exploration will be presented on potential SMC combination alternatives to overcome the most common pitfalls of SP+AQ, as SMC has proven an effective strategy for malaria prevention in children under five years old, one the highest risk groups for this disease.

2. Methods

A systematic literature search was conducted on January 17th, 2022 in three online search databases: Embase (27), PubMed (28) and Web of Science (29). A combination of the search terms “seasonal”, “malaria”, “chemoprevention”, “chemoprotection” and “intermittent preventive treatment” was used, with the term “pregnancy” for exclusion (See Supplementary Table 1 for literal search queries per database). Only articles in English were selected from the search output, and no date limits were used. The selection of articles was based on the PRISMA statement. It stands for The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) and it is a set of guidelines to help researchers write a transparent review (30,31). It was used in the present report to help guide the choice and selection of articles.

All articles were uploaded in an EndNote database (EndNote version X9 (The EndNote Team, 2013) (32). The literature search was followed by four selection steps within EndNote. Firstly, deduplication of articles was completed using the EndNote deduplication tool, to remove any duplicate articles identified by the different databases. Secondly, the titles and abstracts were screened using the inclusion and exclusion criteria described below. Thirdly, full text articles were assessed according to inclusion and exclusion criteria. All excluded articles were categorised and saved in separate folders. Lastly, using the snowballing method, references within the final selected set of articles were also screened using the same inclusion criteria to add any relevant references that had not appeared in the original search.

The **inclusion criteria** for the review were: i) the study was conducted in Sub-Saharan Africa, ii) the study included seasonal malaria treatment with monthly drug administrations, iii) study main endpoint was incidence and/or prevalence of malaria, and iv) the study population included children between three months and five years of age. Studies that reported on an older age range were still included in the review, if data on children under five years old were also present. Only research articles were included.

The **exclusion criteria** include: i) study population older than five years of age, ii) studies with children with comorbidities (e.g., anaemia, HIV, sickle cell anaemia, malnutrition), iii) the study reported on IPTi, iv) studies reporting on non-seasonal administration of IPT, v) studies reporting on other malaria control measures (e.g., vaccination, mosquito nets, among others), vi) studies reporting on malaria treatment/drug mass administration (and not chemoprevention) or IPT post-discharge, vii) studies reporting on malaria epidemiology, viii) studies that uniquely reported on immune response and resistance development while receiving SMC/IPTc, ix) modelling studies, x) studies reporting on exclusively on cost-

effectiveness, xi) qualitative studies solely on people's perceptions of SMC/IPTc , and xii) studies reporting on other diseases or unrelated topics to malaria. Additionally, any article that evaluated intermittent preventive treatment in pregnancy (IPTp) that might have appeared in the original search, was excluded. Conference/meeting abstracts and papers, editorials, notes, letters, and proposals were also excluded.

Data were extracted from each full text article included in the review. The following information was collected: i) general details, such as author, country, and type of study, ii) information on SMC implementation, such as target population, drugs used, and delivery methods, and iii) information on effectiveness of the programme. Effectiveness measures differed per study, parameters included were morbidity and mortality, hospitalisations, anaemia status, fever status and gametocytaemia. Adverse reaction and resistance markers details were also collected when reported. An overall overview of all available treatments was created and a more detailed compilation of data from each individual study was presented in the Supplementary materials.

Afterwards, to achieve the first aim of the current review, SP+AQ characteristics found in the literature were summarised and compared between studies to analyse its effectiveness and identify pitfalls of the combination drug applied in SMC. To answer the second research question, characteristics of different drugs, mainly focusing on DHA+PQ, were similarly summarised and analysed to identify if these can be potential SMC alternatives and overcome the pitfalls of SP+AQ.

3. Results

The database search resulted in a total of 1339 records identified (Embase 496, PubMed 306, Web of Science 537). After deduplication (n = 659) and title/abstract screening using the inclusion and exclusion criteria, 61 full text articles remained for further screening. After screening of 61 full text articles using the inclusion and exclusion criteria, and literature snowballing, a final total of 31 articles were included in the present review (Figure 1).

In total, 55% (n = 17) were interventional studies, 32% (n = 10) observational studies, and 13% (n = 4) of studies reported on original interventional studies. All studies but two were conducted and/or reported in West African Countries (Senegal, Burkina Faso, Ghana, The Gambia, Guinea, Mali, Niger, Nigeria). The two exceptions reported on Central Africa (Chad). All of these countries are situated in the Sahel and sub-Saharan region with highly seasonal malaria transmission. The baseline prevalence of malaria in the study regions prior to the study was not reported by all papers. The entomological inoculation rate (EIR) was used in several studies, and ranged from one to 177 infective bites per person per year in The Gambia (20), 173 in Burkina Faso (13), ten in Senegal (11), and up to 60 in Mali (33). Supplementary Table 2 shows the detailed general characteristics for each of the 31 studies included in the present review.

For 68% (n = 21) of articles, SMC's target population was children between three and 59 months old. Two studies (6%) also included two month old children, and two further studies (6%) started the age range at six-months-old. Additionally, two studies extended the children's

age until 72 months, and four studies (13%) included children receiving SMC until 10 years of age (34–37).

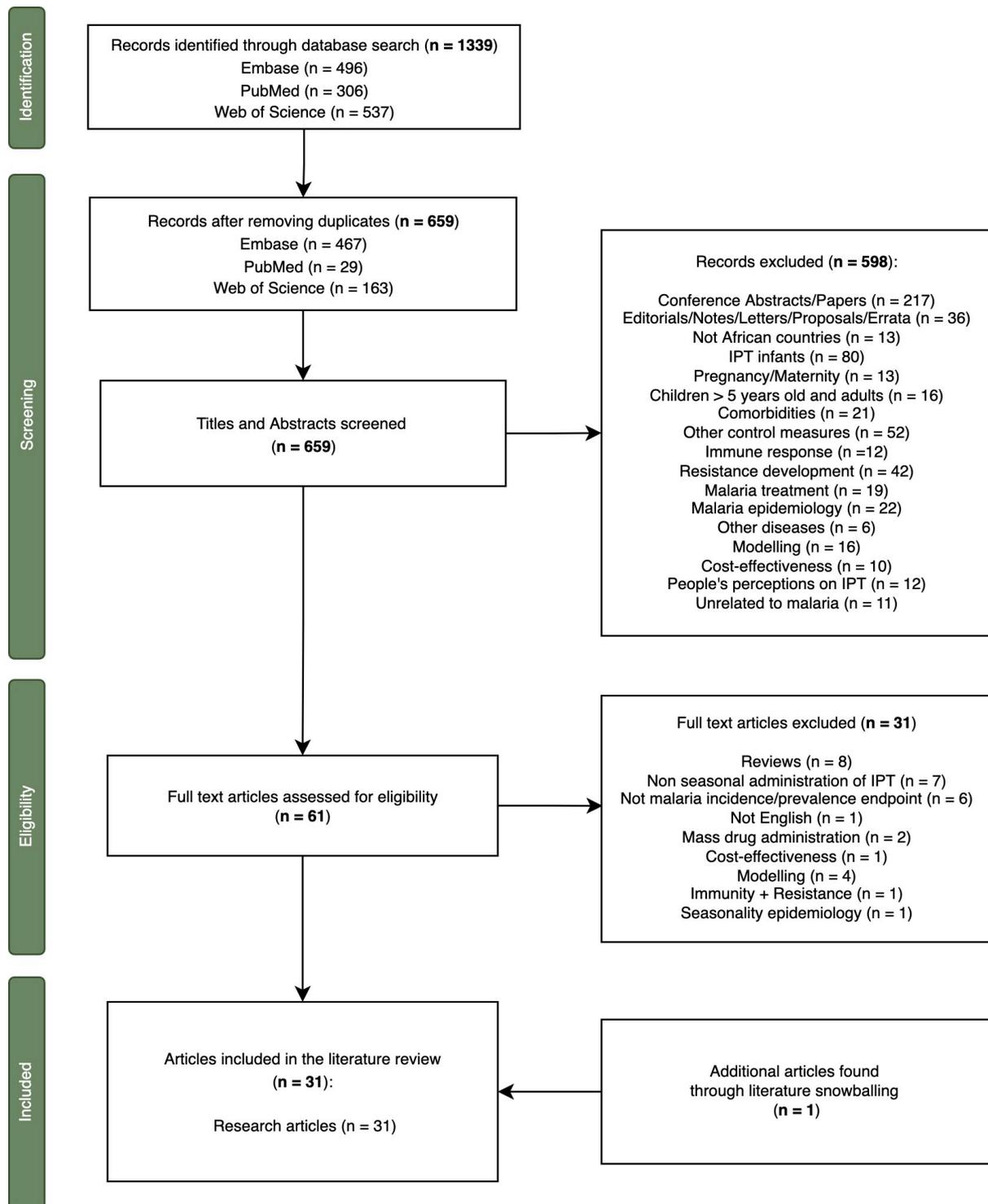


Figure 1 – PRISMA flow diagram for study selection process.

Regarding the intervention drugs used for SMC, the main combination used was SP+AQ, with 27 studies reporting use of this drug combination. Three clinical trials included

dihydroartemisinin-piperazine (DHA+PQ) (17,19,38), two trials sulfadoxine-pyrimethamine with piperazine (SP+PQ) (17,19), two further studies sulfadoxine-pyrimethamine with artesunate (SP+AS) (11,15), and one study the combination of amodiaquine with artesunate (AQ+AS) (15). Trials were in Phase II/III for DHA+PQ (17,19,38), SP+PQ (17,19), and SP+AS (11,15). AQ+AS combination was studied in a Phase III trial (15). The main combination SP+AQ was studied in both Phase III and IV trials (18,21,36,37,39).

All these combinations are recommended by the WHO, and included in the WHO Guidelines for Malaria. DHA+PQ, AQ+AS, and SP+AS, all artemisinin-based combinations, are used as treatment for uncomplicated malaria in children. SP+AQ is recommended for SMC (40). SP+PQ combination is not licensed (17) and not included in the WHO Guidelines for Malaria (40).

Both clinical trials and observation studies reported on monthly rounds of SMC. The number of SMC rounds per season ranged from two in one trial (34) to five in two articles (37,39). Most of studies included three (n = 15) or four (n = 12) rounds of treatment.

Overall, there were two main delivery methods for SMC. Firstly, all drug doses were administered at a fixed point, which could be in the community (delivered by a community health worker), or at the health centre by a health worker and/or nurse (facility-based delivery), or study centre by trial staff and/or nurse. Secondly, the first dose was administered by a nurse, health worker, or study staff at a fixed point or door-to-door, and the following doses were given by caregivers at home. Usually, all these administrations were registered in a card that parents would keep, in order to know how many doses and rounds of SMC the child received. In a trial environment, when the drugs were administered by study staff, then field workers at home, all doses received were supervised, therefore all children received the treatment (38). Two studies compared delivery by the community health care workers and by health centres, and both methods were effective. However, the community based method was slightly more effective (18,21).

The WHO has an age-based dosing recommendation for SP+AQ. WHO recommends a single oral dose of SP in the strength 500/25mg and of 153mg AQ. Children between three and 11 months old receive half tablet, and children between 12 and 59 months old receive one full tablet (10). In the present review, most studies (n = 15) followed the WHO's recommendation with regards to drug dosing of SP+AQ, and followed an age-based dosing. Studies including children up to ten years old increased the dosing to 1½ tablets of each drug for children between six and ten years old (34,35,37). This dosing schedule for older children seemed to decrease the possibility of overdosing and underdosing. Contrarily, in some trials (n = 8) the drug dosing scheme was based on weight. The remaining eight studies, mostly observational, did not specify the dosing used. Tables 1 and 2 show the general dosing for each drug combination.

