Infection and Drug Resistance

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Seasonal Malaria Chemoprevention Implementation: Effect on Malaria Incidence and Immunity in a Context of Expansion of *P. falciparum* Resistant Genotypes with Potential Reduction of the Effectiveness in Sub-Saharan Africa

Séni Nikiema[1,2], Issiaka Soulama[1,3], Salif Sombié[1], André-Marie Tchouatieu[4], Samuel Sindie Sermé[5], Noëlie Béré Henry[5], Nicolas Ouedraogo[1], Nathalie Ouaré[1,6], Raissa Ily[1,6], Oumarou Ouédraogo[3], Dramane Zongo[3], Florencia Wendkuuni Djigma[2], Alfred B Tiono[1], Sodiomon B Sirima[5], Jacques Simporé[2,7]

[1]Research Department, Centre National de Recherche et de Formation sur le Paludisme (CNRFP)/Institut National de Santé Publique (INSP), Ouagadougou, Burkina Faso; [2]Laboratoire de Biologie Moléculaire et de Génétique (LABIOGENE), Université Joseph KI-ZERBO, Ouagadougou, Burkina Faso; [3]Biomedical and Public Health Department, Institut de Recherche en Sciences de la Santé (IRSS)/Centre National de Recherche Scientifiques et Technologiques (CNRST), Ouagadougou, Burkina Faso; [4]Access and Product Management – Chemoprevention Department, Medicines for Malaria Venture (MMV), Geneva, Switzerland; [5]Direction Scientifique, Groupe de Recherche Action en Santé, Ouagadougou, Burkina Faso; [6]Institut Supérieur des Sciences de la santé (IN.S.SA), Université Nazi Boni, Bobo Dioulasso, Burkina Faso; [7]Centre de recherche biomoléculaire Pietro Annigoni (CERBA), Ouagadougou, Burkina Faso

Correspondence: Issiaka Soulama, Institut de Recherche en Sciences de la Santé /CNRST, 06 BP 9067, Ouagadougou, Burkina Faso, Tel +226707571190, Email iss.soulama@gmail.com

Abstract: Seasonal Malaria Chemoprevention (SMC), which combines amodiaquine (AQ) with sulfadoxine-pyrimethamine (SP), is an effective and promising strategy, recommended by WHO, for controlling malaria morbidity and mortality in areas of intense seasonal transmission. Despite the effectiveness of this strategy, a number of controversies regarding the impact of the development of malaria-specific immunity and challenges of the strategy in the context of increasing and expanding antimalarial drugs resistance but also the limited coverage of the SMC in children make the relevance of the SMC questionable, especially in view of the financial and logistical investments. Indeed, the number of malaria cases in the target group, children under 5 years old, has increased while the implementation of SMC is been extended in several African countries. This ambivalence of the SMC strategy, the increase in the prevalence of malaria cases suggests the need to evaluate the SMC and understand some of the factors that may hinder the success of this strategy in the implementation areas. The present review discusses the impact of the SMC on malaria morbidity, parasite resistance to antimalarial drugs, molecular and the immunity affecting the incidence of malaria in children. This approach will contribute to improving the malaria control strategy in highly seasonal transmission areas where the SMC is implemented.

Keywords: seasonal malaria chemoprevention, immunity, resistance, sulfadoxine-pyrimethamine, amodiaquine

Background

Malaria is still a leading cause of morbidity and mortality despite all the efforts made to control the disease. Over 80% of malaria cases and 90% of malaria deaths occur in Africa and mainly in children.[1] Although the incidence of malaria is declining in many parts of sub-Saharan Africa, it remains an important public health problem, especially in risk groups such as infants, children, and pregnant women. In this region of Africa, most of the malaria cases and deaths occur during or immediately after the rainy season (approximately from July to October) and children below 5 years of age are at the greatest risk; world malaria report 2021 data indicate that 60–75% in 2009–2017 still occurred in children aged under 5

Received: 18 May 2022
Accepted: 1 August 2022
Published: 13 August 2022

years.[1] In order to strengthen the fight against malaria in children, a new preventive strategy was developed and recommended by the World Health Organization (WHO) in 2012 following a report of the Technical Expert Group (TEG) of Preventive Chemotherapy. Seasonal Malaria Chemoprevention (SMC), previously referred to as Intermittent Preventive Treatment in children (IPTc), is defined as the intermittent administration of full treatment courses of an antimalarial drug to children during the peak of the malaria transmission season with the aim of preventing malaria-associated mortality and morbidity[2] by a malaria prevention strategy in children living in the Sahel sub-regions of Africa.[3,4] The Sahel stretches from Senegal on the Atlantic coast, through parts of Mauritania, Mali, Burkina Faso, Niger, Nigeria, Chad, and Sudan, to Eritrea on the Red Sea coast. According to the WHO policy recommendation, SMC involves the repeated administration of therapeutic doses of Sulfadoxine-Pyrimethamine (SP) and Amodiaquine (AQ) drugs at monthly intervals during the malaria transmission period in areas where malaria is endemic and seasonal.[5–7] SP +AQ is a non-artemisinin combination treatment.

Mali was one of the first countries in the Sahel region to implement SMC in 2012, which has now been gradually rolled out to cover the entire country.[8] As of 2020, 13 countries have adopted SMC (Benin, Burkina Faso, Cameroon, Chad, Gambia, Ghana, Guinea, Guinea Bissau, Mali, Niger, Nigeria, Senegal, and Togo) at different scales of implementation.[9] Several studies in Africa have shown that this intervention is cost-effective, safe, and feasible for the prevention of malaria among children in areas with highly seasonal malaria transmission.[10,11] The number of children reached with at least one dose of SMC has increased steadily from nearly 0.2 million in 2012 to about 33.5 million in 2020 in 13 countries in the African Sahel.[1]

Methodology

We considered as relevant all articles published online in PubMed by using the search terms "SMC" or "Seasonal malaria chemoprevention". As a precursor term of the SMC strategy, we have also included the term "intermittent preventive treatment in children" or "IPTc" in our search. We concluded the literature research on April 5, 2022. Finally, we considered the studies eligible only if they met the following inclusion criteria: a) the articles were written in English and published by April 5, 2022, b) the study was carried out in Sahelian Africa region participants (except those used to discuss the review), and c) Sulfadoxine-Pyrimethamine and Amodiaquine, Dihydroartemisinin-Piperaquine should be used as antimalarial drugs.

