Effectiveness of seasonal malaria chemoprevention administered in a mass campaign in the Kedougou region of Senegal in 2016: a case-control study [version 3; peer review: 2 approved]

Isaac Akhenaton Manga¹, Fassiatou Tairou¹, Amadou Seck¹, Ekoue Kouevidjin¹, Khadime Sylla¹, Doudou Sow¹, Alioune Babara Gueye², Mady Ba², Magatte Ndiaye¹, Roger Clément Kouly Tine¹, Omar Gaye¹, Babacar Faye¹, Jean Louis Abdourahim Ndiaye¹,³

¹Department of Parasitology-Mycology/Faculty of medicine, pharmacy and odontology, University of Cheikh Anta Diop, Dakar, Senegal
²Ministry of Health and Social Action, National Malaria Control Program, Dakar, Senegal
³Service of Parasitology Mycology/Departement of medical biology, UFR Santé/University Iba Der Thiam, Thies, Senegal

Abstract

Background: Seasonal malaria chemoprevention (SMC) with sulfadoxine-pyrimethamine plus amodiaquine (SPAQ) is a malaria prevention strategy recommended since 2012 by the World Health Organization (WHO) for children under 5 years. In Senegal, the scaling up of SMC started in 2013 in the south-eastern regions of the country with an extension of the target to 10 years old children. The scaling up of SMC requires regular evaluation of the strategy as recommended by the WHO. This study was conducted to evaluate the effectiveness of SMC.

Methods: A case-control study was conducted in some villages of the health districts of Saraya and Kedougou in the Kedougou region from July to December 2016. A case was a sick child, aged 3 months to 10 years, seen in consultation and with a positive malaria rapid diagnostic test (RDT). The control was a child of the same age group with a negative RDT and living in the same compound as the case or in a neighbouring compound. Each case was matched with two controls. Exposure to SMC was assessed by interviewing the mothers/caretakers and by checking the SMC administration card.

Results: Overall, 492 children, including 164 cases and 328 controls, were recruited in our study. Their mean ages were 5.32 (+/- 2.15) and...
4.44 (+/-2.25) years for cases and controls, respectively. The number of boys was higher in both cases (55.49%; CI 95%=47.54-63.24%) and controls (51.22%; CI 95%=45.83-56.58%). Net ownership was 85.80% among cases and 90.85% among controls (p=0.053). The proportion of controls who received SMC was higher than that of cases (98.17% vs 85.98% and p=1.10^{-7}). The protective effectiveness of SMC was 89% (OR= 0.12 (CI 95%=0.04-0.28)).

**Conclusions:** SMC is an effective strategy in the control of malaria in children. Case-control studies are a good approach for monitoring the efficacy of drugs administered during SMC.

**Keywords**
Seasonal malaria chemoprevention, Effectiveness, Case-control study, Senegal

4.44 (+/-2.25) years for cases and controls, respectively. The number of boys was higher in both cases (55.49%; CI 95%=47.54-63.24%) and controls (51.22%; CI 95%=45.83-56.58%). Net ownership was 85.80% among cases and 90.85% among controls (p=0.053). The proportion of controls who received SMC was higher than that of cases (98.17% vs 85.98% and p=1.10^{-7}). The protective effectiveness of SMC was 89% (OR= 0.12 (CI 95%=0.04-0.28)).

**Conclusions:** SMC is an effective strategy in the control of malaria in children. Case-control studies are a good approach for monitoring the efficacy of drugs administered during SMC.

**Keywords**
Seasonal malaria chemoprevention, Effectiveness, Case-control study, Senegal

4.44 (+/-2.25) years for cases and controls, respectively. The number of boys was higher in both cases (55.49%; CI 95%=47.54-63.24%) and controls (51.22%; CI 95%=45.83-56.58%). Net ownership was 85.80% among cases and 90.85% among controls (p=0.053). The proportion of controls who received SMC was higher than that of cases (98.17% vs 85.98% and p=1.10^{-7}). The protective effectiveness of SMC was 89% (OR= 0.12 (CI 95%=0.04-0.28)).

**Conclusions:** SMC is an effective strategy in the control of malaria in children. Case-control studies are a good approach for monitoring the efficacy of drugs administered during SMC.

**Keywords**
Seasonal malaria chemoprevention, Effectiveness, Case-control study, Senegal

4.44 (+/-2.25) years for cases and controls, respectively. The number of boys was higher in both cases (55.49%; CI 95%=47.54-63.24%) and controls (51.22%; CI 95%=45.83-56.58%). Net ownership was 85.80% among cases and 90.85% among controls (p=0.053). The proportion of controls who received SMC was higher than that of cases (98.17% vs 85.98% and p=1.10^{-7}). The protective effectiveness of SMC was 89% (OR= 0.12 (CI 95%=0.04-0.28)).