Most studies reported on any malaria control measures used in addition to SMC. Bed nets (insecticide treated nets – ITN or long-lasting insecticide treated nets – LLIN) usage ranged from below or around 30% (11,15,17,18,38), between 60%-70% (19,21,36,41–43), and up to 80-95% (20,34,37,39,44–48) in the study areas. Studies in which bed nets were provided to participants, the usage was higher, around 95-99% (13,22,33,49). Additionally, indoor residual spraying (IRS) of insecticide was reported as an extra control measure in four articles (33,43,47,50). Older studies (up to 2010) reported no difference in SMC efficacy between

children that slept under a bed net and the ones who did not. However, in these studies bed net usage was low and nets were found in poor conditions (11,15,17). Two of the studies reviewed evaluated the interaction between LLINs and SMC, and indicated that SMC provides additional protection against clinical malaria in children who slept under a LLIN (13,22). Furthermore, it was suggested that the combined usage of SMC, IRS and LLIN is more effective than each individual measure (33,43).

In most trials and observational studies, if children presented malaria symptoms prior to SMC administration, malaria diagnosis was pursued via rapid diagnostic test and confirmed with blood smear. If the child was diagnosed with a case of clinical malaria, SMC was not given, instead malaria treatment was administered. In older studies (before 2010), a combination of artesunate and amodiaquine was used to treat malaria (17,18). In more recent studies which reported on malaria treatment, the drug used was lumefantrine-artemether. According to the WHO, throughout the period of SMC and where it is implemented, treatment of malaria infections should not include SP or AQ (which are not artemisinin derivatives). Artemisinin based combinations that are effective for treatment of clinical malaria should instead be used in these settings (10,40).

SP+AQ was the most studied SMC drug combination in trials and assessed in observational studies. Within the 27 studies, study outcomes differed slightly, reporting on protective efficacy (PE) expressed as a reduction of parasitaemia levels, incidence, and/or prevalence. Detailed values can be consulted in the Supplementary Table 3 of the present report. PE was mostly evaluated for parasitaemia $\geq 5000/\mu\text{l}$ or any parasitaemia. Overall, SP+AQ was found to be a highly effective intervention for prevention of malaria infection over the four week period between rounds of SMC. SP+AQ's PE from clinical malaria with any parasitaemia ranged from around 60% to around 85% when measured within 28 days after SMC administration (13,21,22,34,35,38,44). One trial with five rounds of SMC with SP+AQ reported a PE for the overall rounds of 48%. The authors report a low coverage of all five SMC cycles as well, which could account for the low PE achieved (39). PE 42 days after SMC administration was found to be lower across studies, decreasing from 88% to 61% (45,48). The PE of monthly SMC against severe malaria ranged from 48% (47), 69% (13), to 87% (22). Together, these findings suggest that SP+AQ remains effective at both preventing clinical cases of malaria and severe disease for the duration of the period between SMC rounds, with decreasing PE in the weeks following. Studies that included children up to ten years of age reported high levels of PE in this age group, suggesting that SP+AQ is also effective at preventing infection in older age groups. It ranged from 61% (36) to 83% (37) in children between five and ten years old.

DHA+PQ followed as the most evaluated alternative to SP+AQ, although only three studies reported on this combination. Overall, DHA+PQ had a PE with any parasitaemia of 74% for clinical malaria. Both prevalence and incidence of malaria remained similar to SP+AQ, and the duration of the protection conferred by both combination treatments was maintained for four weeks, followed by a decrease in DHA+PQ's PE to around 50% at 5 weeks after treatment (38). The two remaining studies which reported on DHA+PQ did not include a control group; therefore, efficacy was not determined. However, results in prevalence and incidence of malaria were similar between DHA+PQ and SP+AQ groups (17,19).

Table 1 – Overview of SMC drug combination SP+AQ and alternative DHA+PQ.

Drug combination	SP+AQ	DHA+PQ
Drug regimen	Day 1: 1 SP + 1 AQ Day 2: 1 AQ Day 3: 1 AQ	Day 1: 1 DHA+PQ Day 2: 1 DHA+PQ Day 3: 1 DHA+PQ
Dosing target	SP 25/1.25 mg/kg AQ 10 mg/kg	DHA 4 mg/kg PQ 18 mg/kg
Protective efficacy	Any parasitaemia: 60% to 85% Within 28 days: 88% Between 29 to 42 days: 61%	Malaria parasitaemia \geq 3000/ μ l: 79% Any parasitaemia: 74% Within 4 weeks after SMC
Parasitaemia prevalence	Reduction of prevalence and lower prevalence when compared to control groups	Similar prevalence to SP+AQ.
Anaemia prevalence	Lower prevalence when compared to control groups, but also no significant difference in some cases.	Similar prevalence to SP+AQ.

The combination of SP+PQ was evaluated in only two studies as previously mentioned. Both studies reported low malaria prevalence and incidence at baseline but indicated this combination to be equally as effective as SP+AQ (17,19). For detailed values of prevalence and incidence in each study and for each drug, see Supplementary Table 3. In a non-inferiority analysis (that is, a study to test if one treatment is not less effective than the treatment it is compared to), which compared SP+AQ, DHA+PQ and SP+PQ, Cissé et al. (2009) reported that both combinations containing PQ were non-inferior to SP+AQ (95% confidence interval) (17).

When comparing SP+1AS and SP+3AS, the latter (which includes receiving 3 consecutive doses of artesunate) seemed more effective in lowering parasitaemia levels, prevalence, and incidence. Both SP+1AS and SP+3AS resulted in a lower haemoglobin concentration, which could confer less protection against anaemia, when compared to groups receiving SP+AQ or AQ+AS. Among all 4 combinations in the study, SP+3AQ was the most effective when considering incidence of clinical malaria (SP+3AQ: 4.9%, SP+1AS: 9.5%, SP+3AS: 8.7%, 3AQ+3AS: 10.8%) and malaria prevalence (15).

Coverage of SMC, that is if children received all rounds of preventive treatment during the transmission season, differed among reviewed studies. Coverage in clinical trials ranged from around 40% in a study in which five rounds of SMC were administered (39), to 97% when all SMC dosages were supervised by the study team (38). Five rounds of SMC were given in areas of extended seasonal transmission (37,39), however, one trial reported low PE (48%) and low coverage (40%) (39), whereas the other reported high PE (83%) and high coverage (around 90% in each round) (37). Contrastingly, in observational studies that evaluated the SMC programmes with 4 rounds implemented in certain countries, an average coverage of around 55% was reported, with a high coverage in Burkina Faso of around 91%, and a very low coverage in Chad of around 14%. PE was higher in Burkina Faso (95%) and lower in Chad

(79%). Nonetheless, in other countries studied, results are not as straightforward, such as Mali, where PE was lower and coverage was higher (73%, 57% respectively) than Chad, and the Gambia, with higher PE and low coverage (93%, 44% respectively) (45).

Across all studies and trials, all different SMC combinations were generally well tolerated. Only two articles (one trial and one observational study) reported a low number of possible serious adverse events related to SP+AQ, but no severe skin reactions (36,45). The most common adverse effects were vomiting, fever, and diarrhoea. Regarding differences between drug combinations, Sokhna *et al.* (2008) reported a higher prevalence of adverse effects when the SP+AQ combination was used, followed by AQ+AS, with SP+AS combinations having the lowest prevalence of adverse effects (15). Both SP+AQ and DHA+PQ combinations seem to be similarly well tolerated (19,38). However, Cissé *et al.* (2009) reported that adverse effects were more common in the SP+AQ group compared to DHA+PQ and SP+PQ. Vomiting, for example, occurred in 31% of children that received SP+AQ, 14% DHA+PQ and 17% SP+PQ (17).

Table 2 – Overview of other drug combination alternatives found through literature review.

Drug combination	SP+PQ	SP+AS	AQ+AS
Drug regimen	Day 1: 1 SP + 1 PQ Day 2: 1 PQ Day 3: 1 PQ	Day 1: 1 SP + 1 AS OR Day 1: 1 SP + 1 AS Day 2: 1 AS Day 3: 1 AS	Day 1: 1 AQ + 1 AS Day 2: 1 AQ + 1 AS Day 3: 1 AQ + 1 AS
Dosing target	SP 500/25 mg: ½ tablet ≤10 kg 1 tablet if >10 kg PQ 250 mg: ½ tablet ≤11 kg 1 tablet >12 kg	SP 25/1.25 mg/kg AS 4 mg/kg	AS 50 mg: 1 tablet <12kg 1.25 tablets ≥12 kg AQ 200 mg: ¾ tablet <12kg 1.25 tablets ≥12 kg
Protective efficacy	Not possible to determine (no control group in study)	88% first 4 weeks 61% 5 weeks after last dose	Not possible to determine (no control group in study)
Parasitaemia prevalence	Low prevalence (similar to SP+AQ)	Reduced in treatment group compared to control group. Lower in SP+3AS.	Lower than SP+1AS, but higher than SP+3AS and SP+AQ
Anaemia prevalence	Hb concentration was similar to SP+AQ.	Not different between treatment and control group. Lower Hb concentration than AQ+AS or SP+AQ.	Higher Hb concentration

The presence and prevalence of resistance markers to SP and AQ were investigated in 36% (n = 11) of studies. The *P. falciparum* multidrug resistance gene 1 (*Pfmdr1*) confers resistance to amodiaquine. Point mutations in *P. falciparum* dihydropteroate synthase (*Pfdhps*) and *P.*

falciparum dihydrofolate reductase (*Pfdhfr*) confer resistance to sulfadoxine and pyrimethamine (51). Trials conducted in older years (before 2010) investigated mostly *pfdhfr* triple (*pfdhfr* 51, 59, 108), and *pfdhps* 437 gene mutations (11,15,17). Whereas the more recent the study, the more resistant codons were investigated, such as more *pfdhps* gene codons (codons 431, 436, 540, 581, and 613), and *pfmdr1* gene mutations (codons 86 and 184) (13,22,36–38,41,44,48). Overall, the prevalence of resistance genes in populations studied was low. However, some differences between studies could be denoted. The trial of Konaté *et al.* (2011) reported no differences in resistance prevalence between SMC and control groups at baseline, but an overall slight increase at the end of the intervention (13). While other trials described that the SMC arm had higher prevalence of resistant genes in the parasites with regards to the control arm (11,13). Particularly, the *pfdhps* 437 gene was more frequent in SMC receiving children (37,49), and *Pfmdr1-86Y* was more common in SMC group in one study (36), whereas it was similar between treatment and control areas in another (49). Regarding differences between drug combinations, Sokhna *et al.* (2008) did not report any different resistance prevalence among the combinations (15), whereas Cissé *et al.* (2009) denoted that children who received a combination including PQ had a slightly lower prevalence of resistance (17). The frequency of resistance markers at the end of the transmission season was higher than at baseline in the SP+AQ group, but this did not occur in the DHA+PQ group (38).

