The effect of Seasonal Malaria Chemoprevention (SMC) in Moïssala, Chad, 2014-2022

Study report - Octobre 2023

Alastair Clements, Anton Camacho, Francesco Grandesso, Jessica Sayyad Hilario

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MEDECINS SANS FRONTIERES

Project details

First version	February 2023
Type of study	Retrospective analysis of routinely collected data
Study participants	Children under five years of age who received antimalarial treatment at a health centre in the Moïssala, Bedjondo, Goundi or Koumra health districts, Chad, between 2014 and 2022 (inclusive) Children under five years of age who were hospitalised at the MSF malaria management unit in the Moïssala health district, Chad, between 2014 and 2022 (inclusive)
Study period	2014-2022 (inclusive)
Study site(s)	Moïssala, Bedjondo, Goundi or Koumra health districts, Chad
Project investigators	Alastair Clements, Epicentre Paris, France (Alastair.Clements@epicentre.msf.org) Jessica Sayyad Hilario, Epicentre Paris, France (Jessica.Sayyad@epicentre.msf.org) Francesco Grandesso, Epicentre Paris, France (Francesco.Grandesso@epicentre.msf.org) Anton Camacho, Epicentre Paris, France (Anton.Camacho@epicentre.msf.org) Dr Saschveen Singh, MSF Paris, France (Saschveen.Singh@paris.msf.org) Pascal Ouedraogo, Epicentre Ndjamena, Chad (Pascal.Ouedraogo@epicentre.msf.org) Arielle Calmejane, MSF Paris, France (Arielle.Calmejane@paris.msf.org) Dr Felix Kouassi, MSF Paris, France (Felix.Kouassi@paris.msf.org) Dr Kodbesse Boulitogam, PNLP Chad, Ndjamena, Chad (Kodbesse1@yahoo.fr)

	Elkoussin Djovouna, Epidemiologist/Biostatistician, Monitoring and Evaluation Section, Ndjamena, Chad Dr Mahamat Saleh Issakha DIAR, National Coordinator, NMCP (issakhadiarmi@hotmail.com)
Collaborating institutions	Ministry of Public Health of Chad (PNLP) National Malaria Control Programme (NMCP), Chad

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List of abbreviations and acronyms

Abbreviation/acronym	*Definition*
MSF	Médecins sans Frontières
SMC	Seasonal Malaria Chemoprevention
SP	Sulfadoxinepyrimethamine
AQ	Amodiaquine
SP-AQ	Sulfadoxinepyrimethamine - amodiaquine
WHO	World Health Organisation
ACCESS-SMC	Achieving Catalytic Expansion of SMC in the Sahel (partnership)
NMCP	National Malaria Control Programme
CHIRPS	Climate Hazards Group InfraRed Precipitation with Station data

1. Introduction

1.1 Seasonal Malaria Chemoprevention (SMC)

Malaria constitutes a serious global health problem [1], particularly in the Sahelian region of Chad where most malaria-related morbidity and mortality occurs during and after the rainy season. Many interventions and treatments have been developed against malaria [2] and a course of repeated antimalarial drugs taken during the rainy season has been shown to be effective in preventing malaria and reducing deaths in children.

Seasonal malaria chemoprevention (SMC) consists of treatment with sulfadoxinepyrimethamine (SP) and amodiaquine (AQ) given to children under five years of age at one-month intervals during the transmission season. Since 2012, it has been recommended by the World Health Organisation (WHO) for administration in areas of the Sahel sub-region with high malaria transmission [3] and by 2021 over 44 million children were being treated with SMC per cycle across sub-Saharan Africa [1].

Many studies have previously investigated the effectiveness of SMC and evidence of its effectiveness in real-world settings is growing. It is believed that individuals adhering to a full three-day round of SMC can benefit from its effect for approximately 28 days [4]. Strategies have been found to significantly reduce malaria cases and hospitalisations across different areas at different scales [5-8] and provide a high level of individual protection. In particular, it has been found to reduce malaria episodes by as much as 83% (95% CI: 72-89%) and severe malaria by as much as 77% (95% CI: 45-90%) [9]. The Achieving Catalytic Expansion of SMC in the Sahel (ACCESS-SMC) partnership went further by exhibiting the effects of scaling up SMC to provide treatment to 3.7 million children under five years of age in 2015 and 7.6 million in 2016, in countries across north, west, and central Africa, including Chad [10-12]. Furthermore, at an average cost of less than 4 US$ per child treated per year, the cost-effectiveness of SMC has also been demonstrated [13].