**Conclusions:** SMC is an effective strategy in the control of malaria in children. Case-control studies are a good approach for monitoring the efficacy of drugs administered during SMC.

**Keywords**
Seasonal malaria chemoprevention, Effectiveness, Case-control study, Senegal

4.44 (+/-2.25) years for cases and controls, respectively. The number of boys was higher in both cases (55.49%; CI 95%=47.54-63.24%) and controls (51.22%; CI 95%=45.83-56.58%). Net ownership was 85.80% among cases and 90.85% among controls (p=0.053). The proportion of controls who received SMC was higher than that of cases (98.17% vs 85.98% and p=1.10^{-7}). The protective effectiveness of SMC was 89% (OR= 0.12 (CI 95%=0.04-0.28)).

**Conclusions:** SMC is an effective strategy in the control of malaria in children. Case-control studies are a good approach for monitoring the efficacy of drugs administered during SMC.

**Keywords**
Seasonal malaria chemoprevention, Effectiveness, Case-control study, Senegal
List of abbreviations

AQ  Amodiaquine
CI  Confidence interval
CHWs  Community health workers
D2  Day 2
D3  Day 3
HBCP  Home-based care provider
LLIN  Long-lasting impregnated mosquito net
OR  Odd Ratio
RDT  Rapid Diagnostic Test
SMC  Seasonal malaria chemoprevention
SP  Sulfadoxine-Pyrimethamine
SPAQ)  Sulfadoxine-Pyrimethamine plus Amodiaquine
TBS  Thin blood smear
TDS  Thick drop slide
WBC  White blood cells
WHO  World Health Organization

Introduction

Seasonal malaria chemoprevention (SMC) is a strategy for malaria prevention in children under 5 years of age living in areas of moderate to high malaria transmission in sub-Saharan Africa. It consists of intermittent full treatment with an antimalarial drug during the season of high malaria transmission to prevent the disease, with the objective of maintaining therapeutic levels of antimalarial drug in the blood during the period when the risk of contracting malaria is the highest. This idea was submitted to WHO, which endorsed it, thus enabling the country, with the support of its technical and financial partners, to implement SMC for this age group.

While recommending the implementation of SMC on a large scale, WHO also specifies the need to monitor several parameters such as pharmacovigilance, coverage rate, malaria morbidity and mortality, and the appearance of drug-resistant strains of parasites. This study was therefore conducted to assess the effectiveness of SMC campaign in Senegal, using a case-control study.

Methods

Study site

This study took place in the region of Kédougou, at 700 km from Dakar, the country’s capital. Located on the banks of the Gambia River, Kédougou is in the extreme southeast of Senegal and borders Mali and Guinea. This region is characterized by a sahelian climate with an average temperature of 29.3°C and an average rainfall of 926.2 mm. It includes three departments (Kédougou, Salémata and Saraya) corresponding to the three health districts of the region (Figure 1). Malaria in Kédougou is a real public health problem because, in 2019 for example, the proportional morbidity of malaria was 27%. The positivity rate of the tests used (RDT and microscopy) to determine this morbidity was 51% in the general population. In children under 5 years of age, the rate was 26%. The proportional mortality due to malaria in this region was 27% and 50% of these deaths were in children under 5. (NMCP. Epidemiological report, 2019). These different conditions made this region eligible for SMC, which has been implemented there since 2013. This study was conducted in villages with either a head nurse, or with a community health worker (CHW), or also a DSDOM (Home health care provider) in the health districts of Kédougou and Saraya (Figure 1).

Study type, time period, and population

A case-control study was conducted from July to December 2016. Assuming a two-sided confidence level of 95% with a
a power of 80% and a match of one case to two controls, and a percentage of exposed cases of approximately 50%, the Epi info 7.1.3.3 software (RRID:SCR_021682) estimated our study population at 152 cases and 304 controls. Being between 0 to 10 years of age, residing in our study sites and for whom the parents had given free and informed written consent, were the main inclusion criteria for this study. Any child who met the inclusion criteria, self-referred to a health facility in the study site and had a positive rapid diagnostic test (RDT) for malaria was considered as a “case”. The “control” was a child of the same age group, living in the same compound or in a neighboring compound within 10 meters. Controls were recruited at concession level based on an apparent good health (without any clinical symptom) and a negative RDT. Each case was matched with two controls.