The manuscripts with only abstracts available were excluded as we could not access the full text. We then reviewed the following: deployment and implementation progression, the impact of SMC on the prevalence of malaria cases in high-risk individuals, the factors affecting the effectiveness of the Seasonal Malaria Chemoprevention, and the interaction of the SMC with malaria immunity and the coverage of the SMC.

Results and Discussions

Specificity and Outcomes of the Selected Studies for Review

From the PubMed search using the specific terms mentioned above, 249 articles were found and 185 studies met the inclusion criteria, as presented in Figure 1.

Although we sought out the bulk of articles on SMC with full texts, the reality of our review focused primarily on data collected in the Sahelian part of Africa where the SMC is the WHO recommendation. Of course, we have used some data from Nigeria and Ghana, parts of which have a seasonal malaria transmission pattern. We believe that focusing the review on articles published on studies conducted in Burkina Faso, Mali, Niger, and Senegal will essentially help to better show the effect of SMC on malaria morbidity, resistant genotypes, or immunity that we are looking for because at the moment the WHO requirements and recommendations are focused in this area.

The published studies on Seasonal Malaria Chemoprevention were predominantly conducted in West Africa (168/185, 90.8%). Three countries in the Sahelian regions (Senegal, Mali, and Burkina Faso) account for more than 80% (136/166) of the studies conducted in the West African region (Figure 2). The first pilot studies on the intermittent prevention treatment in children were carried out in Senegal in 2006,[12] and Mali[13] and Burkina Faso[14] started this evaluation in 2008 as a multi-center study. Looking at the report from WHO,[3] it is important to note that the results of the evaluations in

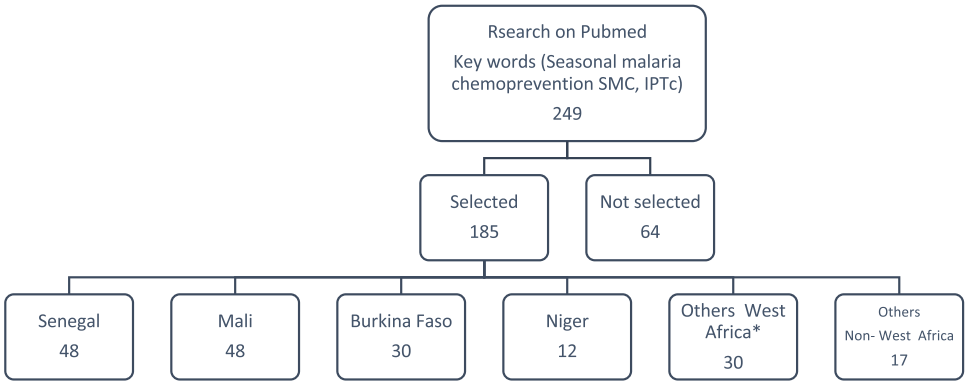

Figure 1 Paper mining flowchart. *Others West Africa include Gambia, Nigeria, Ghana, Côte D'Ivoire, Guinea, Chad, and Mauritania.
Abbreviations: SMC, Seasonal Malaria Chemoprevention; IPTc, Intermittent Preventive Treatment in Children.

Figure 2 Three countries accounting for more than 80% of the SMC studies in West Africa.

Burkina Faso, Mali, and Senegal were extremely decisive in WHO's decision to adopt this preventive strategy called SMC as one of the strategies that can contribute significantly to the reduction of malaria morbidity and mortality in the area where malaria transmission is seasonal. Many articles reflect the same topics. Then, to avoid redundancy many are not included in the list of author references.

SMC Deployment and Implementation in Sub-Saharan Africa

The implementation of SMC in Sahelian countries has been gradual from a pilot phase in the various countries to a full-scale phase to the entire population of concerned countries. By organizing the implementation in this way, the actors learn from the lessons and failures and then improve the progress. This implementation process has been strongly supported by committed organizations (Medicines for Malaria Venture, Malaria Consortium, UNICEF, Global Fund, UNITAID, WHO, World Bank, PMI) alongside National Malaria Control Programs in Sub-Saharan Africa. This synergy remains today a winning combination in the implementation of SMC in Sub-Saharan Africa. Indeed, by bringing in their experience in program management, by building bridges between the different countries implementing this strategy and bringing additional financial and logistical resources, the scale up of SMC has been remarkable to reach the majority of eligible children in the Sahelian countries. Countries like Burkina Faso took about 6 years (2014 to 2019) to cover the country's entire health districts (about 70 health districts) with the support from the Malaria Consortium, USAID, PMI, Unitaid, Global Fund, and World Bank (Figure 3).

It is important that the organizational approach (3 days dose administration for each child during four cycles) is well respected by the parties implementing the strategy by putting in place procedures to better monitor planned activities. Although the WHO policy recommendation is for four monthly cycles, countries can set their own policies according to the local context. In that context five cycles are now implemented in several countries, including Burkina Faso (across the southern half of the country), in areas where the peak of transmission season is slightly longer. But the core of the SMC strategy still remains the 4 months of implementation. One of the expansion approaches of the SMC also concerns the targeted ages, with the option to extend above 5 years. There are some studies that have focused on older ages,[15–19] with arguments related to the shift of the transmission curve in the tranche from 5 to 10 years. Senegal is a pilot country in extending the age target from 5 to 10 years.[15,19] Confirmation of the interest of the extension of the age range is strongly awaited to further enlighten the scientific community on the cost-benefit of this extension. In addition, the potential benefit of expanding the age group eligible for preventive treatment needs to be weighed against its potential risks, including development of drug resistance and/or the risk of hindering acquisition or maintenance of immunity. However, the WHO Technical Advisory Committee felt that any adjustment should be tailored to the needs of each