4. Discussion

This review aims to give an overview of the drug combinations used for SMC in the Sahel region of Sub-Saharan Africa in under 5-year-olds, with an emphasis on SP+AQ, the drug combination recommended for SMC by the WHO. Overall, based on this review, it was clear that SP+AQ is indeed the most used combination in SMC thus far. In a total of 31 studies reviewed, 27 reported the usage of SP+AQ either in trials or, more recently, as implemented in a national programme within the study area. SP+AQ was generally found to be an effective combination for malaria prevention when applied in the SMC context. Different PE values were presented per study, which could be related to the differences in baseline incidence of malaria in each study, due to differences in malaria transmission intensity in the different study areas. Additionally, it has been noted that the PE against clinical malaria cases is high in the 28 days post administration, and between 29 to 42 days this efficacy rapidly declines (45,48), meaning that monthly administration is necessary to maintain protection against malaria between rounds of SMC with SP+AQ during the high transmission season.

In general, parasitaemia prevalence was consistently lower at the end of the transmission season in children receiving SMC compared to those receiving a placebo. Only a few studies reported efficacy against severe malaria, showing that SP+AQ can provide some protection in these cases (13,22,47). Anaemia prevalence was not evaluated in all studies, and results were not always significant. However, haemoglobin concentrations were generally found to be higher in children who received SMC, and the prevalence of mild and moderate anaemia was lower as well. Therefore, SMC with SP+AQ can contribute to reduction of anaemia caused by malaria.

The second most studied treatment combination was DHA+PQ, which was reported on in three clinical trials. All three studies had similar results, DHA+PQ was highly effective. PQ is a long acting antimalaria drug, and Zongo *et al.* (2015) reported that a decrease in malaria incidence could be associated with an increase of PQ dosing, but similarly to SP+AQ, at four weeks post DHA+PQ administration the efficacy starts to rapidly decline (38). Thus, also for DHA+PQ there is the requirement to have strict monthly administrations to maintain efficacy against malaria cases. Prevalence of parasitaemia at the end of transmission season decreased similarly with this combination as it did with SP+AQ. Anaemia was more common in the DHA+PQ group when compared to SP+AQ in one study (17), but similar to SP+AQ in another trial (38). Therefore, no conclusions on protection against anaemia can be made in this review. The combination DHA+PQ is a strong potential candidate for SMC, as it is effective in the prevention of clinical malaria in seasonal transmission settings, noted in the clinical trials presently reviewed, and is already approved and used for treatment of uncomplicated malaria (40), which could facilitate its implementation in SMC programmes.

WHO recommends implementing SMC in children under five years of age (three to 59 months old), and the target population of most clinical trials reviewed were children in this same age range. However, recent research has shown that malaria prevalence is higher in older children when compared to under five year olds in areas receiving SMC (33,52). Four of the trials reviewed, which were conducted in Senegal, have shown that SMC with SP+AQ is effective in children up to ten years of age (34–37). Similarly, Konaté *et al.* (2022) reported a decrease in malaria prevalence in five- to 14-year-old children who received monthly SP+AQ during the transmission season in Mali. Additionally, the authors described a good acceptance for this intervention in the community (53). Given these outcomes in older children, it could be useful to increase the target age for SMC programmes. Nevertheless, it is important to consider what implications could arise from the expansion of a SMC programme to older ages. Contrarily to younger children, coverage of the older age groups could be easier to achieve as these children do not necessarily need parental support to take the medication (53), and other delivery methods could be introduced, such as through schools. Furthermore, the costs of a SMC programme would most likely increase if extended to older ages, thus it would also be important to carry out a cost-effectiveness analysis on a larger scale implementation (53). One concern could be related to the prevalence of resistance markers, and if it would be likely to increase due to expansion of SMC to older children. One recent review on drug resistance related to malaria chemoprevention, suggested that SMC programmes do not necessarily accelerate the rise of resistance. However, extensive usage of antimalarial drugs over the years could increase resistance (54), therefore an efficient surveillance system should be in place, and decisions to expand SMC programmes to older children should be made based on available evidence.

As for the number of SMC rounds, the WHO recommends a course of four rounds during the transmission season. The majority of the studies reviewed in this report included three or four SMC rounds per season. However, certain countries and regions have longer transmission seasons that extend beyond four months. Only two clinical trials in this review evaluated increasing the number of rounds, in geographical areas of longer seasonal transmission. Ndiaye *et al.* (2019) showed that increasing the number of rounds is very efficacious (37), which could potentially improve malaria control in these extended transmission regions. The other trial, however, identified that PE on clinical malaria was not very high (48%), which could

be related to the low coverage noted for all five cycles of SMC (39). Recently, another trial by Konaté *et al.* (2022) suggested that increasing SMC to five rounds was effective in reducing malaria prevalence in the study area (with extended seasonal transmission) (53). Based on the evidence available, it appears that to increase WHO's recommendation of four SMC rounds, further studies are needed. Additional clinical trials in which a comparison of different number of rounds would be studied with regards to efficacy and coverage of SMC, could be useful to inform this potential change of number of rounds, if no ethical issues would arise.

Coverage, the proportion of children that received all rounds of SMC during the transmission season, varied between studies reviewed, and different countries had different levels of SMC coverage as well. This is particularly well observed in the Achieving Catalytic Expansion of SMC in the Sahel (ACCESS-SMC) project, which reached seven countries, and evaluated the implementation of SMC with SP+AQ. Between these countries, coverage varied, which could be accounted for by a difference in delivery method. Authors reported that door-to-door delivery achieved a higher coverage. Furthermore, there are other aspects that could be related to variation in coverage, such as, the existent infrastructure and logistics in place, as well as, efficient communication about distribution campaigns (45). In a study by Barry *et al.* (2018), a comparison between door-to-door or fixed-point distribution, and directly observed or not directly observed administration, was carried out. The study demonstrated that door-to-door distribution of SMC resulted in a higher number of children receiving the complete three-day course in all the SMC rounds (55). In this review, the administration of drugs was done by direct observation in many studies, particularly clinical trials, in some cases for the three days of treatment, but this could be hard to logistically maintain on a large scale or national programme. Therefore, also in other studies reviewed, direct observation was done for the first day of treatment, and subsequent doses were given by caregivers at home. If children do not receive the next two day treatments, coverage, and consequently, efficacy of SMC, could potentially decrease. Barry *et al.* (2018) reported that the proportion of children who received all three treatments in all the rounds was similar between directly observed and not directly observed administration of second and third doses (55). This indicates that caregivers' administration of second and third doses (not directly observed) is a suitable option and does not appear to lead to a decrease in coverage, as well as requiring the implementation of less resources.

In the current review, SMC was not associated with a high number of serious adverse events. Mild adverse effects occurred, with vomiting and fever being the most common overall. During three years, in Senegal, the safety of SMC with SP+AQ was evaluated on a large scale (around 780,000 treatment courses administered) with increased surveillance (active follow-up and passive surveillance at health centres). The authors reported no serious events associated with administration of SMC, and the most common effect was vomiting (56). However, the number of adverse effects may have been underreported, because health workers and caregivers might not be able to recognize symptoms as adverse events of treatment with SP+AQ, therefore not notifying what could be an adverse reaction to SMC. Ndiaye *et al.* (2018) evaluated two different strategies for reporting adverse effects. Higher reporting rates were obtained through training of health workers and staff at health centres and usage of a mobile phone application, with good feasibility and acceptance (57).

Between SP+AQ and DHA+PQ, SP+AQ was found to elicit a higher number of adverse reactions. It is important to note that adverse effects can be related with dosing of drugs used. The dosing can be age-based or weight-based, as previously mentioned. The standard tablet of SP is 500/25mg, but both 200mg and 153mg formulations are available for AQ. Earlier studies used the first AQ formulation and the WHO recommendation is for the second formulation. Therefore, more recent studies have used AQ tablet of 153mg. Age-based dosing and weight-base in groups (that is, with two weight groups) have been associated with children receiving higher doses, which can lead to an increased occurrence of vomiting. The safety and tolerance of these medications could improve if a higher accuracy in dosing was applied. Weight-based dosing seems to be a more accurate method, but it has limitations in lower resource settings, and can be impractical in large scale distribution of treatments such as SMC (58).

One of the major concerns with any chemoprevention practice is the development of parasite resistance to the drugs, as the effectiveness of the drug combinations used could decrease (25). In the current review, the markers of resistance were generally found at low frequencies. This finding is well illustrated by the ACCESS-SMC project; in seven different countries in the Sahel region where large-scale SMC implementation took place, resistance was present but had low prevalence, and mutations that confer high resistance were less common. In children younger than 5 years old, a prevalence of 1.3% in 2016 and 0.5% in 2018 was reported for *pfprt-CVIET*, *pfmdr1-86Tyr*, and *pfmdr1-184Tyr* variants (related to AQ resistance). Prevalence of 0.4% and 0.7%, in 2016 and 2018 respectively, for quintuple mutation (associated with SP resistance) (45). Other studies, which focused on monitoring the presence of resistance rather than SMC's efficacy, reported identical outcomes, in Niger (59), Senegal (60) and Mali (61). Resistance markers increased post SMC, but had no significant increase in the general population after two years of SMC administration (61). Additionally, and similarly to the present review, one recent malaria chemoprevention drug resistance review described that some studies reported increased resistance following SMC, while others did not. There was no evidence of an increase in mutations that confer high resistance to SP, as well as in mutations related to AQ resistance, after SMC administration (54). Nevertheless, even if resistance is low and not common, it is important to carry on with surveillance of the frequency of resistance, to guarantee the continuous effectiveness provided by SMC. Combinations with piperazine, such as DHA+PQ, appear to be associated with a lower resistance frequency, which would indicate their potential use in areas where resistance to SP is high, such as South East Africa, or as an alternative to SP+AQ if treatment failure or a considerable decrease in SP+AQ's prophylactic effect is observed in the Sahel region. It is important not only to better assess the effectiveness of this drug combination, but also monitor the development of resistance, which could hinder its usage as an alternative drug for SMC.

Most trials and studies reviewed reported on the usage of other malaria control measures while SMC was being implemented, as well as the treatment used if a malaria case was diagnosed. SMC is primarily a preventive intervention, therefore needs to be implemented with good case control to ensure that cases that escape SMC's protectiveness still get treated. A study combined SMC with community case management (CCM), where delivery of SMC was combined with the prompt usage of rapid diagnostic tests, and treatment for uncomplicated malaria, in cases where children presented malaria symptoms. Results from the study showed that SMC with CCM was associated with a higher decrease in malaria cases when compared

with CCM alone, guaranteeing this way a good management and prevention of malaria in young children (37). Additionally, SMC does not confer full protection at the population level, that is PE and coverage are not 100%, and only children up to 5 years old are treated, as could be identified from the current review. Consequently, there is the need to layer SMC with other effective control measures, especially methods that target the vector. Research has suggested that the combined usage of SMC with an additional control measure, such as LLIN or IRS, is more effective than each measure on its own (13,22,33,43).

In the search for alternative drug combinations for future use in SMC, it is important to highlight that in this review, apart from SP+AQ, only other four combinations have been briefly studied in the SMC context, DHA+PQ being the most promising. There is the need to research other new potential combinations and their effectiveness when applied in SMC, in a way to anticipate the development and increase of resistance. Chalon *et al.* (2022) conducted a Phase I clinical trial to assess the safety of the combination of atovaquone-proguanil (ATV-PG) and AQ in a cohort of healthy adults. ATV-PG is mostly used for chemoprophylaxis in travellers. Extrapyrasidal adverse effects, considered serious adverse effects related to the central nervous system, occurred in participants who received the combination studied. Therefore, ATV-PG+AQ was deemed unusable for SMC in children. Nonetheless, this was a good example of a trial that attempted to find a new combination for SMC, and demonstrated the importance of thoroughly investigating the safety of combining pharmaceuticals (62).