Despite these encouraging results, much remains unknown about the effectiveness of SMC, with calls for more sharing of information on and research into optimal strategies and implementation [14, 15]. Since 2022, the WHO recommendations on malaria now encourage approaches tailored to local epidemiology and demographics [2]. As such, it is increasingly important that the impact of SMC strategies is investigated in the context of their geography, demography, and epidemiology.

1.2 Malaria and SMC in Chad

Malaria is considered the biggest health problem in Chad, being the leading cause of illness, morbidity, and mortality [16]. The prevalence of malaria has been estimated at 40.8% in the general population [16] and 70% of deaths occur in children under five years of age and pregnant women. An earlier study in 2014-15 found that one in eight children in Chad under five years of age die from malaria [Demographic and health Survey 2015].

Three levels have been used to classify malaria endemicity in Chad: regions in the north are free of transmission; regions in the Sahelian zone experience hypo-endemic malaria; regions in the Sudanian savanna experience hyper-endemic malaria. Approximately two-thirds of the population live in the latter of these [17].

Malaria transmission is seasonal with a peak from July to October each year, corresponding with the rainy season. It is usual convention that the central areas of Chad with a short rainy season are prioritised for SMC intervention and these regions have been found to benefit from the implementation of SMC in previous years.

1.3 MSF and NMCP interventions using SMC in Chad

MSF programmes to control malaria in Chad commenced in July 2010, focussing on access to effective treatment for patients and exploring ways to reduce severe malaria cases. SMC was introduced in the health district of Moïssala from 2012 until 2018, with 23 health centres supported for the treatment of childhood malaria, and a malaria unit open six months of the year. Chad also adopted SMC in other districts with a short rainy season from 2013. Since 2015, MSF's activities have been concentrated in the district of Moïssala, with the number of areas of responsibility for administering SMC scaled up to 20 from 13 in previous years. In 2018, the malaria unit in Moïssala became a paediatric unit with admission throughout the whole year.

Treatments were distributed each year with four rounds at one-month intervals from July to October. Each round lasted three days, with the first day consisting of SP-AQ administered under observation, followed by two days of AQ taken by individuals at home.

In 2019, the NMCP did not authorise SMC for distribution in Moïssala. The longer rainy season meant that the district was considered non-priority and ineligible for SMC in alignment with criteria detailed in the WHO 2013 SMC guide [3]. However, following a sharp increase in malaria cases that year, SMC was re-authorised in 2020, with the NMCP requesting further evidence of efficacy, and that SMC be delivered in alignment with national control measures for SARS-Cov-2. As such, the four rounds were distributed either door-door or at fixed sites, ensuring no more than 50 people attended the same site, with each round lasting five days.

SMC was authorised again in 2021 and 2022, however the NMCP requested that treatment be increased to five rounds to cover the longer transmission season. Rounds were distributed door-door, with each taken over three days rather than five.

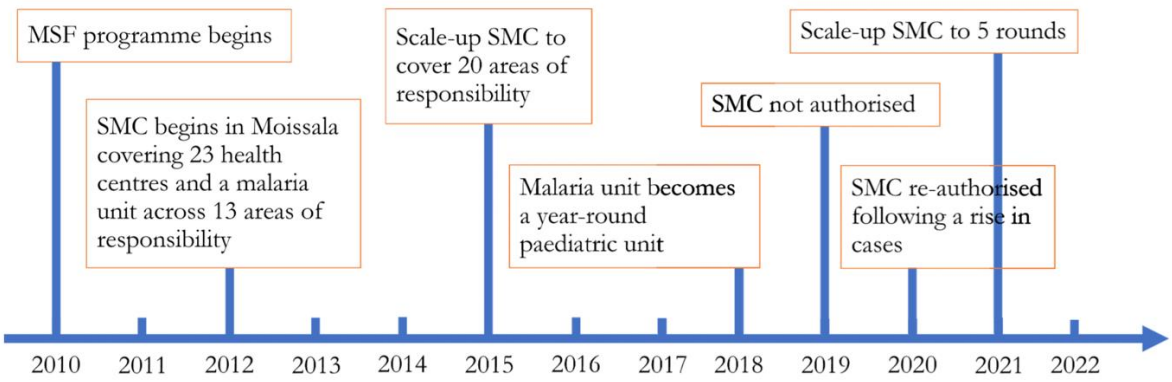


Figure 1 Timeline of MSF involvement with malaria and SMC programmes in Moïssala.