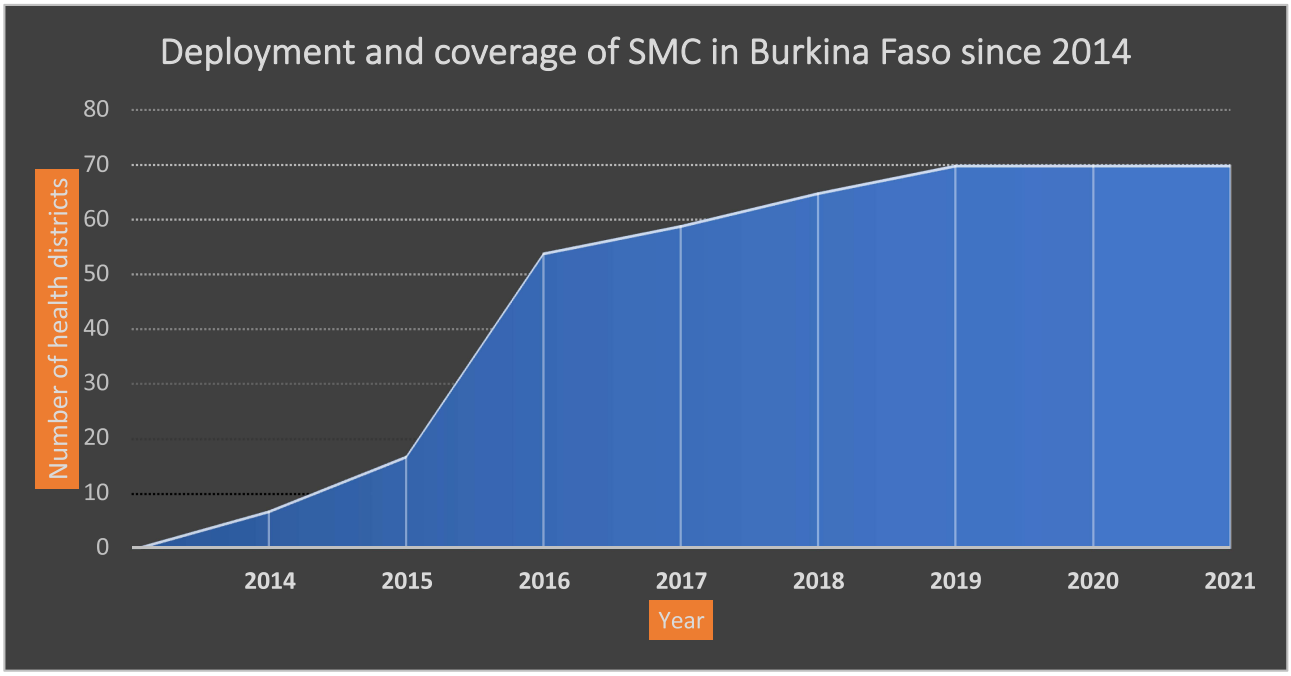

Figure 3 Example of Seasonal Malaria Chemoprevention deployment and coverage in Burkina Faso (unpublished data from Malaria Consortium).

country and its context. This is especially important as countries should be supported to develop or revisit their strategies for greater effectiveness.

Impact of SMC on the Prevalence of Malaria Cases in High-Risk Individuals

Pilot Studies as a Proof of Concept of the SMC Strategies

To confirm SMC as a strategy that can positively influence the prevalence or incidence of malaria in a population of children at risk of malaria, pilot studies were conducted mainly in Burkina Faso, Mali, and Senegal, under the known names of intermittent preventive treatment in children. These studies, considered to be the "ancestors" of the SMC, involved more than 3,000 children in each of these countries. The results generated from those studies[2,15,16,20] allowed WHO to recommend the strategy for scaling up in the Sahel while the following should be noted.

Indeed, results from studies in Senegal from Cissé et al's[12] study showed a malaria reduction incidence of 86% among children who received seasonal intermittent preventive treatment. The same trends of malaria incidence rate reduction were confirmed in a case-control study in Mali with 3.2 episodes in the treatment group vs 5.8 episodes in the control group, with age-adjusted Protective Efficacy (PE) of 42.5% (95% CI=28.6–53.8%).[13]

A parallel study was conducted during the same period in Burkina Faso. Malaria incidence defined as fever or history of fever with parasitaemia ≥5,000/µL, assessed during this study, was estimated at 2.88 (95% CI=2.70–3.06) per child in the control arm versus 0.87 (95% CI=0.78–0.97) in the intervention arm with a protective efficacy (PE) of 70% (95% CI=66–74%) ($p<0.001$). The results from this study showed a reduction of 69% (95% CI=6–90%) in the incidence of severe malaria ($p=0.04$) and a 46% reduction (95% CI=7–69%; $p=0.03$) in the incidence of all-cause hospital admissions. Remarkably, data were in line with a reduction of the prevalence of malaria infection at the end of the malaria transmission season by 73% (95% CI=68–77%; $p<0.001$) while moderately severe anemia decreased by 56% (95% CI=36–70%; $p<0.001$).

