Effectiveness of seasonal malaria chemoprevention administered in a mass campaign in the Kedougou region of Senegal in 2016: a case-control study [version 2; peer review: 1 approved with reservations]

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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

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Approval Status ?

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30 Sep 2022
version 1
19 Aug 2022

1. Drissa Konaté¹, Malaria Research and Training Center, Bamako, Mali

Any reports and responses or comments on the article can be found at the end of the article.
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 (WHO Report on the Technical consultation on SMC, 2011, Implementation of Seasonal Malaria Chemoprevention: A report of two meetings). One single dose of Sulfadoxine-Pyrimethamine (SP) and 3 daily doses of amodiaquine (AQ) are administered monthly to obtain the preventive dose. The drugs should be administered from the beginning of the transmission season, up to a maximum of four monthly cycles. The effectiveness of SMC has been demonstrated by numerous studies, which have also shown that it is well tolerated and inexpensive (NMCP. Epidemiological report, 2019). These studies, conducted mostly between 2002 and 2011, showed that SMC would have prevented about 75% of all uncomplicated malaria attacks and also about 75% of severe malaria attacks. It would also have reduced child mortality by about 1 per 1000 and reduced the incidence of moderate anemia. Then SMC has been well received as a new tool offering a high degree of personal protection at a moderate cost and was recommended since 2012 by the World Health Organization (WHO) as an additional prevention strategy for malaria control. Senegal, like many African countries in the south of the Sahara, has adopted and implemented SMC on a large scale since 2013 in the regions of the country, that are eligible according to WHO implementation criteria. SMC is administered through a door-to-door strategy based on the community system.

In Senegal, the SMC target was children aged 3 months to 10 years because numerous in-country and operational research studies on intermittent preventive treatment of malaria in children and SMC had shown that children 5–10 years of age were just as vulnerable as those under 5.

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 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). 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 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,
Recruitment period

<table>
<thead>
<tr>
<th></th>
<th>Case (N=164)</th>
<th>Control (N=328)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>91 (55.49%; CI 95%=47.54-63.24%)</td>
<td>168 (51.22%; CI 95%=45.83-56.58%)</td>
</tr>
<tr>
<td>Girls</td>
<td>73 (44.51%; CI 95%=36.76-52.46%)</td>
<td>160 (48.78%; CI 95%=43.42-54.17%)</td>
</tr>
<tr>
<td><strong>Recruitment period</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>July</td>
<td>3 (1.82%; CI 95%=0.38-5.25%)</td>
<td>2 (0.6%; CI 95%=0.17-2.20%)</td>
</tr>
<tr>
<td>August</td>
<td>49 (29.87%; CI 95%=22.99-37.51%)</td>
<td>95 (28.96%; CI 95%=24.32-34.09%)</td>
</tr>
<tr>
<td>September</td>
<td>43 (26.22%; CI 95%=19.67-33.65%)</td>
<td>75 (22.86%; CI 95%=18.65-27.71%)</td>
</tr>
<tr>
<td>October</td>
<td>37 (22.56%; CI 95%=16.41-29.73%)</td>
<td>71 (21.65%; CI 95%=17.53-26.42%)</td>
</tr>
<tr>
<td>November</td>
<td>26 (15.85%; CI 95%=10.63-22.36%)</td>
<td>65 (19.82%; CI 95%=15.86-24.47%)</td>
</tr>
<tr>
<td>December</td>
<td>6 (3.66%; CI 95%=1.35-7.79%)</td>
<td>20 (6.10%; CI 95%=3.98-9.23%)</td>
</tr>
</tbody>
</table>
**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=1.10^-7). 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%=74.24-88.27%) 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%=20.35-34.5%) 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=1.10^-4). 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=0.0000004). 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=1.10^-4) and D3 (Chi-square=54.43 and p=1.10^-4). 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.