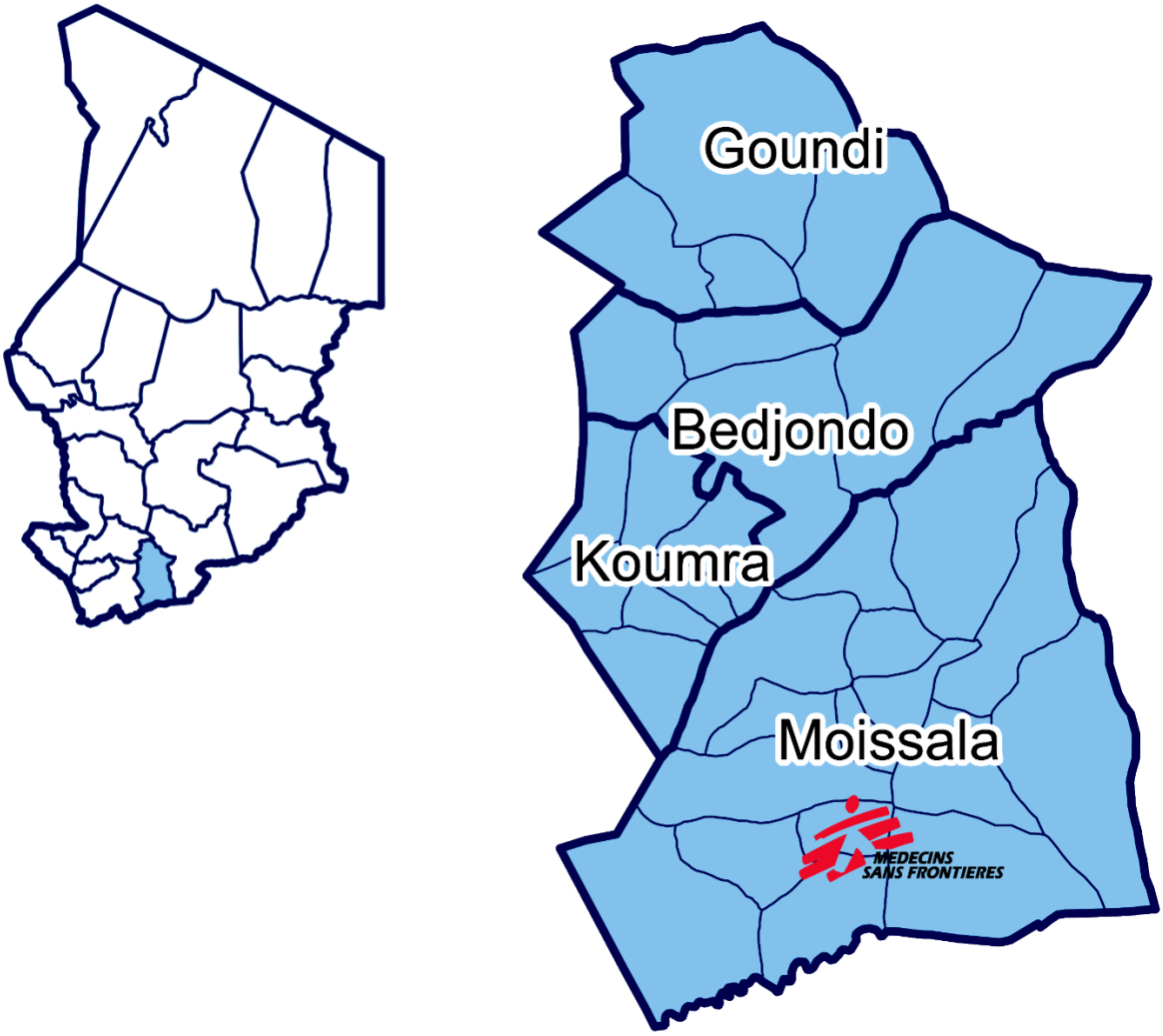


Figure 2 Maps highlighting the Mandoul region within Chad and the districts of Moïssala, Bedjondo, Goundi, and Koumra.