Evidence of SMC Influence on the Reduction of Malaria Incidence and Prevalence in Children Under 5 Years

Whatever the data sources, it is well highlighted children under 5 years are at high risk of malaria in endemic areas and have typically been targeted for malaria control interventions, along with pregnant women.[14] Based on the success of the seasonal malaria chemoprevention from previous pilot studies, WHO has recommended that, in high transmission areas, Sulfadoxine-Pyrimethamine combined with Amodiaquine be given once a month at least a month apart during 4 months.[15] Importantly, several studies demonstrated the influence of the SMC in the decline of the risk of malaria infections in the under 5 years group through the use of sulfadoxine– pyrimethamine (SP) combined with amodiaquine.[16–20] Great support on the strategy comes from the modeling studies,[21,22] which indicated a strong effect of SMC as a promising intervention. However, the gap of information on the evidence for long-term routine implementation of a such strategy needs to be filled. For instance, studies conducted in Mali showed that treatment of children with only one round during the SMC campaign positively influence malaria symptoms and improve the anemia status of children aged 6–59 months,[22,23] confirming the potential impact of the SMC on malaria morbidity and mortality. As stated previously, the SMC is greatly implemented in Burkina Faso. A study conducted in Burkina Faso by Konaté et al[14] confirms the impact of the SMC in malaria burden, with a 62% reduction in malaria prevalence during a routinely implemented SMC campaign. In 2014 and 2015, a specific approach study assessing observable and time-invariant non-observable confounding factors concluded there was a reduction of the parasitemia by 3.3, with protective effects of 51% and 62%, respectively, while the likelihood of getting moderate-to-severe anemia was reduced by 32%.[24]

Many others studies in Mali[7,25] and Ghana[26] reinforced the influence of the SMC on the reduction of the prevalence of parasitemia at the end of the high transmission season, which was lower in areas receiving SMC compared to those not receiving SMC.[27] However, studies confirmed the potential impact of the SMC to prevent malaria cases and childhood deaths each year will greatly depend on the successful delivery to the population at risk.[4,28–30]

This effectiveness of SMC has been strongly confirmed by the large study conducted between 2015 and 2016 through the ACCESS-MCH project in seven West African countries (Burkina Faso, Chad, Gambia, Guinea, Mali, Niger, and Nigeria), which assessed coverage, intervention effectiveness, safety, feasibility, drug resistance, and cost-effectiveness.[29] These findings, while supporting efforts of the scaling up of SMC with high levels of coverage in west and central Africa,

emphasize the need to set up a resistance monitoring system in view of the potential risks of resistance to sulfadoxine-pyrimethamine and amodiaquine.[29]

Factors Affecting the Effectiveness of the SMC

SMC Coverage and Limitations

The SMC requires that children 3–59 months of age receive an antimalarial treatment for 3 consecutive days during the months of SMC. This is extremely important, as shown in early pilot studies,[30] for the success of the preventive strategy. It is also important that coverage, defined as the proportion of the children aged 3–59 months at the time of SMC who received the 3 days treatment of that specific round, or during all four rounds of SMC (full SMC coverage), which is a key factor in the success of the strategy, remains sufficient to ensure good protection in the target population.[30]

A very good coverage will result in a substantial reduction in malaria cases and deaths in the target population. SMC high levels of coverage can be achieved through door-to-door delivery, as assessed by the Malaria Consortium in Burkina Faso.

Although coverage is key to the success of the SMC, the availability of drug supplies and the timing of cycles to correspond with the high transmission period would inevitably affect the effectiveness of this strategy. Local contingencies may have reduced the adherence to SMC during its implementation and, consequently, limited its effectiveness in the specific area. Indeed, in a previous study assessing coverage of the SMC in children, self-reported coverage for the first cycle of the round was 76% and 83% at the household and individual levels (children <5 years), respectively.[31] This study found that coverage for children was 100% at the first cycle, then gradually decreased to 69% at the fourth cycle. Several factors could explain the limited coverage for households and for children, notably their absence during the rainy season. Indeed, it is common for some household members to spend all day in the fields. Some even leave their homes and temporarily live in shelters closer to the fields.[32] Also, it is common for young children to stay with their mother during the day and accompany her wherever she goes. This could explain why, even if a household was visited, some children did not receive SMC treatment. Under these conditions, planning the implementation of SMC is of great importance in order to anticipate the possible issues. Previous implementation experiences have served and continue to serve for better organization of SMC, especially for countries that are just starting to implement SMC. And the role of partners such as MMV, Malaria Consortium, and others to organize the different actors involved and to consolidate the achievements in perfect synergy is of paramount importance in the success of the SMC.

Molecular Markers of Resistance to Sulfadoxine-Pyrimethamine (PfdhfrPfdhps)

During their evolution, the microorganisms have been able to thwart the traps set for them by the environment and especially their host (immunity and use of anti-infectious molecules). The emergence and spread of antimalarial drug resistance represent a serious public health problem. *Plasmodium falciparum* is now resistant to all antimalarials used, even the latest marketed artemisinin-based combinations.[33]

In the context of large implementation of antimalarial drugs, chemoprevention with Sulfadoxine-Pyrmethamine (SP) combined with Amodiaquine, as is currently the case with SMC in the African Sahel region, malaria parasite is under deep drugs pressure and subject to resistance. As previously defined, antimalarial drug resistance corresponds to the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug in doses equal to or higher than those usually recommended but within the limits of tolerance of the subject.[34]

Previous studies have shown that SMC would affect the prevalence of resistant strains of the parasite through the evaluation of molecular markers of resistance. Obviously in the context of SMC, the mutations concerned are carried by *P.falciparum* genes affecting the metabolism of the Sulfadoxine-Pyrimethamine and amodiaquine: they are mainly: the *pfcrt* (*Plasmodium falciparum chloroquine resistance transporter*), *pfmdr1*(*Plasmodium falciparum* multidrug resistance 1), *dhfr* (dihydrofolate reductase), *and the dhps* (dihydropteroate synthetase) genes. In the context of tracking the susceptibility of the parasite against the combination Sulfadoxine-Pyrimethamine +Amodiaquine, the assessment of the prevalence of the above mutations represents a great interest.[5] The combination of different points of mutation such as *Pfdhfr* allele N51I/C59R/S108 N and the haplotype, A437G and K540E of the *Pfdhps* gene, known as quintuple mutation is strongly associated with clinical failure of SP treatment.[3,35,36] Fortunately, the profile of the quintuple mutation is rare in most of the West African countries, while the