Conduct of the study
The purpose and objectives of the study were first shared with the health authorities in the region, prior to the training of the field staff including community health workers (CHWs) and the head nurses for data collection. Each case and control will therefore be visited at home to record the current level of mosquito bed net use (based on inspection of where the child sleeps, the type and condition of the net at the time of case detection); other interventions like the rate of SMC dosing; and the coverage of mosquito bed net use and other protective measures at concessions in the vicinity of the person’s home.

A capillary blood sample was also taken from the pulp of the finger from each subject included in the study, for a rapid diagnostic test (RDT) and the preparation of a thick and a thin blood smear. The slides were stained for 15 minutes with a 10% Giemsa R solution (RAL, REF: 320310-2500; LOT: 037834) and then read by technicians from two different facilities. The slides were read at objective 100 with immersion oil on LEICA DM500 microscopes. Parasite density was assessed by counting the number of asexual parasites per 200 white blood cells (WBC) and estimated by the number of parasites per µl using the following formula: number of parasites × 8,000/200 assuming a WBC count of 8,000 cells/µl. Thick and thin blood smears were considered negative after microscopic reading of 100 fields with no parasites detected. Their reading was done according to the recommendations of the national guidelines for biological diagnosis of malaria in the laboratory (NMCP. National diagnostic guidelines for malaria, 2018.).

Data management and analysis
The different questionnaires and biological results were entered on a data entry mask developed with Microsoft Excel 2019, 16.60 (22041000) (RRID:SCR_016137) software. Data was
analyzed with Epi Info 7.1.3.3 software (RRID:SCR_021682). Quantitative variables were described in means and standard deviation. Inter-group comparisons were made using the ANOVA test or Student’s t-test according to the conditions of application of these tests. When these tests were not applicable, non-parametric tests (MannWhitney, Kruskall Wallis) were used. Categorical variables were presented in percentage with confidence interval (CI). Proportions were compared using Chi-square test or Fisher exact test (univariate analysis). Risk factors were assessed by multivariate survey logistic regression models. The significance level of the different tests was 0.05 two-tailed. The effectiveness of the different malaria prevention methods investigated in this study was calculated using the following formula: Efficiency = 1-OR (Médicin sans frontière. Efficacité vaccinale | Guides médicaux). Only patients included in the study were taken into account in the data analysis.

Ethics considerations
This study received in October 2013 approval from the National Health Research Ethics Committee of Senegal under the number CNERS SEN13/57. Informed written consent from the parents or legal representative was a prerequisite for inclusion in the study. In order to respect confidentiality, an identification code was given to each participant.

Results
Socio-demographic characteristics
A total of 492 children aged 4 months to 10 years with a mean age of 4.73 (+/- 2.25) years were recruited in this study11. They consisted of 164 cases and 328 controls. The number of boys was higher in both cases (55.49%; CI 95%=47.54-63.24%) and controls (51.22%; CI 95%=45.83-56.58%) and there was no statistically significant difference compared to those of the opposite sex (p=0.1868). Recruitment was as follows for cases: 1.82% (CI 95%=0.38-5.25%) in July; 29.87% (CI 95%=22.99-37.51%) in August; 22.56% (CI 95%=16.4-29.73%) in October; 15.85% (CI 95%=10.63-22.36%) in November and 3.66% (CI 95%=1.35-7.79%) in December. For controls, there was 0.6% (CI 95%=0.17-2.20%) in July; 28.96% (CI 95%=24.32-34.09%) in August; 22.86% (CI 95%=18.65-27.71%) in September; 21.65% (CI 95%=17.53-26.42%) in October; 19.82% (CI 95%=15.86-24.47%) in November and 6.10% (CI 95%=3.98-9.23%) in December. However, there was no relationship between the period of recruitment of cases and controls (p=0.5009) (Table 1)11.

Thick blood count was positive in 87.80% (CI 95%=81.8-92.39%) of cases and 2.74% (CI 95%=1.45-5.135%) of controls. There was an association between the result of the thick blood test and whether the child was a case or a control (chi-square-corrected (Yates)=365.23 and p<0.0001). Plasmodium falciparum was the only species found on positive slides for both cases and controls. The mean parasite density was 13820.18 (+/-19393.43) in cases versus 4119.66 (+/- 3827.74) in controls and this difference was statistically significant (T-test=4.71 and p=0.0001).

Malaria prevention
Mosquito net. Net ownership was much higher among controls (90.85%; CI 95%=87.24-93.52%) than among cases (85.80%; CI 95%=79.7-90.9%) and this difference was not statistically significant (chi-square-corrected (Yates)=2.22 and p=0.13). The rate of net use was higher among controls who had slept under a net the day before the survey (99.65%; CI 95%=98.06-99.99%) compared to cases (96.24%; CI 95%=91.44-98.77%). This difference was statistically significant (chi-square-corrected (Yates)=5.23 and p=0.0007). Comparing the possession or not of a long-lasting impregnated mosquito net (LLIN) in cases and controls, an odds ratio of 0.61 (CI 95%=0.34-1.10) was found. This gives an effectiveness of the LLIN of 39% in this study.