2. Project rationale

SMC is greatly relied upon as a reportedly effective measure to prevent malaria cases and reduce morbidity and mortality, especially in children under five years old. The WHO have set out national guidelines for SMC and it is continuing to be distributed in areas across many countries which contribute highly to the global burden of malaria. However, documentation of different approaches in different areas has been lacking and calls for further evidence of efficacy and sharing of information gave been made. Furthermore, the WHO updated their guidelines in 2022, now advising the extension of SMC to regions with longer transmission seasons and adaptation of the number of cycles delivered to the length of the season among other local epidemiology and demographic factors.

The Moïssala district of Chad experiences high numbers of malaria cases, morbidity, and mortality every year and SMC has been implemented in the district since 2012, except in 2019. The rainy season begins in May, with rainfall increasing up to August and an increase in cases follows from June up to July. Only once cases begin to peak at this time, is SMC started and the number of cases subsequently decrease. However, there are questions about whether SMC is continuing to protect individuals against malaria in Moïssala and concerns surrounding apparent rebounds in cases after the last rounds of recent years.

It is therefore important to understand how SMC interventions in Moïssala in previous years, and their absence, have impacted the evolution of malaria cases. Moreover, it is important to investigate how such interventions could be improved for the future, in terms of factors such as the number and timing of rounds, and coverage.

The stop and restart of SMC in Moïssala constitute a unique natural experiment, providing an invaluable opportunity to measure the effectiveness of SMC at the population level. Additionally, the impact of a 5th round at the end of the 4th round in 2021 and 2022 remains to be assessed. Particularly, it remains unclear whether this additional round would have a more substantial impact at the beginning or at the end of the SMC season. This study aims to address these critical questions, offering insights that could optimize SMC strategies and support ongoing programs by MSF, the NMCP, and local authorities to reduce malaria incidence, morbidity, and mortality in Moïssala, while also advocating for its potential benefits in other regions.

3. Project aims

The aim of this study is to better understand the impact of seasonal malaria chemoprevention (SMC) on the evolution of malaria cases in Moïssala.

The study will be broken down into two sub-aims:

1) Describe the performance of real-world SMC strategies between 2014 and 2022 and compare it to the dynamics of malaria cases in Moïssala.

2) Compare the expected impact of alternative SMC strategies to identify the most promising one.

This will enable to inform future MSF strategy for SMC distribution in Moïssala.

4. Definitions and methods

4.1 Definitions

Malaria cases are defined as patients under five years of age who received antimalarial treatment in the health centres of the Moïssala, Bedjondo, Goundi, and/or Koumra health districts between 2014 and 2022 (inclusive).

Malaria hospitalisations are defined as patients under five years of age who were hospitalised in the MSF malaria management unit in the Moïssala health district between 2014 and 2022 (inclusive). All patients who met these criteria were included.

4.2 Data sources

This is a retrospective study of routinely collected data from MSF's malaria control programme activities in the Moïssala health district and NMCP monitoring activities in Moïssala, and the neighbouring districts of Bedjondo, Goundi, and Koumra. Data on the daily amount of rainfall in Moïssala, Bedjondo, Goundi, and Koumra were sourced from satellite imagery provided by the CHIRPS online database to study environmental factors.

4.2.1 Malaria cases and hospitalisations

Weekly data on simple malaria cases in Moïssala were collected from health centre records as part of MSF's programme monitoring purposes. Weekly data on hospitalisations (severe malaria cases) in Moïssala were collected from malaria management unit records as part of MSF's programme activities. The data were extracted from Praxis (after 2018) in aggregated form, having been compiled in Microsoft Excel files.

Monthly data on simple malaria cases in Moïssala, Bedjondo, Goundi, and Koumra were made available by the NMCP, collected from consultations in health centres as part of their monitoring activities. The data were pseudonymised and shared in aggregated form, having been compiled in Microsoft Excel files.

4.2.2 SMC coverage

Data on the estimated population coverage with SMC in Moïssala for each round during each year were obtained from retrospective coverage surveys conducted by MSF after the end of the last round of SMC each year. The surveys were conducted by Epicentre for every year of the study period except in 2018, when it was known that SMC would not be authorised the following year, and 2019, when SMC was not authorised. Estimates of the SMC coverage, verified either by card only or by also allowing for verbal confirmation, and their 95% confidence intervals, were taken from survey reports for each year and manually recorded by week in a Microsoft Excel file alongside information taken from the MSF clinical datasets about which weeks of the year each round of SMC was distributed.