individual mutations are frequent. However, the existence of the individual mutation in high frequency still threatens the efficacy of the combination including the Sulfadoxine-pyrimethamine, which is also the combination used for the intermittent preventive treatment of women in the last two trimesters of pregnancy (IPTp).[29] WHO recommendation has anticipated the alternative drugs for IPTp in the case when these quintuple mutant parasites prevalence is greater than 50%. Countries in East and Central Africa are now struggling with a high prevalence of triple mutants *pfdhps* allele 437G/540E/581G that complicate the use of SP.[37,38] Even the prevalence is low, the triple mutant *pfdhfr* has been remarkably notified inWest Africa, as reported in Burkina Faso, neighboring Benin, Mali, nor Nigeria.[36,37] However, the origin of the mutation in West Africa still depends on the hypothesis of spreading of parasites that carry the imported *pfdhfr* Southeast Asian allele from East African sources.[39,40] In such conditions, decisions about whether to introduce SMC or IPTp as additional malaria preventive strategies partly depend on the local level of resistance to the antimalarial drugs being used.[3,29]

Molecular Markers of Resistance to Amodiaquine (pfmdr1 and Pfcrt)

When studying molecular markers associated with resistance to antimalarial drugs such as Sulfadoxine – Pyrimathamine + Amodiaquine combination, it is important to consider, in addition to mutations on the *dhfr* and *dhps* genes, the importance of *pfcrt* and *pfmdr1* mutations. Indeed, mutations in the *pfcrt* and *pfmdr1* genes are strongly associated with amodiaquine resistance, as demonstrated in several previous studies.[41–43]

Obviously, the increase in the prevalence of these mutations and in particular that of the 86Y/184Y/1246Y *pfmdr1* triple mutation constitutes a serious threat to the efficacy of amodiaquine and consequently to the CPS strategy.[41–43] The prevalence of such mutations are variably distributed in the West African Sahelian region. Indeed, in Niger, the F184FY mutation is found to be the most frequent, with 37% of sequences displaying this mutation, while the 86Y, 1042D and 1246Y mutations were less common, with a prevalence of around 0.1. Even though most of the evidence were focused on the point of mutations, it also demonstrated that the increase in the copy number (more than 2) of the *pfmdr1* wild type is also highly associated with four aminoquinolines like amodiaquine.[44]

Effect of Sulfadoxine Pyrimethamine-Amodiaquine-Based SMC on Plasmodium

Falciparum Resistant Genotypes

After testing several single-use molecules, the most suitable design for the SMC strategy was to combine two molecules with different mechanisms of action: Sulfadoxine-Pyrimethamine and amodiaquine. Amodiaquine ensures rapid parasite clearance and Sulfadoxine-Pyrimethamine due to its half-lasting effect ensures a prolonged antimalarial effect on residual parasites. Obviously, this concept is based on the assumption that the efficacy of these antimalarials is not affected by parasite susceptibility.[45] Interestingly, Lo et al[45] assessed the impact the of SP+AQ combination over the course of years on the prevalence of molecular markers of resistance and demonstrated that the prevalence of the *pfmdr1*-86Y was higher in children with SMC treatment. In general, results from the Lo et al[45] study showed that the prevalence of genotypes associated to SP were significantly lower in the SMC treatment group. It is clear that the progression of such mutations is a serious threat to the effectiveness of SMC, but also of IPTp strategy in pregnant women. Today more than ever, the emergence of mutations associated with artemisinin-based combination therapies with new molecular mechanisms dangerously undermines our antimalarial tools, in addition to the mutations mentioned above. Of courses, we need to set up strategies to monitor these mutations in order to help policy-makers to adapt the therapeutic policies in the management of malaria disease. This is the clear reason why WHO is now encouraging countries to consider molecular monitoring of malaria as a strong necessity if we are to defeat malaria altogether.

Could SMC Impact Malaria Immunity?

Although SMC remains an effective strategy, as mentioned above, as with any intervention strategy, its long-term implementation is still an area of concern, especially the influence it may have on the development of malaria-specific immunity. Some authors confirmed this impact of SMC on the immunity through an evaluation of antigens, notably GLURP and AMA1.[2] However, it might be important to highlight other factors, not measured in this study, such as the level of malaria transmission, the heterogeneity of exposure and higher previous exposure that are significant predictors

of higher antibody responses.[2] Using antigens that develop a strong antigenic response such as GLURP, the glutamate-rich protein (GLURP) an exoantigen expressed in all stages of the *Plasmodium falciparum* life cycle in humans, Ndiaye et al[2] aimed to assess an anti-GLURP antibodies response that can inhibit parasite growth in the presence of monocytes via antibody-dependent cellular inhibition (ADCI). From the description of the GLURP protein structure, the N-terminal R0 region of the protein is clearly highlighted as a major parasite-inhibitory region[46] which demonstrated the importance in malaria immunity assessment; In addition to GLURP-R0 antigen, Apical MembranAntiogen1 (AMA 1) constitutex a protein present in the merozoite and sporozoites membrane and which plays a central role in parasite invasion of erythrocytes and potentially hepatocytes. This antigen is also considered as a potential candidate in assessing malaria immunity that can be inhibited by anti-AMA1 antibodies.[47,48] In any case, their interest and use in the evaluation of antimalarial immunity in the context of the SMC contribute in assessing the impact of the strategy. For example, in a study in Senegal, the evaluation of immunity based on these two antigens showed a higher level of total IgG response in non-SMC areas compared to the area without SMC implementation. The same trend was observed in a study conducted by Boulager et al,[49] with children receiving SMC presenting a slightly lower level of anti-Plasmodium schizont antibodies compared with non-treated control children after 8 months of implementation. In that perspective, it might be important to consider that the implementation of the SMC would most likely in the long-term be aligned with a lower development of acquired immunity towards malaria.[2] Therefore, while considering the proven effectiveness of this strategy, it remains important that its systematic annual renewal in a high transmission area be included in the malaria control policy and strategies. It is obviously in this respect that WHO and other partners are working to make SMC a generalized and large-scale strategy which will allow a significant reduction in malaria-related morbidity and mortality in this Sahelian region. Although the impact of the SMC on the immunity remains an important scientific topic of discussion, there are still positive points that need to be highlighted, such as those linking SMC with greater weight gain or improvement of malnutrition indices.[31,32] This remains an important point. Indeed, child malnutrition, and particularly stunting, may down-regulate the anti-*Plasmodium falciparum* Ab response, both in terms of prevalence of immune responders and specific IgG Ab level. In any case, in the particular context of malaria, we need to balance the short-, medium-, and long-term benefits and risks on malaria disease control in order to make the best decision for the health of children in sub-Saharan Africa.