Table 1. Distribution of the study population according to sociodemographic characteristics.

|                  | Case (N=164)          | Control (N=328)        |
|------------------|-----------------------|------------------------|
| **Sex**          |                       |                        |
| Boys             | 91 (55.49% ; CI 95%=47.54-63.24%) | 168 (51.22% ; CI 95%=45.83-56.58%) |
| Girls           | 73 (44.51% ; CI 95%=36.76-52.46%) | 160 (48.78% ; CI 95%=43.42-54.17%) |
| **Recruitment period** |                 |                        |
| July             | 3 (1.82% ; CI 95%=0.38-5.25%) | 2 (0.6% ; CI 95%=0.17-2.20%) |
| August          | 49 (29.87% ; CI 95%=22.99-37.51%) | 95 (28.96% ; CI 95%=24.32-34.09%) |
| September       | 43 (26.22% ; CI 95%=19.67-33.65%) | 75 (22.86% ; CI 95%=18.65-27.71%) |
| October         | 37 (22.56% ; CI 95%=16.41-29.73%) | 71 (21.65% ; CI 95%=17.53-26.42%) |
| November        | 26 (15.85% ; CI 95%=10.63-22.36%) | 65 (19.82% ; CI 95%=15.86-24.47%) |
| December        | 6 (3.66% ; CI 95%=1.35-7.79%) | 20 (6.10% ; CI 95%=3.98-9.23%) |
Exposure to SMC. This study has also assessed the use of SMC among case and controls. It was reported that the controls (98.17%; CI 95%=96.07-99.16%) had taken more SMC than the cases (85.98%; CI 95%=79.7-90.9%) and this difference of proportion was statistically significant (chi-square-corrected (Yates)=27.15 and p<0.0001). Comparing the use or not of SMC between cases and controls, an odds ratio of 0.12 (CI 95%=0.04-0.28) was found. This gives an effectiveness of 88% to this strategy. Of the cases who received SMC, 68.38% (CI 95%=59.86-76.08%) were recruited after less than 28 days from the last time they took SMC, 27.94% (CI 95%=20.59-36.28%) between 29 and 42 days, and 3.68% (CI 95%=1.20-8.37%) more than 43 days. For controls who received the drug, 79.10% (CI 95%=74.24-83.25%) were recruited before 28 days, 18.65% (CI 95%=14.71-23.35%) between 29 and 42 days, and 2.25% (CI 95%=1.09-4.57%) after more than 43 days.

There was no statistically significant difference between cases and controls, regardless of the time period between the date of the last administration of SMC and the date of recruitment (with the Fisher’s exact, p=0.05). Among the cases, 26.99% (CI 95%=20.35-34.54%) had not received any SMC cycle; 23.93% (CI 95%=17.60-31.22%) received one cycle; 21.47% (CI 95%=15.44-28.58%) two cycles; 16.56% (CI 95%=11.21-23.18%) three and 11.04% (CI 95%=6.68-16.89%) four. For controls, the proportions of children also varied according to the number of cycles received. Indeed, 4.27% (CI 95%=2.56-7.04%) had not received any; 22.56% (CI 95%=16.41-29.73%) one; 25.30% (CI 95%=20.9-30.28%) two; 24.09% (CI 95%=19.77-29%) three and 17.07% (CI 95%=13.39-21.52%) four cycles. These differences in proportions between these two groups of children according to the number of cycles received, were statistically significant (Chi-square=54.88 and p=0.0001). In the case group, 82.55% (CI 95%=75.49-88.27%) of the children reported that the community health worker had left the doses of day 2 (D2) and day 3 (D3), compared to 98.45% (CI 95%=96.42-99.33%) of the controls. This difference was statistically significant (p<0.0001). Compliance with these doses was more observed in the controls with 98.43% (CI 95%=96.38-99.33%) having taken the dose on D2 and 96.24% (CI 95%=93.54-97.84%) on D3. In the cases, the compliance was 86.51% (CI 95%=79.28-91.94%) for D2 and 73.02% (CI 95%=64.38-80.53%) for D3. There was a statistically significant difference between cases and controls for both D2 (Chi-square=27.89 and p=0.0001) and D3 (Chi-square=54.43 and p=0.0001). The number of controls who used both net and SMC (84.45%) was higher than that of cases (60.97%). This difference in proportion was statistically significant (p=0.032) (Table 2).