New alternative drugs to be investigated would have to meet certain requirements based on what SMC with SP+AQ achieves. Any potential candidate would have to maintain a comparable PE, which would give protection against clinical malaria of at least 28 days, the drug safety profile would have to be similar, and no more than 3 doses in one round would be needed to achieve acceptable effectiveness results. Furthermore, for future implementation of SMC, it would be potentially useful to extend or reduce the number of rounds, to increase the age limits, and to authorise the usage of other drugs. However, it would be highly important to ensure that areas or countries where the programme would be implemented, have previously and thoroughly studied local malaria epidemiology and transmission patterns. It would be important to survey which ages are at a higher risk of severe disease, as well as to determine the duration of transmission season, and accordingly implement the appropriate number of rounds. Post implementation it would be important to maintain a surveillance protocol for effectiveness of the programme in order to make changes as needed.

In the control of infectious diseases, modelling can be a very useful tool, as it allows for simulation of different control strategies and treatment efficacies for varying transmission settings. It has been used extensively to guide policy makers define malaria control strategies, with regards to resistance (63), prioritisation of strategies (64), and combination of different interventions (65). As an example, modelling can be used to quantify the changes in public health outcomes of delayed malaria treatment (66). Similarly, it could be valuable for SMC to determine how coverage, or different drug dosing, could impact the efficacy of SMC. Additionally, modelling is useful to evaluate the cost-effectiveness of implementing a SMC programme in a particular area/region/country. Therefore, it could be an extremely useful tool to inform countries and regions where implementation is being planned, as well as, to measure the effects of a SMC established routine programme.

The current review has some limitations. Methodologically the review was performed as a systematic review using the PRISMA framework. However, this cannot be considered a precise systematic literature review as the selection of articles was made by only one person instead of two researchers independently screening all articles. This slightly increases the chance that during the process of literature search and screening articles, valuable papers were missed and not included. Furthermore, difficulty in comparisons between studies was encountered due to a wide range of differences between the types of studies, the treatment regimen, the settings in which they took place, the people they studied, as well as their epidemiological outcome measures. Notwithstanding the limitations here presented, this review shows a broad overview of the benefits and pitfalls of SP+AQ as a SMC drug combination, providing updated insights on its protective efficacy, coverage, safety, presence of resistance from a wide range of studies. The fact that this review links the pitfalls of SP+AQ to potential alternative treatments makes it a valuable addition to the current understanding of SMC, helping scientists and policy makers with continuing and increasing the successes of SMC into the future.

5. Conclusion

The present review provides an overview of drug combinations used in SMC and the possible alternatives. SP+AQ is the currently drug combination of choice for SMC and is considered to be an effective measure for malaria control in children under five years old, which was supported by the trials studied in this review. Nonetheless, their protection against infection is not complete and should be used together with other measures, such as vector control (ITNs or LLINs). So far, SMC using SP+AQ has been implemented in 13 countries, and continues to grow in higher capacities. One of the risks identified in this review is the increase in parasite resistance against the treatment, which is favoured by non-compliance of the treatment regime. Therefore, it is important to focus on the monitoring of the presence of resistance. Additionally, it could be useful to extend SMC programmes to include older children as well as increase the number of monthly treatment rounds, as were both identified in this review to increase the effectivity of the treatment programmes in reducing incidence and prevalence of malaria.

Besides SP+AQ, DHA+PQ was identified in this review as an appropriate alternative treatment combination for situations where the use of SP+AQ might not be any longer suitable due to drug resistance, which currently is highest in areas of South East Africa. However, further studies, that mainly focus on the efficacy of DHA+PQ and its coverage when implemented at a larger scale, are necessary to fully evaluate its potential as an alternative treatment combination for SMC.

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Supplementary material

Supplementary Table 1 – Search strategy for online search databases.

Search database	Search terms used
Embase	(seasonal AND malaria AND (chemoprevention:ab,ti OR chemoprotection:ab,ti) OR 'intermittent preventive treatment':ab,ti) NOT pregnan*:ab,ti AND [English]/lim
PubMed	(seasonal malaria ((chemoprevention[Title/Abstract]) OR (chemoprotection[Title/Abstract]))) OR ("intermittent preventive treatment"[Title/Abstract]) NOT (pregnan*[Title/Abstract]) English manually filtered.
Web of Science	TS=((seasonal malaria (chemoprevention OR chemoprotection)) OR ("intermittent preventive treatment") NOT (pregnan*)) English manually filtered.

Supplementary Table 2 – General characteristics of studies.

	Cissé et al. (2006) (11)	Sokhna et al. (2008) (15)	Cissé et al. (2009) (17)	Kweku et al. (2009) (18)	Bojang et al (2010) (19)	Bojang et al. (2011) (21)
Type of study	Individually-randomised, double-blind, placebo-controlled trial	Open label trial	Cluster randomised trial	Non-controlled study	Open-label, randomized trial	Open-label, cluster randomised trial
Study site	Niakhar, Senegal	Niakhar, Senegal	Ndoffane district, Senegal.	Jasikan district, Ghana	Basse, The Gambia	Upper River Region, The Gambia
Malaria prevalence or incidence	EIR = 10 infective bites/person/year	Not specified	Not specified	Not specified	EIR = 1 to 50 infective bites/person/year	Not specified
Target population	2 – 59 months old children	6 – 59 months old children	2 – 59 months old children	3 – 59 months old children	6 – 59 months old children	6 – 72 months old children
Drug used	SP+AS monthly	SP+1AS monthly SP+3AS monthly SP+3AQ monthly 3AQ+3AS monthly	SP+AQ monthly SP+PQ monthly DHA+PQ monthly	SP+3AQ monthly	SP+3AQ monthly SP+PQ monthly DHA+PQ monthly	SP+3AQ monthly
Nr of cycles per year	3	3	3	4	3	3
Nr of years/seasons	2	1	1	1	1	1
Dosing	SP 25/1.25 mg/kg AS 4 mg/kg Dosage by weight. Depending on age: ½ to 1 ½ tablets of both drugs	SP 500/25 mg: ½ tablet <12kg 1 tablet ≥12 kg AS 50 mg: 1 tablet <12kg 1.25 tablets ≥12 kg AQ 200 mg: ¾ tablet <12kg 1.25 tablets ≥12 kg	SP 500/25 mg and PQ 250 mg: ½ tablet <12 months 1 tablet ≥12 months AQ 200mg and DHAPQ 40/320 mg: ½ tablet <24 months 1 tablet ≥24 months	SP 500/25 mg AQ 150 mg ¼ tablet 3-5 months ½ tablet 6-11 months ¾ tablet 12 to 23 months 1 tablet 24 months and above	SP 500/25 mg: ½ tablet ≤10 kg 1 tablet if >10 kg AQ 200 mg (Day 1, 2, 3): ½, ½, ¼ tablets ≤10 kg 1, 1, ½ tablets >10 kg PQ 250 mg: ½ tablet ≤11 kg 1 tablet >12 kg DHAPQ 40/250 mg: ½ tablet ≤13 kg 1 tablet >13 kg	SP 500/25 mg: ½ tablet 3-11 months 1 tablet 1-6 years AQ 200mg: ¼ tablet 3-11 months ½ tablet 1-2 years 1 tablet 3-6 years
Control	Placebo	No control group	No control group	No control group	No placebo (control group: children from neighbouring villages)	No placebo (control group: children from same village of delivery arm as detected cases)
Delivery	Health centre by trained nurse under DOT	Trial staff (1 st dose at health centre, rest at home)	CHW (1 st dose) at home Caregivers at home	Health facility or community volunteers at the village (1 st dose) Caregivers at home	Nurse at the health centre	RCH trekking teams or CHW (1 st dose) Caregivers at home
Malaria diagnostic tool	Thick blood smear	Thick blood smear	RDT and blood smear	Thick blood smear	Thick blood smear	RDT and blood smear
Other control measures	Bed nets: 21% treatment group 23% control group	18% slept under an intact or impregnated bed net	29% on average slept under an intact or treated bed net	19% slept under bed net usage, 14% slept under ITN	68% ITN usage	Bed net usage: 64% RCH group, 71% CHW group Intact or treated bed net: 51% RCH group, 64% CHW group

Abbreviations: SP: sulfadoxine-pyrimethamine, AQ: amodiaquine, AS: artesunate, DHA: dihydroartemisinin, PQ: piperaquine, EIR: Entomological inoculation rate, CHW: Community Health Worker, RCH: Reproductive and child health, RDT: rapid diagnostic test, LLIN: long lasting insecticide treated net, IRS: indoor residual spraying, DOT: directly observed treatment, HHM: home-based management of malaria.

Supplementary Table 2 – General characteristics of studies (continuation).

	Dicko et al. (2011) (22) Dicko et al. (2011) (67)	Konaté et al. (2011) (13) Konaté et al. (2011) (68)	Sesay et al. (2011) (20)	Tine et al. (2011) (34) Tine et al. (2014) (35)	Zongo et al. (2015) (38)	Cissé et al. (2016) (36)
Type of study	Individually randomised, placebo-controlled trial	Individually randomised, double-blind, placebo-controlled trial	Double-blind, randomized placebo-controlled trial	Cluster randomized trial	Randomized open trial	Stepped-Wedge Cluster-Randomised Trial
Study site	Kati district, Mali	Boussé district, Burkina Faso	Farafernni, The Gambia	Velingara health district, Senegal	Lena district, Burkina Faso	Mbour, Bambey, and Fatickdistricts, Senegal
Malaria prevalence or incidence	EIR = 8 infective bites/person/season (far from any river) EIR = 37.7 infective bites/person/season (on the bank of the river)	EIR = 173 infective bites/person/year	EIR = 1 – 177 infective bites/person/year	Not specified	Not specified	EIR 2008: 0.3 – 6 bites/night 2009: 0.2 – 10 bites/night 2010: 0.2 – 22 bites/night
Target population	3 – 59 months old children	3 – 59 months old children	3 – 59 months old children	1 – 10 years old children	3 – 59 months old children	3 months to 10-year-old children
Drug used	SP+3AQ monthly	SP+3AQ monthly	SP+3AQ monthly	SP+3AQ monthly	SP+3AQ monthly 3DHA+3PQ monthly	SP+3AQ monthly
Nr of cycles per year	3	3	3	2 (Tine et al. 2011) 3 (Tine et al. 2014)	3	3
Nr of years/seasons	1	1	1	1 (Tine et al. 2011) 2 (Tine et al. 2014)	1	3
Dosing	SP: 175/8.75 mg 5-9 kg 350/17.5 mg 10-18 kg 550/26.25 mg ≥19 kg AQ: 70 mg 5-9 kg 140 mg 10-18 kg 220 mg ≥19 kg	SP: 175/8.75 mg 5-9 kg 350/17.5 mg 10-18 kg 550/26.25 mg ≥19 kg AQ: 70 mg 5-9 kg 140 mg 10-18 kg 220 mg ≥19 kg	SP 500/25 mg: ½ tablet 3-11 months 1 tablet 1-5 years AQ 200mg: ¼ tablet 3-11 months ½ tablet 1-2 years 1 tablet 3-5 years	SP 500/25 mg: ½ tablet <2 years 1 tablet 2-6 years 1 ½ tablets 7-10 years AQ 153 mg: ½ tablet <2 years 1 tablet 2-7 years 1 ½ tablets 8-10 years	SP 25/1.25 mg/kg AQ 10 mg/kg DHA 4 mg/kg PQ 18 mg/kg	SP 500/25 mg AQ 200mg Half dose given to infants.
Control	Placebo	Placebo	Placebo	No placebo (control group: HHM arm)	No placebo (control group: untreated children)	No placebo (control group: untreated children)
Delivery	Study staff at research clinic	Study staff at research clinic	CHW by DOT (1 st dose) Caregivers at home	CHW by DOT at health huts (all doses)	Study nurses at study clinic (1 st dose) Field workers at home	CHW at home (1 st dose) Caregivers at home
Malaria diagnostic tool	RDT and blood smear	RDT and blood smear	RDT and blood smear	RDT and blood smear	RDT and blood smear	RDT and blood smear
Other control measures	LLIN provided during study 99% usage in both treatment and control groups	LLIN provided during study 93% usage in both treatment and control groups	93% slept under an impregnated bed net	96% bed net usage	Treatment group: 36% bed net usage 26% slept under ITN Control group: 32% bed net usage 31% slept under ITN	52% LLIN 1 st year of study 71% LLIN 2 nd year 72% LLIN 3 rd year

Abbreviations: SP: sulfadoxine-pyrimethamine, AQ: amodiaquine, AS: artesunate, DHA: dihydroartemisinin, PQ: piperaquine, EIR: Entomological inoculation rate, CHW: Community Health Worker, RCH: Reproductive and child health, RDT: rapid diagnostic test, LLIN: long lasting insecticide treated net, IRS: indoor residual spraying, DOT: directly observed treatment, HHM: home-based management of malaria.