Conclusion

Seasonal malaria chemoprevention using Sulfadoxine-Pyrimethamine in combination with amodiaquine remains an effective and promising strategy to control malaria morbidity in areas of highly seasonal malaria transmission. However, the effectiveness of this strategy is jeopardized by several factors, including the level of coverage of the target population (subjected to the drug availability, the rainy season, etc), the spread of the single nucleotide resistance to the combination drugs Sulfadoxine and Pyrimethamine, and even the presence of such mutations is not systematically associated to the treatment failure. Although the SMC strategy is standardized in most of the Sub-Sahelian countries it remains relevant to continue to adapt it to the local context of the country to ensure its effectiveness. Under these conditions, the WHO, after having conducted several evaluations, decided in June 2022[50] on a number of extremely important recommendations with a certain flexibility in the prevention of malaria:

- The updated recommendation recognizes that countries in other parts of Africa (outside the Sahel region) with highly seasonal variation in malaria burden could also benefit from SMC, and that the availability of new medicines could make it a viable intervention in these areas.
- The updated guidance states that SMC should be given during peak malaria transmission season, without defining the specific number of monthly cycles.
- While the original recommendation restricted SMC use to children less than 6 years of age, the new recommendation recommends this intervention for children at high risk of severe malaria, which may extend to older children in some locations.

The updated WHO recommendations on SMC are less restrictive than the original recommendations; they do not specify strict age groups, transmission intensity thresholds, numbers of doses or cycles, or specific drugs. As such, they will support the broader use of chemoprevention among young children at high risk of severe malaria in areas with both seasonal and year-round transmission. This will enhance the impact of SMC, especially when used with other interventions such as bed nets and the new malaria vaccine.

In any case, the surveillance of resistance to SP remains an important part of the SMC strategy and resistance should be monitored regularly as it could in the long run be the major challenge, if not already overcome, in the sub-Saharan region.

In addition, although the question of the impact of SMC on malaria immunity is still a scientific debate, it is important in view of the results already available that this should be a priority for research and follow-up in order to confirm or disprove the previous results. Certainly, SP seems to work well for SMC today, but there is still a need to consider alternative therapies. Research must be carried out in these countries to anticipate therapeutic failures.

Abbreviations

SMC, Seasonal Malaria Chemoprevention; *AMA1*, Apical Membrane Antigen 1; AQ, Amodiaquine; *dhps*, dihydropteroate synthetase; *Dhfr*, dihydrofolate reductase; *GLURP-RO*, Glutamate-Rich Protein Region 0; IPTi, Intermittent preventive treatment for malaria in infants; IPTp, Intermittent preventive treatment for malaria in pregnant women; *Pfmdr1, Plasmodium falciparum* multidrug resistance 1; *Pfcrt, Plasmodium falciparum* chloroquine resistance transporter; SP, sulfadoxinepyrimethamine.

Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Acknowledgments

We are grateful to Christian Rassi from Malaria Consortium for his support and guidance for the manuscript conception and writing.

Author Contributions

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

The authors declare that they have no competing interests.

References

1. World Health Organization. *World Malaria Report*; 2021. ISBN978 92 4 004049 6.
2. Ndiaye M, Sylla K, Sow D, et al. Potential impact of seasonal malaria chemoprevention on the acquisition of antibodies against glutamate-rich protein and apical membrane antigen 1 in children living in Southern Senegal. *Am J Trop Med Hyg*. 2015;93(4):798–800. doi:10.4269/ajtmh.14-0808
3. World Health Organization. *Seasonal Malaria Chemoprevention (SMC) for Plasmodium Falciparum Malaria Control in Highly Seasonal Transmission Areas of the Sahel Sub-Regions in Africa*. Geneva, Switzerland: WHO Global Malaria Programme; 2012.
4. Cairns M, Roca-Feltrer A, Garske T, et al. Estimating the potential public health impact of seasonal malaria chemoprevention in African children. *Nat Commun*. 2012;3:1–9. doi:10.1038/ncomms1879
5. Grais RF, Laminou IM, Messe LW, et al. Molecular markers of resistance to amodiaquine plus sulfadoxine – pyrimethamine in an area with seasonal malaria chemoprevention in south central Niger. *Malar J*. 2018;17:1–9. doi:10.1186/s12936-018-2242-4