### Table 2. Distribution of cases and controls according to the means of prevention (mosquito net and SMC) used.
SMC = Seasonal malaria chemoprevention, LLIN= Long-lasting impregnated mosquito net, CHW= Community health worker.

|                | Cases (N=164) | Controls (N=328) | P (p-value) |
|----------------|---------------|------------------|-------------|
| **LLIN**       |               |                  |             |
| • Possession of a mosquito net | 144 (85.80% ; CI 95%=79.7-90.99%) | 298 (90.85% ; CI 95%=87.24-93.52%) | 0.053       |
| • Net use the day before the survey | 128 (96.24% ; CI 95%=91.44-98.77%) | 284 (99.65% ; CI 95%=98.06-99.99%) | 0.007       |
| **SMC**        |               |                  |             |
| Taking of SMC  |               |                  |             |
| • < 28 days    | 93 (68.38% ; CI 95%=59.86-76.08%) | 246 (79.10% ; CI 95%=74.24-83.25%) | 0.05        |
| • 29–42 days   | 38 (27.94% ; CI 95%=20.59-36.28%) | 58 (18.65% ; CI 95%=14.71-23.35%) |             |
| • > 42 days    | 5 (3.68% ; CI 95%=1.20-8.37%) | 7 (2.25% ; CI 95%=1.09-4.57%) |             |
| **Number of monthly treatments received** |               |                  |             |
| • 0            | 44 (26.99% ; CI 95%=20.35-34.5%) | 14 (4.27% ; CI 95%=2.56-7.04%) | 0.0001      |
| • 1            | 39 (23.93% ; CI 95%=17.60-31.22%) | 96 (22.56% ; CI 95%=16.41-29.73%) |             |
| • 2            | 35 (21.47% ; CI 95%=15.44-28.58%) | 83 (25.30% ; CI 95%=20.9-30.28%) |             |
| • 3            | 27 (16.56% ; CI 95%=11.21-23.18%) | 79 (24.09% ; CI 95%=19.77-29.29%) |             |
| • 4            | 18 (11.04% ; CI 95%=6.68-16.89%) | 56 (17.07% ; CI 95%=13.39-21.52%) |             |
| Tablets delivered by CHW for D2 and D3 | 123 (82.55% ; CI 95%=75.49-88.27%) | 317 (98.45% ; CI 95%=96.42-99.33%) | p<0.0001    |
| Taking the tablet at D2 | 109 (86.51% ; CI 95%=79.28-91.94%) | 314 (98.43% ; CI 95%=96.38-99.33%) | 0.0001      |
| Taking the tablet at D3 | 92 (73.02% ; CI 95%=64.38-80.53%) | 307 (96.24% ; CI 95%=93.54-97.84%) | 0.0001      |
| LLIN and SMC   | 60.97% (100) | 84.45% (277) | 0.032       |
Discussion
In this case-control study chosen to evaluate the effectiveness of SMC administered in a mass campaign in Senegal, the same difficulties as those described by Cairns et al., and related to the rigor required for this type of study, were encountered. The usefulness of case-control studies for determining the efficacy of SMC as well as that of a vaccine has been reported. Indeed, this type of study would allow a better understanding of many parameters that could have an impact on it. Home visits to collect information were not facilitated by the rainy season, which sometimes made access to the villages difficult, but which was also linked to farming activities. This case-control study has resulted in a protective efficacy of 89% of the SMC not exceeding 28 days. Similar results, with an efficacy of 88% in the first 28 days. The same effectiveness were also almost obtained in a study that evaluated SMC in 5 West African countries where SMC was also implemented. The Access SMC consortium, which supervised the scaling up of SMC in West and Central Africa, also found during its evaluation that this strategy, similar to ours, was protective. This very good efficiency of the SMC around 90%, had already been demonstrated in many studies conducted in the research context. This observation shows that the transition from research to scale-up of this strategy does not affect its effectiveness. However, it is strongly related to the complete treatment as demonstrated by this and several other studies.

In this study, the evaluation of the efficacy of the net was also conducted at the same time as the SMC. It was found that SMC was more effective than the net (89% vs 45%). The same observation was also made by Cairns et al., in 2015 in Gambia (85% vs. 49.9% in 2015). The efficacy of the net around 50% found in this study had also been showed in other studies that sought to evaluate. On the other hand, efficiencies higher than ours can also be noted.

In this study, controls had higher use of both SMC and nets. This indicates the need to strengthen advocacy for the integrated use of all malaria prevention strategies to have a greater impact on malaria indices (NMCP. Epidemiological report, 2019.), (NMCP. National strategic plan for malaria control in Senegal 2016-2020). Although the combination of malaria control strategies is a strong recommendation from WHO and many health authorities, the use of new approaches in their deployment would have a greater impact (NMCP. National strategic plan for malaria control in Senegal 2016–2020.). The strengthening of awareness and education strategies for health promotion for and by the populations themselves could be reinvigorated. A generalization of SMC administration to the whole population with mass drug administration campaigns could be a good approach as adults constitute an important parasite reservoir.