Supplementary Table 2 – General characteristics of studies (continuation).

	Tagbor et al. (2016) (39)	Diawara et al. (2017) (49)	Druetz et al. (2018) (44)	Ndiaye et al. (2019) (37)	Ambe et al. (2020) (41)	Baba et al. (2020) (45)
Type of study	Individually randomised clinical trial	Non-randomized pre-post trial	Pre–post nonrandomized control study	Cluster randomized trial	Cross-sectional study	Observational study
Study site	Ashanti region, Ghana	Kita, Mali	Kaya, Burkina Faso	Saraya district, Senegal	Borno State, Nigeria	Burkina Faso, Chad, The Gambia, Guinea, Mali, Niger, Nigeria
Malaria prevalence or incidence	Not specified	36.9% prevalence in children 6-59 months old in the study region (2013 data)	1.1 infections/child/year on average	Not specified	78.5% prevalence children < 5 years; 43.2–84.2% during rainy season	Not specified
Target population	3 – 59 months old children	3 – 59 months old children	3 – 71 months old children	3 – 119 months old children	3 – 59 months old children	3 – 59 months old children
Drug used	SP+3AQ monthly	SP+3AQ monthly	SP+3AQ monthly	SP+3AQ monthly	SP+3AQ monthly	SP+3AQ monthly
Nr of cycles per year	5	4	4	5	4	4
Nr of years/seasons	1	1	1	1	1	2
Dosing	1-4 years: SP 500/25 mg AQ 153 mg Infants: SP 250/12.5 mg AQ 76.5 mg	3-11 months: SP 250/12.5 mg AQ 75 mg 12-59 months: SP 500/25 mg AQ 150 mg	3-11 months: SP 250/12.5 mg AQ 75 mg 12-59 months: SP 500/25 mg AQ 150 mg	SP 500/25 mg: ½ tablet 3-11 months 1 tablet 1-5 years 1 ½ tablets 6-9 years AQ 153 mg: ½ tablet 3-11 months 1 tablet 1-5 years 1 ½ tablets 6-9 years	Doses as described by WHO: SP 500/25mg AQ 153 mg 3-11 months: ½ tablet 12-59 months: 1 tablet	SP 500/25 mg AQ 150 mg 1 tablet 12-59 months ½ tablet 3-11 months
Control	Placebo + AL Placebo + DP	No placebo (control group: untreated district)	No placebo (control group: children who did not receive SMC)	No placebo (control group: CCM arm)	No placebo (control group: children who did not receive SMC)	No placebo (control group: children who did not receive SMC)
Delivery	Under observation by study team (1 st dose) Caregivers at home	CHW at fixed points (1 st dose) Caregivers at home	CHW (door-to-door, 1 st dose) Caregivers at home	CHW (door-to-door, 1 st dose) Caregivers at home	Not specified	Door to door (supplemented by fixed point distribution) CHW (1 st dose) Caregivers at home
Malaria diagnostic tool	RDT and blood smear	RDT and blood smear	RDT	RDT and blood smears	Blood smears	Blood smears
Other control measures	82% slept under an insecticide-treated net	ITN provided prior to the study. Pre-survey: treatment group 99.7%, control 99.1% Post-survey: treatment 98.8%, control 97.1%	95% slept under a bed net	94% slept under an ITN	62% slept under bet net	87% slept under LLIN (1 st year of study) 86% slept under LLIN (2 nd year of study)

Abbreviations: SP: sulfadoxine-pyrimethamine, AQ: amodiaquine, AS: artesunate, DHA: dihydroartemisinin, PQ: piperaquine, EIR: Entomological inoculation rate, CHW: Community Health Worker, RCH: Reproductive and child health, RDT: rapid diagnostic test, LLIN: long lasting insecticide treated net, IRS: indoor residual spraying, DOT: directly observed treatment, HHM: home-based management of malaria

Supplementary Table 2 – General characteristics of studies (continuation).

	Cairns et al. (2020) (42) Data from Chandramohan et al. (2019) (69)	Issiaka et al. (2020) (46)	Konaté et al. (2020) (70)	Maiga et al. (2020) (71)	Wagman et al. (2020) (43)
Type of study	Household-randomised, placebo-controlled trial	Historical cohort study	Cohort study	Cross-sectional study	Observational study
Study site	Houndé district, Burkina Faso Bougouni district, Mali	Ouelessebougou, Mali	Dangassa, Mali	Koutiala district, Mali	Ségou region, Mali
Malaria prevalence or incidence	Not specified	2 episodes/child/year (children < 5 years of age during transmission season)	Not specified	Not specified	Not specified
Target population	3 – 59 months old children	3 – 59 months old children	3 – 59 months old children	3 – 59 months old children	3 – 59 months old children
Drug used	SP+3AQ monthly	SP+AQ monthly	SP+AQ monthly	SP+AQ monthly	SP+AQ monthly
Nr of cycles per year	4	4	3	3 (1 st year) 4 (2 nd year)	4
Nr of years/seasons	3	1	2	2	1
Dosing	3-11 months: SP 250/12.5 mg AQ 75 mg 1-4 years: SP 500/25mg AQ 150 mg	Not specified	Not specified	Not specified	Not specified
Control	Placebo	No placebo (control group: children who did not receive SMC in different sub-districts)	No placebo (control group: same areas in earlier years without SMC)	No control group	No placebo (control group: areas where SMC was not implemented)
Delivery	Trial staff	Not specified	Drug given at community health centre	Fixed point and door-to-door strategies	Not specified
Malaria diagnostic tool	RDT and blood smear	RDT	Not specified	RDT and blood smear	RDT
Other control measures	73% LLIN usage prior to study New LLIN given upon study enrolment	84% slept under impregnated bed nets	Not specified (There was a distribution campaign in 2014)	Not specified	73% slept under LLIN (in previous survey) IRS with > 90% coverage

Abbreviations: SP: sulfadoxine-pyrimethamine, AQ: amodiaquine, AS: artesunate, DHA: dihydroartemisinin, PQ: piperaquine, EIR: Entomological inoculation rate, CHW: Community Health Worker, RCH: Reproductive and child health, RDT: rapid diagnostic test, LLIN: long lasting insecticide treated net, IRS: indoor residual spraying, DOT: directly observed treatment, HHM: home-based management of malaria

Supplementary Table 2 – General characteristics of studies (continuation).

	Ahmad et al. (2021) (50)	Ansah et al. (2021) (47)	Cairns et al. (2021) (48)	Coldiron et al. (2021) (52)	Coulibaly et al. (2021) (33)
Type of study	Prospective study	Quasi-experimental design, with pre and post cross-sectional surveys	Case-control study	Cross-sectional study	Cohort study
Study site	Eastern region, The Gambia	Lawra district and West Mamprusi, Ghana	Burkina Faso, Chad, Mali, Nigeria, and The Gambia	Magaria district, Niger	Bandiagara, Mali
Malaria prevalence or incidence	Not specified	Not specified	Not specified	Not specified	Up to 60 infective bites per person per month in August or September (transmission peak)
Target population	24 – 59 months old children	3 – 59 months old children	3 – 59 months old children	3–59 months old children (received SMC), 5–9 years old children, and people aged 10 years and older	6 months to 15 years old children 3-59 months old received SMC
Drug used	SP+3AQ monthly	SP+3AQ monthly	SP+3AQ monthly	SP+3AQ monthly	SP+AQ monthly
Nr of cycles per year	Not specified	4	4	4	4
Nr of years/seasons	2	1	2	2	2
Dosing	Not specified	SP 500/25 mg AQ 153 mg 3-11 months: ½ tablet 12-59 months: 1 tablet	Not specified	Not specified	Not specified
Control	Control group: 5-8 years old children who did not receive SMC	Control group: district in which SMC was not administered	Control group: children matched on neighbourhood	No control group	No control group
Delivery	DOT by the CHW (1 st dose) Caregivers at home	DOT by the CHW (1 st dose) Caregivers at home	Not specified	DOT by the CHW at a fixed point (1 st dose) Caregivers at home Or caregivers (all 3 doses)	Not specified
Malaria diagnostic tool	RDT	RDT and blood smear	Blood smear	RDT and blood smear	Blood smear
Other control measures	IRS and INT implemented in the study region	Treatment group: ITN: 99%, IRS: 98% Control group: ITN: 70%, IRS: 92%	LLIN usage ranged from 84.6% (Nigeria) to 97.5% (Burkina-Faso), similar in both intervention and control groups Exception: 38.6% in Chad	Not specified	IRS and LLINs implemented before and during study 98% slept under ITN

Abbreviations: SP: sulfadoxine-pyrimethamine, AQ: amodiaquine, AS: artesunate, DHA: dihydroartemisinin, PQ: piperazine, EIR: Entomological inoculation rate, CHW: Community Health Worker, RCH: Reproductive and child health, RDT: rapid diagnostic test, LLIN: long lasting insecticide treated net, IRS: indoor residual spraying, DOT: directly observed treatment, HHM: home-based management of malaria.

Supplementary Table 3 – Effect of seasonal malaria chemoprevention on several parameters.