6. World Health Organization. *Monitoring Antimalarial Drug Resistance: Report of a WHO Consultation*. Geneva, Switzerland: World Health Organization; 2002.
7. Dicko A, Diallo AI, Tembine I, et al. Intermittent preventive treatment of malaria provides substantial protection against malaria in children already protected by an insecticide-treated bednet in Mali: a randomised, double-blind, placebo-controlled trial. *PLoS Med*. 2011;8(2):e1000407. doi:10.1371/journal.pmed.1000407
8. Attaher O, Zaidi I, Kwan JL, et al. Effect of seasonal malaria chemoprevention on immune markers of exhaustion and regulation. *J Infect Dis*. 2020;221(1):138–145. doi:10.1093/infdis/jiz415
9. World Health Organization. *Malaria Prevention Works, Let's Close the Gap*. Geneva, Switzerland: World Health Organization; 2017:127–129.
10. Sylla K, Kouly Tine RC, Sow D, NDiaye M, Sarr A, Tshibola Mbuyi ML. Effect of Seasonal Malaria Chemoprevention (SMC) with sulfadoxine pyrimethamine (SP) and amodiaquine (AQ) on the acquisition of antiAMA1 and anti-MSP1_42 antibodies among children under 10 years living in the Southern part of Senegal (Velingara). *Malar Chemother Control Elimin*. 2017;6:155.
11. Pitt C, Ndiaye M, Conteh L, et al. Large-scale delivery of seasonal malaria chemoprevention to children under 10 in Senegal: an economic analysis. *Health Policy Plan*. 2017;32(9):1256–1266. doi:10.1093/heapol/czx084
12. Cissé B, Sokhna C, Boulanger D, et al. Seasonal intermittent preventive treatment with artesunate and sulfadoxine-pyrimethamine for prevention of malaria in Senegalese children: a randomised, placebo controlled, double-blind trial. *Lancet*. 2006;367:659–667. doi:10.1016/S0140-6736(06)68264-0
13. Dicko A, Sagara I, Sissoko MS, et al. Impact of intermittent preventive treatment with sulphadoxine-pyrimethamine targeting the transmission season on the incidence of clinical malaria in children in Mali. *Malar J*. 2008;7:123. doi:10.1186/1475-2875-7-123
14. Konaté AT, Yaro JB, Ouédraogo AZ, et al. Intermittent preventive treatment of malaria provides substantial protection against malaria in children already protected by an insecticide-treated bednet in Burkina Faso: a randomised, double-blind, placebo-controlled trial. *PLoS Med*. 2011;8(2):e1000408. doi:10.1371/journal.pmed.1000408
15. NDiaye JL, Cissé B, Ba EH, et al. Safety of Seasonal Malaria Chemoprevention (SMC) with sulfadoxine-pyrimethamine plus amodiaquine when delivered to children under 10 years of age by district health services in senegal: results from a stepped-wedge cluster randomized trial. *PLoS One*. 2016;11(12):e0168421. doi:10.1371/journal.pone.0168421
16. Tine RC, Faye B, Ndour CT, et al. Combining community case management of malarial and seasonal malaria chemoprevention for children less than 10 years in Senegal: feasibility, impact on malaria and Anemia. *Am J Trop Med Hyg*. 2014;91(5 SUPPL. 1):75.
17. Ndiaye JLA, Ndiaye Y, Ba MS, et al. Seasonal malaria chemoprevention combined with community case management of malaria in children under 10 years of age, over 5 months, in south-east Senegal: a clusterrandomised trial. *PLoS Med*. 2019;16(3):e1002762. doi:10.1371/journal.pmed.1002762
18. Traore A, Donovan L, Sawadogo B, et al. Extending seasonal malaria chemoprevention to five cycles: a pilot study of feasibility and acceptability in Mangodara district, Burkina Faso. *BMC Public Health*. 2022;22:442. doi:10.1186/s12889-022-12741-9
19. Cissé B, Ba EH, Sokhna C, et al. Effectiveness of seasonal malaria chemoprevention in children under ten years of age in senegal: a SteppedWedge cluster randomised trial. *PLoS Med*. 2016;13(11):e1002175. doi:10.1371/journal.pmed.1002175
20. Sokhna C, Cissé B, Milligan P, et al. A trial of the efficacy, safety and impact on drug resistance of four drug regimens for seasonal intermittent preventive treatment for malaria in senegalese children. *PLoS One*. 2008;3(1):e1471. doi:10.1371/journal.pone.0001471
21. Cisse B, Cairns M, Faye E, et al. Randomized trial of piperaquine with sulfadoxine-pyrimethamine or dihydroartemisinin for malaria intermittent preventive treatment in children. *PLoS One*. 2009;4(9):e7164. doi:10.1371/journal.pone.0007164
22. Cairns M, Cheung YB, Xu Y, et al. Analysis of preventive interventions for malaria: exploring partial and complete protection and total and primary intervention effects. *Am J Epidemiol*. 2015;181(12):1008–1017. doi:10.1093/aje/kwv010
23. Druetz T. Evaluation of direct and indirect effects of seasonal malaria chemoprevention in Mali. *Sci Rep*. 2018;8:8104. doi:10.1038/s41598-018-26474-6
24. Druetz T, Corneau-Tremblay N, Millogo T, et al. Impact evaluation of seasonal malaria chemoprevention under routine program implementation: a quasi-experimental study in Burkina Faso. *Am J Trop Med Hyg*. 2018;98(2):524–533. doi:10.4269/ajtmh.17-0599
25. Diawara F, Steinhardt LC, Mahamar A, et al. Measuring the impact of seasonal malaria chemoprevention as part of routine malaria control in Kita, Mali. *Malar J*. 2017;16(1):325. doi:10.1186/s12936-017-1974-x
26. Kweku M, Liu D, Adjuik M, et al. Seasonal intermittent preventive treatment for the prevention of anaemia and malaria in Ghanaian children: a randomized, placebo-controlled trial. *PLoS One*. 2008;3(12):e4000. doi:10.1371/journal.pone.0004000
27. Meremikwu MM, Donegan S, Sinclair D, Esu E, Oringanje C. Intermittent preventive treatment for malaria in children living in areas with seasonal transmission. *Cochrane Database Syst Rev*. 2012;2012(2):CD003756. doi:10.1002/14651858.CD003756.pub4
28. Zongo I, Milligan P, Compaore YD, et al. Randomized noninferiority trial of dihydroartemisinin-piperaquine compared with sulfadoxine-pyrimethamine plus amodiaquine for seasonal malaria chemoprevention in Burkina Faso. *Antimicrob Agents Chemother*. 2015;59(8):4387–4396. doi:10.1128/AAC.04923-14
29. Baba E, Hamade P, Kivumbi H; ACCESS-SMC Partnership. Effectiveness of seasonal malaria chemoprevention at scale in west and Central Africa: an observational study. *Lancet*. 2020;396:1829–1840. doi:10.1016/S0140-6736(20)32227-3
30. Harrington WE, Mutabingwa TK, Kabyemela E, Fried M, Duffy PE. Intermittent treatment to prevent pregnancy malaria does not confer benefit in an area of widespread drug resistance. *Clin Infect Dis*. 2011;53(3):224–230. doi:10.1093/cid/cir376
31. Ntab B, Cissé B, Boulanger D, et al. Impact of intermittent preventive anti-malarial treatment on the growth and nutritional status of preschool children in rural Senegal (West Africa). *Am J Trop Med Hyg*. 2007;77(3):411–417. doi:10.4269/ajtmh.2007.77.411
32. Janin P. Gestion spatio-temporelle de la soudure alimentaire dans le Sahel burkinabé. *Revue Tiers Monde*. 2004;180(4):909–933. doi:10.3917/rtm.180.0909
33. Pradines B, Dormoi J, Briolant S, Bogreau H, Rogier C. Resistance to antimalarial drugs . *Rev Francoph des Lab*. 2010;2010(422):51–62. doi:10.1016/S1773-035X(10)
34. Basco L, Ringwald P. Drug-resistant malaria: problems with its definition and technical approaches. *Cahiers d'études et de Recherches Francophones Santé*. 2000;10(1):47–50.
35. Picot S, Olliaro P, de Monbrison F, et al. A systematic review and meta-analysis of evidence for correlation between molecular markers of parasite resistance and treatment outcome in falciparum malaria. *Malar J*. 2009;8:89. doi:10.1186/1475-2875-8-89