Conclusion
This study showed that this strategy was very effective in preventing malaria in children. However, the sustainability of SMC should also include an evaluation of its efficacy in vitro and at the molecular level.

Data availability
Underlying data
Dryad: Effectiveness of seasonal malaria chemoprevention administered in a mass campaign in the Kédougou region of Senegal in 2016: a Case-control study. https://doi.org/10.5061/dryad.j9kd51cg6

This project contains the following underlying data:
- Data file: Case-control 2016.xlsx

Extended data
This project contains the following extended data:
- CRF case-control.pdf
- map_of_Kedougou_region.pdf
- Positive_slide_with_P._falciparum_in_the_middle.png

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

Acknowledgements
We thank Dr. Latyr Ndiaye and Dr. Youssoupha Ndiaye who spared no effort to achieve the objectives of this study; the chief doctors of the respective health districts of Saraya and Kédougou; the people, community health workers and head nurses of the villages in these two districts where the study took place; and all the staff of the Parasitology-Mycology Department of the Faculty of Medicine of the Cheikh Anta Diop University of Dakar and the National Malaria Control Programme of Senegal.

References
1. Organisation mondiale de la santé: Chimioprévention du paludisme saisonnier par administration de sulfadoxine-pyrémethamine et d’amodiaquine aux enfants. Guide de terrain, juillet, 2013.
2. Greenwood B: Review: Intermittent preventive treatment—a new approach to the prevention of malaria in children in areas with seasonal malaria transmission. Trop Med Int Health. 2006; 11(7): 983-91.

Page 7 of 16
3. Druetz T: Evaluation of direct and indirect effects of seasonal malaria chemoprevention in Mali. Sci Rep. 2018; 8(1): 8104. PubMed Abstract | Publisher Full Text | Free Full Text

4. ACCESS-SMC Partnership: Effectiveness of seasonal malaria chemoprevention at scale in west and central Africa: an observational study. Lancet. 2020; 396(10265): 1829–40. PubMed Abstract | Publisher Full Text | Free Full Text

5. Ndiaye JL, 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 cluster-randomised trial. von Seidlein L editor. PLoS Med. 2019; 16(3): e1002762. PubMed Abstract | Publisher Full Text | Free Full Text

6. Sokhna C, Cissé B, Ba EH, 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. PubMed Abstract | Publisher Full Text | Free Full Text

7. Ndiaye Y, Ndiaye JL, Cisse B, et al.: Community case management in malaria: review and perspectives after four years of operational experience in Saraya district, south-east Senegal. Malar J. 2013; 12: 240. PubMed Abstract | Publisher Full Text | Free Full Text

8. Cissé B, Ba EH, Sokhna C, et al.: Effectiveness of Seasonal Malaria Chemoprevention in Children under Ten Years of Age in Senegal: A Stepped-Wedge Cluster-Randomised Trial. Noor AM editor. PLoS Med. 2016; 13(11): e1002175. PubMed Abstract | Publisher Full Text | Free Full Text

9. Yang GG, Kim D, Pham A, et al.: A Meta-Regression Analysis of the Effectiveness of Mosquito Nets for Malaria Control: The Value of Long-Lasting Insecticide Nets. Int J Environ Res Public Health. 2018; 15(3): 546. PubMed Abstract | Publisher Full Text | Free Full Text

10. Henry MC, Assi SB, Rogier C, et al.: Protective efficacy of lambda-cyhalothrin treated nets in Anopheles gambiae pyrethroid resistance areas of Côte d’Ivoire. Am J Trop Med Hyg. 2005; 73(5): 859-64. PubMed Abstract | Publisher Full Text

11. Manga IA, Tairou F, Seck Al, et al.: Effectiveness of seasonal malaria chemoprevention administered in a mass campaign in the Kedougou region of Senegal in 2016: a Case-control study. Dryad. [Dataset]. 2022. http://www.doi.org/10.5061/dryad.j9kd51cg6

12. Cairns M, Ceesay SJ, Sagara I, et al.: Effectiveness of seasonal malaria chemoprevention (SMC) treatments when SMC is implemented at scale: Case-control studies in 5 countries. PLoS Med. 2021; 18(9): e1003727. PubMed Abstract | Publisher Full Text | Free Full Text

13. ACCESS-SMC Partnership: Efficacité de la chimioprévention du paludisme saisonnier à l’échelle de l’Afrique de l’Ouest et de l’Afrique centrale : une étude d’observation. Lancet. 2020; 396(10265): 1829-40. Reference Source
Open Peer Review

The authors have improved the article very well. It explains more clearly the results.