Study	Coverage	Efficacy	Malaria incidence	Asexual parasitaemia prevalence	Gametocyte prevalence	Anaemia	Adverse reactions	Resistance markers
Cissé et al. (2006) (11)	99% received 1 st dose, 97% 2 nd dose and 93% 3 rd dose. Similar in treatment and control groups.	Protective efficacy of: 88% for the first 4 weeks, 94% for the 4 weeks between the second and third doses, 61% for the 5 weeks after the third dose. Efficacy during the first 4 weeks of the last period of observation was 77%.	Active drugs: 308 episodes per 1000 person-years at risk. Controls: 2250 episodes per 1000 person-years at risk. (Protective efficacy of 86%) Overall reduction in malaria morbidity of 91% over the 13 weeks of follow-up.	14% in treatment group. 37% in control group.	5% in treatment group. 19% in control group.	Prevalence of anaemia was 11.8% in control group and 9.5% in treatment group (difference not statistically significant).	Most common AEs: vomiting, nervousness, and, pruritus. More frequent in treatment group. No SAEs.	Triple pfdhfr mutation: 95% treatment group, 75% control group (prevalence difference of +20%). Pfdhps mutation: prevalence difference of +42%. 2003 season: prevalence difference for pfdhfr 19% and for pfdhps 27%. Little change in control group.
Sokhna et al. (2008) (15)	74% received all 3 treatments.	Not possible to determine the efficacy as no control group present.	Cumulative: SP+1AS: 9.5% SP+3AS: 8.7% SP+3AQ: 4.9% 3AQ+3AS: 10.8%	SP+1AS: 8.7% SP+3AS: 1.8% SP+3AQ: 1.1% 3AQ+3AS: 3.4%	Less than 1% in all groups.	Hb concentration was slightly greater in the 3AQ+3AS and SP+3AQ groups (10.0 g/dL in each group) than in the SP+1AS group (9.7 g/dL).	Most common AE: fever and vomiting. No SAEs. SP+1AS: 8.1% SP+3AS: 9.6% SP+3AQ: 32% 3AQ+3AS: 24%	Mutations were detected in almost all parasite positive samples. dhfr triple mutation: SP+1AS 24/24 SP+3AS 4/5 SP+3AQ 5/5 3AQ+3AS 9/9 dhps 437: SP+1AS 27/28 SP+3AS 3/3 SP+3AQ 5/5 3AQ+3AS 6/9

Abbreviations: AE: adverse event, SAE: severe adverse event, CI: confidence interval, Hb: haemoglobin PE: protective efficacy, SMC: seasonal malaria chemoprevention.

Supplementary Table 3 – Effect of seasonal malaria chemoprevention on several parameters (continuation).

Study	Coverage	Efficacy	Malaria incidence	Asexual parasitaemia prevalence	Gametocyte prevalence	Anaemia	Adverse reactions	Resistance markers
Cissé et al. (2009) (17)	Similar in all groups. 70% overall.	Not possible to determine the efficacy as no control group present.	Cumulative: (Any parasitaemia) SP+AQ: 5.4% DHA+PQ: 5.3% SP+PQ: 3.4% Both PQ containing regimens are non-inferior to SP+AQ (CI 95%).	SP+AQ: 5.3% DHA+PQ: 4.8% SP+PQ: 3.3%	0.9% overall prevalence. Nr of children: SP+AQ 4 DHA+PQ 5 SP+PQ 2	Prevalence was higher in DHA+PQ group than SP+AQ. Mean Hb concentration was lower in DHA+PQ group than SP+AQ. Hb concentration was similar between SP+PQ and SP+AQ.	Most common AE: fever, vomiting and headache. No SAEs. AEs more common in SP+AQ group.	Triple Pfdhfr mutations was very low in all groups. 53% positive for the dhfr triple mutation. 38% positive for the dhps-437 mutation. Slightly lower in the groups that received piperazine.
Kweku et al. (2009) (18)	Mean coverage: Community-based arm (90.5%), Facility-based arm (86.6). Proportion of children who received all four courses: Community-based arm (69.1), Facility-based arm (65.5). (Differences not statistically significant).	Not evaluated.	Not evaluated.	Pre-implementation: Community-based arm (10.2%), Facility-based arm (11.5%). Post-implementation: Community-based arm (7.5%), Facility-based arm (6.7%). (Differences not statistically significant).	Not evaluated.	Not evaluated.	No SAEs. Most common AEs: vomiting/spitting drugs, drowsiness/general bodily weakness. To a less extent: diarrhoea, body itch, abdominal pains, common cold and a swollen face. Incidence reduced with time, by the fourth course, less than 2% reported AEs.	Not evaluated.

Abbreviations: AE: adverse event, SAE: severe adverse event, CI: confidence interval, Hb: haemoglobin PE: protective efficacy, SMC: seasonal malaria chemoprevention.

Supplementary Table 3 – Effect of seasonal malaria chemoprevention on several parameters (continuation).

Study	Coverage	Efficacy	Malaria incidence	Parasitaemia prevalence	Gametocyte prevalence	Anaemia	Adverse reactions	Resistance markers
Bojang et al. (2010) (19)	Completion of 3 treatment courses: SP+AQ 77% SP+PQ 87.5% DHA+PQ 86%	Not evaluated.	SP+AQ 0.06 SP+PQ 0.06 DHA+PQ 0.10 Control group 0.79 Percentage reduction: SP+AQ 93% SP+PQ 93% DHA+PQ 87%	SP+AQ 0.3% SP+PQ 0.6% DHA+PQ 2.2%	Not evaluated.	Mean Hb concentration: SP+AQ 10.1 g/dL SP+PQ 10.1 g/dL DHA+PQ 10.4 g/dL Moderate anaemia: SP+AQ 4% SP+PQ 7% DHA+PQ 5%	No SAEs. Most common AEs: coughing, diarrhoea, vomiting, loss of appetite and abdominal pain. Similar between all treatment groups.	Not evaluated.
Bojang et al. (2011) (21)	Completion of 3 treatment courses: CHW arm 74% RCH arm 48% (Risk difference of 27%)	Efficacy of SMC given in the previous 28 days. Protective efficacy: malaria parasitaemia \geq 5000/ μ l 87%. If malaria parasitaemia <5000/ μ l cases included, then efficacy of 80%.	Malaria parasitaemia \geq 5000/ μ l: CHW arm 1.2 RCH arm 2.8 Per 1000 child months (Rate difference 1.6) Any parasitaemia: CHW arm 4.5 RCH arm 8.2 Per 1000 child months (Rate difference 3.7)	End of transmission survey: Malaria parasitaemia \geq 5000/ μ l: CHW arm 1.1% RCH arm 0.6% Any parasitaemia: CHW arm 2.3% RCH arm 3.3%	Not evaluated.	Mean Hb concentration: CHW arm 10.4 g/dl RCH arm 10.3 g/dl Moderate anaemia: CHW arm 4.8% RCH arm 6.1%	Most common AEs: fever, vomiting, diarrhoea, and abdominal pain.	Not evaluated.

Abbreviations: AE: adverse event, SAE: severe adverse event, CI: confidence interval, Hb: haemoglobin PE: protective efficacy, SMC: seasonal malaria chemoprevention.

Supplementary Table 3 – Effect of seasonal malaria chemoprevention on several parameters (continuation).

Study	Coverage	Efficacy	Malaria incidence	Parasitaemia prevalence	Gametocyte prevalence	Anaemia	Adverse reactions	Resistance markers
Dicko et al. (2011) (22)	Not evaluated.	Malaria parasitaemia \geq 5000/ μ l: protective efficacy of 82%.	Malaria parasitaemia \geq 5000/ μ l: treatment arm 0.34, control arm 1.9 episodes per child/year.	Malaria prevalence at weekly active surveillance visits: Treatment arm 1.9%, control arm 13.2% (PE = 85%).	Not evaluated.	Anaemia (Hb <11 g/dl): treatment arm 53.9%, control arm 61.1%. (PE = 12%)	No SAEs.	Frequencies of dhfr, dhps, triple dhfr (51, 59, 108) and quadruple dhfr (51, 59, 108) + dhps 437 mutations were higher in the treatment arm at the end of the surveillance period.
		Any parasitaemia: protective efficacy of 83%.	Any parasitaemia: treatment arm 0.41, control arm 2.4 episodes per child/year.	End of transmission season: PE = 46%.		Moderate anaemia (Hb <8 g/dl): treatment arm 1.9%, control arm 3.5%. (PE = 47%)	Most common AEs: fever coughing, vomiting and diarrhoea.	Frequencies similar in both treatment and control groups, except for vomiting and loss of appetite, which were higher in treatment group.
Dicko et al. (2011) (67)	Not evaluated. Note: proportion of children who completed the whole study was 89.8% in the treatment arm and 90.9% in the control arm.	Not evaluated.	Overall incidence – transmission season: treatment arm 1.87, control arm 1.73 episodes per child/year.	Malaria prevalence at weekly survey: Treatment arm 7.4%, control arm 7.5%.	Not evaluated.	Anaemia (Hb <11 g/dl): treatment arm 56.2%, control arm 55.6%.	Not evaluated.	Not evaluated.
			Overall incidence – whole post intervention: treatment arm 0.82, control arm 0.77 episodes per child/year.	End of transmission season: Treatment arm 16.3%, control arm 14.1%.		Moderate anaemia (Hb <8 g/dl): treatment arm 2.9%, control arm 2.7%.		

Abbreviations: AE: adverse event, SAE: severe adverse event, CI: confidence interval, Hb: haemoglobin PE: protective efficacy, SMC: seasonal malaria chemoprevention.

Supplementary Table 3 – Effect of seasonal malaria chemoprevention on several parameters (continuation).

Study	Coverage	Efficacy	Malaria incidence	Parasitaemia prevalence	Gametocyte prevalence	Anaemia	Adverse reactions	Resistance markers
Konaté et al. (2011) (13)	Full course of treatment (three doses): 1 st round – treatment arm 72%, control arm 70%. 2 nd round – treatment arm 80%, control arm 73%. 3 rd round – treatment arm 84%, control arm 73%.	Malaria parasitaemia \geq 5000/ μ l: protective efficacy of 70%. Any parasitaemia: protective efficacy of 71%. Protective efficacy for severe malaria of 69%.	Malaria parasitaemia \geq 5000/ μ l: treatment arm 0.87, control arm 2.88 episodes per child/year. Any parasitaemia: treatment arm 1.11, control arm 3.78 episodes per child/year. Severe malaria: treatment arm 0.01, control arm 0.032 episodes per child/year.	Malaria prevalence at weekly active surveillance visits: Treatment arm 18.6%, control arm 45.8% (PE = 59%). End of transmission season: Treatment arm 11.4%, control arm 41.5% (PE = 73%).	Prevalence during intervention: treatment arm 2.4%, control arm 10.3%. End of transmission season: Treatment arm 2%, control arm 9.3% (risk reduction of 73%).	Anaemia (Hb <11 g/dl): treatment arm 44.2%, control arm 65.5%. (PE = 33%) Moderate anaemia (Hb <8 g/dl): treatment arm 2.7%, control arm 6.2%. (PE = 56%)	No SAEs. Most common AEs: fever, vomiting, diarrhoea and coughing. The risk did not differ between treatment and control groups for all AEs, except vomiting, which was higher in the treatment group.	No difference in mutation proportions between treatment and control groups during post-intervention survey. Overall increase in proportion of triple dhfr mutations only and triple dhfr plus a single dhps (codon 437) mutations, in the post-intervention survey.
Konaté et al. (2011) (68)	Not evaluated. Note: proportion of children who completed the whole study was 93.8% in the treatment arm and 93.0% in the control arm.	Not evaluated.	Overall incidence – transmission season: treatment arm 3.84, control arm 3.45 episodes per child/year. Overall incidence – whole post intervention: treatment arm 1.48, control arm 1.33 episodes per child/year.	Malaria prevalence at weekly survey: Treatment arm 37.6%, control arm 42.1%. End of transmission season: Treatment arm 40.4%, control arm 40.1%.	Not evaluated.	Anaemia (Hb <11 g/dl): treatment arm 51.2%, control arm 48.4%. Moderate anaemia (Hb <8 g/dl): treatment arm 3.7%, control arm 4.7%.	Not evaluated.	Not evaluated.

Abbreviations: AE: adverse event, SAE: severe adverse event, CI: confidence interval, Hb: haemoglobin PE: protective efficacy, SMC: seasonal malaria chemoprevention.