36. Wernsdorfer WH, Noedl H. Molecular markers for drug resistance in malaria: use in treatment, diagnosis and epidemiology. *Curr Opin Infect Dis*. 2003;16(6):553–558. PMID: 14624105. doi:10.1097/00001432-200312000-00007
37. Gutman J, Kalilani L, Taylor S, et al. The A581G mutation in the gene encoding plasmodium falciparum dihydropteroate synthetase reduces the effectiveness of sulfadoxine-pyrimethamine preventive therapy in Malawian pregnant women. *J Infect Dis*. 2015;211(12):1997–2005. doi:10.1093/infdis/jiu836
38. Somé AF, Zongo I, Compaoré YD, et al. Selection of drug resistance-mediating Plasmodium falciparum genetic polymorphisms by seasonal malaria chemoprevention in Burkina Faso. *Antimicrob Agents Chemother*. 2014;58(7):3660–3665. doi:10.1128/AAC.02406-14
39. Happi CT, Gbotosho GO, Folarin OA, et al. Polymorphisms in Plasmodium falciparum dhfr and dhps genes and age related in vivo sulfadoxine-pyrimethamine resistance in malaria-infected patients from Nigeria. *Acta Trop*. 2005;95(3):183–193. doi:10.1016/j.actatropica.2005.06.015
40. Ngondi JM, Ishengoma DS, Doctor SM, et al. Surveillance for sulfadoxinepyrimethamine resistant malaria parasites in the Lake and Southern Zones, Tanzania, using pooling and next-generation sequencing. *Malar J*. 2017;236. doi:10.1186/s12936-017-1886-9
41. Holmgren G, Gil JP, Ferreira PM, Veiga MI, Obonyo CO, Björkman A. Amodiaquine resistant Plasmodium falciparum malaria in vivo is associated with selection of pfcrt 76T and pfmdr1 86Y. *Infect Genet Evol*. 2006;6(4):309–314. doi:10.1016/j.meegid.2005.09.001
42. Holmgren G, Hamrin J, Svärd J, Mårtensson A, Gil JP, Björkman A. Selection of pfmdr1 mutations after amodiaquine monotherapy and amodiaquine plus artemisinin combination therapy in East Africa. *Infect Genet Evol*. 2007;7(5):562–569. doi:10.1016/j.meegid.2007.03.005
43. Beshir K, Sutherland CJ, Merinopoulos I, et al. Amodiaquine resistance in Plasmodium falciparum malaria in Afghanistan is associated with the pfcrt SVMNT allele at codons 72 to 76. *Antimicrob Agents Chemother*. 2010;54(9):3714–3716. doi:10.1128/AAC.00358-10
44. Gadalla NB, Adam I, Elzaki SE, et al. Increased pfmdr1 copy number and sequence polymorphisms in Plasmodium falciparum isolates from Sudanese malaria patients treated with artemether-lumefantrine. *Antimicrob Agents Chemother*. 2011;55(11):5408–5411. doi:10.1128/AAC.05102-11
45. Lo AC, Babacar F, El-Hadj B, et al. Prevalence of molecular markers of drug resistance in an area of seasonal malaria chemoprevention in children in Senegal. *Malar J*. 2013;12:137. doi:10.1186/1475-2875-12-137
46. Pratt-Riccio LR, Bianco-Junior C, Totino PRR, et al. Antibodies against the Plasmodium falciparum glutamate-rich protein from naturally exposed individuals living in a Brazilian malaria-endemic area can inhibit in vitro parasite growth. *Mem Inst Oswaldo Cruz*. 2011;106(Suppl 1):34–43. doi:10.1590/S0074-02762011000900005
47. Mitchell GH, Thomas AW, Margos G, Dluzewski AR, Bannister LH. Apical membrane antigen 1, a major malaria vaccine candidate, mediates the close attachment of invasive merozoites to host red blood cells. *Infect Immun*. 2004;72(1):154–158. doi:10.1128/IAI.72.1.154-158.2004
48. Silvie O, Franetich JF, Charrin S, et al. A role for apical membrane antigen 1 during invasion of hepatocytes by Plasmodium falciparum sporozoites. *J Biol Chem*. 2004;279(10):9490–9496. doi:10.1074/jbc.M311331200
49. Boulanger D, Sarr JB, Fillol F, et al. Immunological consequences of intermittent preventive treatment against malaria in Senegalese preschool children. *Malar J*. 2010;9:363. doi:10.1186/1475-2875-9-363
50. World Health Organization. *Updated WHO Recommendations for Malaria Chemoprevention and Elimination*. Global Malaria Programme; 2022.