The results are very interesting and I think the discussion could go into them a little more. For example, it would be interesting to know if there were any other confounding factors in the control group. The controls it seems both took the medication better and slept under nets more regularly. Was this because they were younger (slightly on average) or came from smaller families, had more conscientious parents, presence of a grandmother in the house older mothers vs. younger mothers better housing etc?

It was also interesting that 68.38% of cases had received some SMC and got malaria within 28 days. What were the associated factors for this? Even more interesting was that 11.04% of cases had received 4 doses of SMC and 4.27% of controls had not received any SMC, were they older children who might have some immunity already? These are all future research questions perhaps but could be described as being limitations of this study. The conclusion might therefore add some opinion on the unknown. We have one of the know facts seen in this paper is that malaria prevalence is still high in the general population even if slightly lower in children under five years and that this will continue indefinitely unless resources are directed to driving down transmission as well as preventing infection for a short period every year in a defined age group.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Malaria and childhood disease

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
Drissa Konaté
Malaria Research and Training Center, Bamako, Mali

I am ok.

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

---

Prudence Hamade
Malaria Consortium, London, UK

This is an interesting study with interesting results although the results only confirm numerous other cases control studies that have been done across the Sahel

1. It should be made clear when the scaling up to aged 10 years was done.

2. This study was done in 2016 why is it only being published now?

3. The odds ratios presented for both SMC and bed net usage efficacy are crude estimates in that they are not adjusted for confounding by each other. Adjusted (for confounding) odds ratios can be obtained by fitting a multivariable logistic regression model with both explanatory variables. Alternatively adjusted odds ratios could be estimated using stratification.

4. Be consistent with presentation of P values - give them to 4 decimal points only. If smaller than that then present as e.g. P < 0.0001.

5. "Malaria in Kédougou is a real public health problem because, in 2019 for example, the
proportional malaria morbidity was 27%, the rate of test positivity (RDT and blood smear) in the general population was 51%, in children under 5 years of age this rate was 26%. The proportional malaria mortality in this region was 27% and 50% in children under 5 years of age (NMCP. Epidemiological report, 2019,6).

These figures in themselves need a bit of explanation. Proportional malaria morbidity needs to be seen as a proportion of what Total morbidity. Total of suspected malaria cases or cases of fever etc. If malaria mortality in children under five is 50%. 50% of what? 50% of total under five mortality is still shocking in a country which has been implementing SMC for 6 years (2019) However has child mortality reduced significantly so the numbers of children dying from malaria may have been reduced even if proportionate mortality is still 50%

I am not sure what this study has to add to the evidence provided by several other case control studies that have been done to show the effectiveness / efficacy of SMC in reducing malaria cases in the Sahel. Its main difference is that it is conducted in children 3 months to 10 years (number of months) and that the average age of cases in this study was in slightly older children than would be expected if looking at traditional SMC in children from 3 - 59 months. New information of value in this study could have been if SMC was as effective in older children (those over five years) as in the younger age group which might have led to more programmes adopting the strategy of including older children which might in turn have a greater effect in the long run of reducing the malaria burden and leading down the road to actually eliminating malaria which from their data on malaria morbidity and mortality in 2019 was still very high in both the general population and in children under five. SMC it seems reduces morbidity in children especially if all four cycles are completed with 3 days of medication and the protective effect is best in the 28 days following the dose. If in spite of many years of implementation malaria transmission remains high, as it seems to here, we need to develop other strategies if we really want to have a serious effect on morbidity and mortality over the long term as nets and SMC have not led to a reduction in transmission - perhaps this could be mentioned in the discussion even when extended to older children?

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

**Competing Interests:** No competing interests were disclosed.
Reviewer Expertise: Malaria and childhood disease

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 23 Feb 2023
Isaac Akhenaton MANGA

1. In Senegal the target of SMC, since the beginning of its implementation and scaling up in 2013 the southern regions of the country, has been children aged 3 to 120 months. The expansion of the SMC target in Senegal was decided at the time the strategy was adopted by the country's health authorities. This choice was reinforced by the numerous studies on intermittent preventive treatment (IPT) of malaria in children, which had shown that children aged 5 to 10 years were just as vulnerable as those under 5 years. This idea was submitted to WHO, which endorsed it, thus enabling the country, with the support of its technical and financial partners, to implement SMC for this group age.