<table>
<thead>
<tr>
<th></th>
<th>Cases (N=164)</th>
<th>Controls (N=328)</th>
<th>P (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LLIN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Possession of a mosquito net</td>
<td>144 (85.80%; CI 95%=79.7-90.9%)</td>
<td>298 (90.85%; CI 95%=87.24-93.52%)</td>
<td>0.053</td>
</tr>
<tr>
<td>• Net use the day before the survey</td>
<td>128 (96.24%; CI 95%=91.44-98.77%)</td>
<td>284 (99.65%; CI 95%=98.06-99.99%)</td>
<td>0.007</td>
</tr>
<tr>
<td>SMC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taking of SMC</td>
<td>141 (85.98%; CI 95%=79.7-90.9%)</td>
<td>322 (98.17%; CI 95%=96.07-99.16%)</td>
<td>0.00000001</td>
</tr>
<tr>
<td>Last SMC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• &lt; 28 days</td>
<td>93 (68.38%; CI 95%=59.86-76.08%)</td>
<td>246 (79.10%; CI 95%=74.24-83.25%)</td>
<td>0.05</td>
</tr>
<tr>
<td>• 29–42 days</td>
<td>38 (27.94%; CI 95%=20.59-36.28%)</td>
<td>58 (18.65%; CI 95%=14.71-23.35%)</td>
<td></td>
</tr>
<tr>
<td>• &gt; 42 days</td>
<td>5 (3.68%; CI 95%=1.20-8.37%)</td>
<td>7 (2.25%; CI 95%=1.09-4.57%)</td>
<td></td>
</tr>
<tr>
<td>Number of monthly treatments received</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 0</td>
<td>44 (26.99%; CI 95%=20.35-34.5%)</td>
<td>14 (4.27%; CI 95%=2.56-7.04%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>• 1</td>
<td>39 (23.93%; CI 95%=17.60-31.22%)</td>
<td>96 (22.56%; CI 95%=16.41-29.73%)</td>
<td></td>
</tr>
<tr>
<td>• 2</td>
<td>35 (21.47%; CI 95%=15.44-28.58%)</td>
<td>83 (25.30%; CI 95%=20.9-30.28%)</td>
<td></td>
</tr>
<tr>
<td>• 3</td>
<td>27 (16.56%; CI 95%=11.21-23.18%)</td>
<td>79 (24.09%; CI 95%=19.77-29.29%)</td>
<td></td>
</tr>
<tr>
<td>• 4</td>
<td>18 (11.04%; CI 95%=6.68-16.89%)</td>
<td>56 (17.07%; CI 95%=13.39-21.52%)</td>
<td></td>
</tr>
<tr>
<td>Tablets delivered by CHW for D2 and D3</td>
<td>123 (82.55%; CI 95%=75.49-88.27%)</td>
<td>317 (98.45%; CI 95%=96.42-99.33%)</td>
<td>4.10^-4</td>
</tr>
<tr>
<td>Taking the tablet at D2</td>
<td>109 (86.51%; CI 95%=79.28-91.94%)</td>
<td>314 (98.43%; CI 95%=96.38-99.33%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Taking the tablet at D3</td>
<td>92 (73.02%; CI 95%=64.38-80.53%)</td>
<td>307 (96.24%; CI 95%=93.54-97.84%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>LLIN and SMC</td>
<td>60.97% (100)</td>
<td>84.45% (277)</td>
<td>0.032</td>
</tr>
</tbody>
</table>
Discussion
In this case-control study chosen to evaluate the effectiveness of SMC in Senegal, the same difficulties as those described by Cairns et al., and related to the rigorous 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 shown 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.).

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
• Negative_slide_of_thin.jpeg
• 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


Open Peer Review

Current Peer Review Status: ?

Review Version 1

Reviewer Report 15 September 2022

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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, Chi² 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.
Isaac Akhenaton MANGA, University of Cheikh Anta Diop, Dakar, Senegal

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.