Supplementary Table 3 – Effect of seasonal malaria chemoprevention on several parameters (continuation).

Study	Coverage	Efficacy	Malaria incidence	Parasitaemia prevalence	Gametocyte prevalence	Anaemia	Adverse reactions	Resistance markers
Sesay et al. (2011) (20)	Completion of 3 treatment courses: Treatment arm 93.4% Control arm 94.7%	Any parasitaemia: protective efficacy of 66% (not conclusive as number of cases of very low).	The incidence of clinical cases of malaria was very low in both treatment and control groups. No cases of malaria parasitaemia $\geq 5,000/\mu\text{l}$. Any parasitaemia: treatment arm 0.44, control arm 1.32 per 1000 child months at risk.	End of transmission season: Treatment group 0.67%, control group 0.9% (p = 0.73).	Not evaluated.	Moderate anaemia (Hb <8 g/dl): treatment arm 8.6%, control arm 8.4%.	No SAEs. Only one case of skin rash, but not Stevens Johnson syndrome.	Not evaluated.
Tine et al. (2011) (34)	Not evaluated.	Protective efficacy clinical malaria attacks: 79%.	Clinical malaria attacks: SMC arm 7.2, HHM arm 35.6 per 100 children-months at risk. No severe malaria cases in SMC arm.	End of transmission season: SMC arm 2.1%, HHM arm 4.6% (PE = 57%)	Not evaluated.	Anaemia (Hb <11 g/dl): SMC arm 54.11%, HHM arm 60.3%. (PE = 41%).	Not evaluated.	Not evaluated.
Tine et al. (2014) (35)	Completion of full treatment courses: 97.3% in 2010 88.8% in 2011	Overall study period protective effect of SMC arm 85%.	Clinical malaria attacks: SMC arm 4.91, HHM arm 34.4 per 1000 person-months at risk.	Not evaluated.	Not evaluated.	Not evaluated.	No SAEs. SMC arm: 30% of children presented at least one AE. Most common AEs: nausea and/or vomiting, sleepiness, abdominal pain and diarrhoea.	Not evaluated.

Abbreviations: AE: adverse event, SAE: severe adverse event, CI: confidence interval, Hb: haemoglobin PE: protective efficacy, SMC: seasonal malaria chemoprevention.

Supplementary Table 3 – Effect of seasonal malaria chemoprevention on several parameters (continuation).

Study	Coverage	Efficacy	Malaria incidence	Parasitaemia prevalence	Gametocyte prevalence	Anaemia	Adverse reactions	Resistance markers
Zongo et al. (2015) (38)	All daily doses of SMC were supervised. 97% children seen at the end of the transmission season survey.	Malaria parasitaemia \geq 3000/ μ l: DHA+PQ PE = 79% SP+AQ PE = 84% Any parasitaemia: DHA+PQ PE = 74% SP+AQ PE = 80%	Malaria parasitaemia \geq 3000/ μ l: DHA+PQ 0.14, SP+AQ 0.1, Control group 0.92 episodes per child.	DHA+PQ 12% SP+AQ 12% Control group 36%. (Efficacy for each treatment group was 34%).	DHA+PQ 0.8% SP+AQ 0.8% Control group 1.6%. (Efficacy for both treatment groups was 50%).	Anaemia (Hb <8 g/dl): DHA+PQ 15% SP+AQ 16% Control group 14%.	No SAEs. Both treatment groups were well tolerated. Most common AEs: cough, diarrhoea, vomiting, and fever.	Mutations pfdhfr 51I, pfdhfr 59R, dhps437, pfdhfr I51/R59/S108, pfdhfr I51/R59/S108 plus pfdhps G437 more common in SP+AQ group than DHA+PQ group and control group.
Cissé et al. (2016) (36)	Completion of 3 treatment courses: 93% in 2008, 84% in 2009, 93% in 2010	< 5 years PE = 57% 5-9 years PE = 61% Overall PE = 60%	Number of cases < 5 years Control 2008 2.2, 2009 0.51, 2010 4.3 per 1000. SMC 2008 2.8, 2009 0.36, 2010 2.0 per 1000. 5-9 years Control 2009 1.5, 2010 10.0 per 1000. SMC 2009 0.83, 2010 4.1 per 1000.	< 5 years 2008: Control 5.1% SMC 1.6% (Reduction of 68%) 5-9 years 2009: Control 1.3% SMC 0.22% (Reduction of 84%) 2010: SMC 1.86% (Reduction of 30%)	2008: Control 2.6% SMC 0.64% 2009 and 2010: the number of gametocyte prevalence was too low to measure differences between SMC and control groups.	Moderate anaemia < 5 years 2008: Control 29%, SMC 27% 2009: Control 27.6%, SMC 27.9% 5-9 years 2009: Control 9.2%, SMC 8.9% Severe anaemia (Hb < 6 g/dL) 2008: Control 0.32%, SMC 1.07% 2009: Control 2.2%, SMC 1.0% 5-9 years 2009: Control 1.2%, SMC 1.21%	Most common AE: vomiting. 3 SAEs possibly related to SMC administration.	Proportion of pfdhfr and pfdhps mutations was similar in SMC and control groups. CVIET haplotypes of pfcr1 and the 86Y polymorphism of pfmdr1 were more common in SMC groups.

Abbreviations: AE: adverse event, SAE: severe adverse event, CI: confidence interval, Hb: haemoglobin PE: protective efficacy, SMC: seasonal malaria chemoprevention.

Supplementary Table 3 – Effect of seasonal malaria chemoprevention on several parameters (continuation).

Study	Coverage	Efficacy	Malaria incidence	Parasitaemia prevalence	Gametocyte prevalence	Anaemia	Adverse reactions	Resistance markers
Tagbor et al. (2016) (39)	Overall, around 40% of children received all 5 cycles of SMC.	All children PE = 38.5% (relative to AL group) All 5 SMC cycles: PE = 47.4% (relative to AL group)	All children SMC group 141.9, AL group 229.3, DP group 282.2 per 1000 person-years. All 5 SMC cycles: SMC group 155.0, AL group 298.0, DP group 386.4 per 1000 person-years.	Malaria parasitaemia: SMC group 12.4% AL group 20.3% DP group 19.5% Malaria parasitaemia ≥ 3000/μl: SMC group 4.3% AL group 4.2% DP group 4.7%	Not evaluated.	Hb concentrations 5-7.9 g/dl: SMC group 2.7% AL group 3.4% DP group 3.0% 8-10.9 g/dl: SMC group 41.1% AL group 42.2% DP group 41.3% ≥ 11 g/dl: SMC group 56.2% AL group 54.3% DP group 55.6%	Very few mothers reported adverse events to community health workers over the study period.	Not evaluated.
Diawara et al. (2017) (49)	84% for 1 st day of treatment given by CHW at the 1 st round of SMC, declined with rounds, 67% for 4 th round. 53.4% of children received all 3 days of treatment for all 4 rounds.	Not evaluated.	Not evaluated.	Malaria infection: Control district 46%, SMC district 18%. (Reduction of 65%). Clinical malaria: Control district 2.1%, SMC district 0.5% (Reduction of 80%).	Not evaluated.	Anaemia (Hb <11 g/dl): Control district 68.9%, SMC district 49.3%. (Reduction of 53%). Moderate anaemia (Hb <8 g/dl): Reduction of 74%.	SMC drugs well tolerated. No SAEs. Most common AEs: diarrhoea (7.8%), vomiting (4.9%) and itching (1.7%).	Frequencies of individual and multiple mutations in dhfr, dhps, PfCRT-76T and Pfmdr1-86Y similar between control and SMC districts before and after intervention. Single mutation dhps A437G higher in SMC district at the end of the intervention.

Abbreviations: AE: adverse event, SAE: severe adverse event, CI: confidence interval, Hb: haemoglobin PE: protective efficacy, SMC: seasonal malaria chemoprevention.

Supplementary Table 3 – Effect of seasonal malaria chemoprevention on several parameters (continuation).

Study	Coverage	Efficacy	Malaria incidence	Parasitaemia prevalence	Gametocyte prevalence	Anaemia	Adverse reactions	Resistance markers
Druetz et al. (2018) (44)	Coverage of the 1st cycle: 76% at the household level 83% at the individual level.	PE = 51% (positive malaria test result via pLDH RDT). PE = 62% (positive malaria test result via HRP2-based RDT).	Not evaluated.	Point prevalence: 3.3% reduction Period prevalence: 24.6% reduction	Not evaluated.	Prevalence of moderate to severe anaemia: 16.1% reduction (PE = 32%)	Not evaluated.	Not evaluated.
Ndiaye et al. (2019) (37)	Children treated each month: Cycle 1 89.8% Cycle 2 93.2% Cycle 3 92.4% Cycle 4 92.9% Cycle 5 90.6% Children that received SMC: 1 st dose 99.4% 2 nd dose 98.4% 3 rd dose 96.8%	Overall PE = 83% < 5 years PE = 82% 5-9 years PE = 83%	Overall incidence rate: CCM arm 128.3 SMC arm 22.0 cases per 1000/month < 5 years: CCM arm 134.6 SMC arm 23.8 cases per 1000/month 5-9 years: CCM arm 121.6 SMC arm 20.2 cases per 1000/month	Overall: CCM arm 21.5% SMC arm 5.7% (73% reduction) < 5 years: CCM arm 18% SMC arm 5.7% (69% reduction) 5-9 years: CCM arm 25% SMC arm 5.8% (77% reduction)	Overall: CCM arm 2.8% SMC arm 1.1% (61% reduction) < 5 years: CCM arm 3.5% SMC arm 1.1% (69% reduction) 5-9 years: CCM arm 2.1% SMC arm 1.2% (44% reduction)	Overall Anaemia (Hb < 110 g/l) CCM arm 63.1% SMC arm 51.5% (18% reduction) Overall Severe anaemia (Hb < 60 g/l) CCM arm 2.7% SMC arm 1.3% (53% reduction)	Total of 29 AEs reported by CHWs. No SAEs. Most common AEs: vomiting.	Pfmdr1-86Y and -184Y mutations: CCM arm 38% SMC arm 42% The pfdhfr mutations (51I, 59R, and 108N) and pfdhps-437A more frequent in SMC arm.

Abbreviations: AE: adverse event, SAE: severe adverse event, CI: confidence interval, Hb: haemoglobin PE: protective efficacy, SMC: seasonal malaria chemoprevention.

Supplementary Table 3 – Effect of seasonal malaria chemoprevention on several parameters (continuation).