2. This study is part of a project to evaluate the impact of scaling up SMC in Senegal. This evaluation was requested from our organisation by the NMCP and was to be an ongoing process. However, it has not been carried out since 2016, although we had hoped to continue it in order to try to determine the dynamics of the effectiveness of the scaled-up SMC over time. This situation explains why it's took time before to write this article.

3. We accept your recommendation to adjust the odd ratio before the efficiency calculation. We will do this and include it in the new version we submit to the journal.

4. We have standardized the presentation of the p-value as you suggested. The changes have been made in the new version submitted to the journal.

5. We have reworded the sentence because, as noted, it is confusing. We also think that the part about the burden of malaria in the proposed new version helps to present it better. Our study was conducted in children aged 3 to 120 years, unlike those conducted in the Sahel to determine the effectiveness of SMC, all of which, as you rightly pointed out, were targeted at children under the age of 5. We believe that even though we did not carry out an analysis to determine the effectiveness of this strategy in children under and over 5 years of age, this constitutes a strong point for our study. In addition, we believe that the other strength of this study is that the data collection (making mixed smear slides and recruiting both cases and controls, not to mention administering the questionnaires) was done by the trained community level and not by the research team. We have added a recommendation at the end of our discussion to suggest additional strategies that could further reduce malaria-related morbidity.

Competing Interests: No competing interests were disclosed.
I approve this version with one comment:
1. Specify SMC campaign rather than mass.

Drissa Konaté
Malaria Research and Training Center, Bamako, Mali

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
© 2022 Konaté D. This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Drissa Konaté
Malaria Research and Training Center, Bamako, Mali

Introduction (needs more detail):
- Reference: harmonize the reference citations in the main document.
- The author should give more details on study justification because the effectiveness of SMC has already been proven: more cases of malaria are screened despite the SMC?
- Please specify: SMC campaign or mass campaign? If different to SMC campaign, what approaches of mass campaign was used to administer antimalarial drug.
- SMC is recommended in children up to 10 in Senegal?

Methods (need to clarify some points):

**Study Site**
- The rate of test positivity in the general population was 51%: please specify the test (RDT or blood smear).

**Study type, time-period, and population**
- Controls were recruited at concession level based on an apparent good health and a negative RDT.
- Good health: any malaria symptom or any symptom?

**Data management and analysis:**
- The author just needs to specify which tests used and for what comparison: ANOVA, T-test Chi^2 Mann, Kruskall.
- What part of the result section were these test were used?

Results (the interpretation of some sentences needs to be clarified):
- All cases in our study were recruited on the basis of a positive rapid diagnostic test (RDT) and the controls a negative RDT. Thick blood count was positive in 87.80% (CI 95%=81.8-92.39%) of cases and 2.74% (CI 95%=1.45-5.135%) of controls.
- Specify the test used for malaria diagnosis: There was an association between the result of the thick blood test and whether the child was a case or a control (p=1.10^{-9}). Make this part clearer

**Malaria prevention:**

**Mosquito net**
- Net ownership was much higher among controls (90,85%; CI 95%=87.24-93.52%) than among cases (85,80%; CI 95%=79.7-90.9%) and this difference was not statistically significant (p=0.053).
Reword this sentence: Net ownership was much higher among controls because it’s not significant.

○ (p=0.0000004): also harmonizes p-values.

**Conclusion (without aim)**

○ It is not necessary to give against the objective of the study.

---

**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Partly

**If applicable, is the statistical analysis and its interpretation appropriate?**

Partly

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

---

**Author Response 16 Sep 2022**

**Isaac Akhenaton MANGA**

**Introduction**

○ Reference: We have respect the guidelines given by the journal for this part. However if you can give me an example of that I will take in account to improve the presentation of references.

○ Justification of the study: You right when you say that the effectiveness of SMC has already shown, but most often it is in the context of operations research, which we have tried to demonstrate by posing the problem. The justification for this study is that the effectiveness of this strategy in mass campaigns has not been evaluated in
Senegal. We think we have done this, but remain open to improving this part.

- You right when you say SMC campaign and I'll delete mass campaign in the new version
- SMC is not recommended for children up to 10 years but for those aged 3 months to 10 years. We have therefore amended the sentence in the new version to make it clearer.

Method
- Study site: The rate of test positivity is for RDT and blood smear and we add it in the new version of this article.
- Study type, time-period and population: an apparent good health means for us without any clinical symptom. We put it in brackets in the new version for more clarifications.
- Data management and analysis: We take in account your suggestions for the test used and we add in the new version in brackets the test and the p-value for each comparison.

Result
- For the results of the slide reading we have in the new version removed the first sentence. This sentence can be confusing.
- We have also added for each comparison the statistical test used.

Conclusion
- We have deleted the objective in this part as you have suggested

**Competing Interests:** No competing interests were disclosed.