Study	Coverage	Efficacy	Malaria incidence	Parasitaemia prevalence	Gametocyte prevalence	Anaemia	Adverse reactions	Resistance markers
Ambe et al. (2020) (41)	73% received all 4 cycles of SMC.	Not evaluated.	Not evaluated.	SMC 4.9% Control 15.9%	Not evaluated.	Overall mean haematocrit: 34.0 ± 5.3% Lower haematocrit in control clusters and higher in SMC clusters. Higher prevalence of anaemia in control clusters.	No SAEs. 4.9% of children who received SMC had AEs. Included itching, rashes, and vomiting.	Not evaluated.
Baba et al. (2020) (45)	2015: Mean coverage per month: 76.4% 54.5% of children received all 4 treatments. 2016: Mean coverage per month: 74.8% 53% of children received all 4 treatments. Burkina Faso had the highest coverage both years.	Polled estimate of PE (within 28 days of administration of SMC) = 88.2% Pooled estimate of PE (29 to 42 days post administration of SMC) = 61.4%	Detailed results not reported in paper.	Prevalence not evaluated. Overall reduction in malaria mortality: Burkina Faso 42.4% The Gambia 56.6% Overall severe malaria cases reduction: Burkina Faso 27.4% (2015 only) The Gambia 54.8% Overall reductions outpatient malaria cases ranged from 25.5% in Nigeria to 58.8% in The Gambia.	Not evaluated.	Not evaluated.	36 SAEs: 1 rash, 2 fever, 31 gastrointestinal disorders, 1 extrapyramidal syndrome, 1 Quincke's oedema. No severe skin reactions.	Combination of the pfcr1-CVIET, pfmdr1-86Tyr, and pfmdr1-184Tyr: < 5 years: 1.3% in 2016 and 0.5% in 2018. 10-30 years: 0.7% in 2016 and 0.4% in 2018. Quintuple mutation (triple mutation in pfdhfr with pfdhps-437Gly and pfdhps-540Glu): < 5 years: 0.4% in 2016 and 0.7% in 2018. 10-30 years: 0.2% in 2016 and 1.0% in 2018.

Abbreviations: AE: adverse event, SAE: severe adverse event, CI: confidence interval, Hb: haemoglobin PE: protective efficacy, SMC: seasonal malaria chemoprevention.

Supplementary Table 3 – Effect of seasonal malaria chemoprevention on several parameters (continuation).

Study	Coverage	Efficacy	Malaria incidence	Parasitaemia prevalence	Gametocyte prevalence	Anaemia	Adverse reactions	Resistance markers
Cairns et al. (2020) (42)	Burkina Faso: 64.9% to 75.4% of children received all 4 monthly courses. 94.7% to 99.9% children received all 3 daily doses (on the first dose of each cycle).	Malaria hospital admissions or death from malaria: PE = 87.4%	Malaria hospital admissions or death from malaria in the 28 days after SMC: 13.6 cases per 1000 child-years at risk, increased to 51.1 after this period.	Any parasitaemia prevalence at the end of study period: Children who received final SMC cycle ranged from 2.05% to 8.37%	Not evaluated.	Not evaluated.	Not evaluated.	Pfcr1 K76T, pfmdr1 N86Y and combined pfcr1 K76T + pfmdr1 N86Y mutations and Pfdhfr-C59R, pfdhps-A437G and pfdhps-K540E mutations did not increase over the study period.
	Mali: 61.6% to 74.3% of children received all 4 monthly courses. 91.2% to 99.3% children received all 3 daily doses (on the first dose of each cycle).	Uncomplicated malaria: PE = 78.3%	Uncomplicated malaria: first 21 days 402.1 cases per 1000 child-years at risk, increased to 908.4 22 to 28 days after SMC, 2,500 from 29 days onwards.	Children who missed the final SMC cycle ranged from 21.1% to 33.0% in both countries and over the 3-year study period.				Low frequencies of mutations in school-children that did not receive SMC and were residents in the study area.
Issiaka et al. (2020) (46)	Not evaluated.	39% reduction in hospitalizations for all causes.	All-cause hospitalizations SMC arm: 19.60 Control arm: 33.45 per 1000 person-years	Not evaluated.	Not evaluated.	Not evaluated.	Not evaluated.	Not evaluated.
		47% reduction in hospitalizations related to severe malaria.	Severe malaria SMC arm: 13.07 Control arm: 25.41					
		66% reduction in mortality.	all-cause mortality SMC arm: 3.63 control arm: 8.29					

Abbreviations: AE: adverse event, SAE: severe adverse event, CI: confidence interval, Hb: haemoglobin PE: protective efficacy, SMC: seasonal malaria chemoprevention.

Supplementary Table 3 – Effect of seasonal malaria chemoprevention on several parameters (continuation).

Study	Coverage	Efficacy	Malaria incidence	Parasitaemia prevalence	Gametocyte prevalence	Anaemia	Adverse reactions	Resistance markers
Konaté et al. (2020) (70)	Not evaluated.	Reduction of malaria clinical risk: 1 st year 1 st cycle 65% 2 nd cycle 73% 3 rd cycle 62% 2 nd year 1 st cycle 75% 2 nd cycle 77% 3 rd cycle 63% Risk was similar 2 months after SMC in both years.	SMC years: 1 st cycle 5.2% 2 nd cycle 5.2% 3 rd cycle 5.7% Control years: 1 st cycle 10.2% 2 nd cycle 9.3% 3 rd cycle 9.2% Malaria clinical incidence similar 2 months after SMC: SMC group 8% Control 9%	Not evaluated.	SMC years: 1 st cycle 2.4% 2 nd cycle 8.8% Control years: 1 st cycle 15.2% 2 nd cycle 16.6% In the 3 rd cycle and 2 months after SMC, gametocyte prevalence remains similar in both groups.	A significant increase in haemoglobin was reported in 2 nd year of SMC implementation in all cycles.	Not evaluated.	Not evaluated.
Maiga et al. (2020) (71)	Not evaluated.	Not evaluated.	SMC treatment resulted in: significant reduction of malaria infection with incidence ratio of IR = 0.01 and significant reduction in clinical malaria (OR = 0.25).	Malaria infection: Baseline 28.7% Post SMC 12.4% Clinical malaria: Baseline 4.2% Post SMC 0.3%	Baseline 9.1% Post SMC 2.2%	Anaemia (Hb <11 g/dl): Baseline 67.4% Post SMC 50.1%	Not evaluated.	Not evaluated.

Abbreviations: AE: adverse event, SAE: severe adverse event, CI: confidence interval, Hb: haemoglobin PE: protective efficacy, SMC: seasonal malaria chemoprevention.

Supplementary Table 3 – Effect of seasonal malaria chemoprevention on several parameters (continuation).

Study	Coverage	Efficacy	Malaria incidence	Parasitaemia prevalence	Gametocyte prevalence	Anaemia	Adverse reactions	Resistance markers
Wagman et al. (2020) (43)	2013: Pilot district 94.2% of the target population received two rounds of SMC. In 2014: programme expanded and 105% of the target population received 2 rounds of SMC.	SMC intervention: PE = 15% (November – 1 st month after SMC) PE = 60% (months after until February)	Control districts: 3218 cases per 10,000 child-months at risk	Not evaluated.	Not evaluated.	Not evaluated.	Not evaluated.	Not evaluated.
		IRS intervention: PE = 63% (September – 1 st month after campaign), and diminished over time.	SMC districts: 2758 cases per 10,000 IRS districts: 1682 cases per 10,000					
		SMC + IRS: PE = 73% (1 st month) PE = 60% (months after until February)	IRS+SMC districts: 1529 cases per 10,000					
Ahmad et al. (2021) (50)	Caregivers reported to have administered the 2 days of treatment following the 1 st observed dose. However, when cross-checked with the SMC administration card, only 68.7% had 2 nd dose and 66.6% the 3 rd dose.	Not evaluated.	Not evaluated.	Not evaluated.	Before SMC: SMC group 10.7% Control 13.3% Post SMC: Received all doses of treatment SMC group 15.6% Control 12.7% (Differences not statistically significant)	Not evaluated.	27.1% of children vomited the 1 st dose, 14.6% the 2 nd dose, and 12.5% the 3 rd dose.	Not evaluated.

Abbreviations: AE: adverse event, SAE: severe adverse event, CI: confidence interval, Hb: haemoglobin PE: protective efficacy, SMC: seasonal malaria chemoprevention.

Supplementary Table 3 – Effect of seasonal malaria chemoprevention on several parameters (continuation).

Study	Coverage	Efficacy	Malaria incidence	Parasitaemia prevalence	Gametocyte prevalence	Anaemia	Adverse reactions	Resistance markers
Ansah et al. (2021) (47)	87% received 2 nd dose, 80% received 3 rd dose and 85% received last dose.	PE = 48% for severe malaria	Severe malaria: SMC group incidence rate 10 per 1000 person-years at risk	Control group: Baseline 9.0% End-line 21.5%	Control group Baseline 0.6% End-line 5.5%	Anaemia (Hb < 11.0 g/dl) Control group Baseline 54.4% End-line 62.6%	No SAEs.	Not evaluated.
			Control group 20 per 1000 person-years at risk	SMC group: Baseline 31.1% Post SMC 12.1% (19% difference)	SMC group Baseline 1.8% Post SMC 3.2%	SMC group Baseline 52.8% Post SMC 38.6%	Moderate anaemia (Hb < 8.0 g/dl): Control group Baseline 4% End-line 6%	
Cairns et al. (2021) (48)	A very high percentage of cases and controls received all 3 doses of SMC, in all countries. Overall, it ranged from 94.1% in The Gambia to 99.7% in Burkina Faso.	Overall: Clinical malaria PE = 88% (SMC received in the past 28 days)	Overall: Clinical malaria OR = 0.12 (SMC received in the past 28 days)	Not evaluated.	Not evaluated.	Not evaluated.	Not evaluated.	Not evaluated.
		PE = 61% (Past 29-42 days)	OR = 0.39 (Past 29-42 days)					
		PE = 59% (Past 29-42 days)	OR = 0.41 (Past 29-42 days)			SMC group Baseline 4% Post SMC 2%		

Abbreviations: AE: adverse event, SAE: severe adverse event, CI: confidence interval, Hb: haemoglobin PE: protective efficacy, SMC: seasonal malaria chemoprevention.

Supplementary Table 3 – Effect of seasonal malaria chemoprevention on several parameters (continuation).

Study	Coverage	Efficacy	Malaria incidence	Parasitaemia prevalence	Gametocyte prevalence	Anaemia	Adverse reactions	Resistance markers
Coldiron et al. (2021) (52)	88% 1 st cycle 90% 2 nd cycle 72% 3 rd cycle 70% 4 th cycle (2016 independent study)	Not evaluated.	Not evaluated.	3-59 months: High season 1, 2 51.9%, 50.7% Low season 1, 2 48.1%, 39.6%	3-59 months: High season 1, 2 19.3%, 16.4% Low season 1, 2 12.4%, 9.9%	Not evaluated.	Not evaluated.	Not evaluated.
				5-9 years: High season 1, 2 66.2%, 73.2% Low season 1, 2 64.1%, 56.3%	5-9 years: High season 1, 2 18.5%, 16.2% Low season 1, 2 13.1%, 6.3%			
				> 10 years: High season 1, 2 23.6%, 29.9% Low season 1, 2 21.0%, 14.8%	> 10 years: High season 1, 2 4.9%, 5.5% Low season 1, 2 1.5%, 1.6%			
Coulibaly et al. (2021) (33)	Interventions were implemented by Mali NMCP. Coverage rate for each intervention was > 85%, according to the local NMCP worker.	Not evaluated.	< 5 years: Before SMC 1999 3.9 2012 2.0 After SMC 2017-18 0.3 episodes person/year	Overall average prevalence, 2017-18: < 5 years 5.5% 6-10 years 5.7% > 10 years 8.7%	Not evaluated.	Overall prevalence of anaemia, 2017-18 2.3%	Not evaluated.	Not evaluated.
			6-10 years 2017-18 0.5 episodes person/year		6-10 years: Highest 7% (2018)			
			> 10 years 2017-18 0.5 episodes person/year		> 10 years: prevalence did not exceed 5% during the entire study.			

Abbreviations: AE: adverse event, SAE: severe adverse event, CI: confidence interval, Hb: haemoglobin PE: protective efficacy, SMC: seasonal malaria chemoprevention.