4.2.3 CHIRPS amount of rainfall

Daily data on the amount of rainfall in Moïssala, Bedjondo, Goundi, and Koumra were obtained from satellite imagery provided by the Climate Hazards Group InfraRed Precipitation with Station data (CHIRPS) online database. The data were compiled into an RData file using the statistical program R [18]. The code written for this purpose will be made publicly available through GitHub repositories.

4.3 Data cleaning

The datasets were cleaned and checked for consistency using the statistical program R. Code used for data cleaning will be made publicly available through GitHub repositories.

4.4 Data analysis

Trends in malaria cases and hospitalisations, SMC coverage, and rainfall during the period 2014-2022 were analysed using the obtained datasets. Malaria incidences were calculated using population counts for each district in 2014 from the NMCP data as denominators.

Analyses were conducted using the statistical program R. Code used for data analysis to generate each figure will be made publicly available through GitHub repositories.

4.5 Mathematical modelling

A simple mathematical model was built to investigate the dynamics of malaria cases with rainfall and SMC over one year. It is a continuous-time deterministic compartmental model with an SIR (Susceptible-Infectious-Removed) structure for malaria transmission. It also accounts for the impact of rainfall through the addition of a seasonal forcing function, and the impact of SMC is incorporated through a reduction in the transmission coefficient at timepoints falling within the SMC period.

The model was configured to the real-world datasets by inspection in two stages. First, the model was calibrated to imitate the evolution of malaria cases in Moïssala by approximating the number of new infections in the model and the seasonal forcing component to the number of malaria cases and amount of rainfall during 2019, when SMC did not impact cases. After selecting suitable parameters relating to malaria transmission and the impact of rainfall, the remaining parameters relating to SMC were then calibrated by approximating the number of new infections in the model to the number of weekly cases during 2018.

Details of the model equations and parameters can be found in the appendix. The model was coded and analyses with the model conducted using the statistical program R. The code used to implement the model and to generate each figure of the analyses will be made publicly available through GitHub repositories.

5. Ethics

The study uses previously collected routine clinical data from patient records for hospital admissions and health care registers that were collated as part of MSF and the NMCP's existing malaria monitoring programmes in Chad. This data is aggregated and pseudonymised, containing no patient identifiers, and it is not possible for anyone involved in the study to identify patients.

The data are stored securely on password-protected computers and encrypted Epicentre servers for up to five-years before they will be permanently removed.

A data sharing agreement was signed between the NMCP, MSF, and Epicentre. A waiver from MSF's ethical review committee was obtained and authorisation from national authorities and partners according to local regulations. Refer to the annex for details of the waiver.

The study poses no harm nor risk to any individuals and is expected to benefit the local communities and enable health authorities to provide recommendations on strategies using SMC to prevent malaria cases. Members of the NMCP are co-investigators on this project and encourage the ongoing continuation of the study.

6. Results

6.1 Descriptive analyses

To quantify the impact of previous real-world SMC strategies between 2014 and 2022 on the evolution of malaria cases and hospitalisations in Moïssala, we gathered the clinical, intervention coverage, and rainfall datasets and analysed them to better understand patterns and underlying relationships. Our analyses focussed on six main aspects:

1. SMC coverage
2. Malaria cases and hospitalisations
3. Severity of malaria cases
4. Trends between SMC rounds
5. Rainfall and cases
6. Cases and hospitalisations before and after the SMC period

6.1.1 SMC coverage

Figure 3 shows annual percentages of SMC coverage verified either by card or by verbal confirmation (upper panel), or by card only (lower panel) for each year that the coverage survey was conducted by MSF, between 2014 and 2022. The absence of SMC coverage survey in 2018 and 2019 reflects the decision of the NMCP to suspend SMC campaigns during 2019. The coloured bars indicate average coverage percentages and are shown with black line bars indicating 95% confidence intervals. The uptake verified either by card or verbally was consistently high, with some drop-out towards the end of rounds each year. However, when looking at percentages of SMC coverage only verified by card, the uptake was not as high nor consistent. By 2021, the coverages for each round verified by card only were less than half those verified by either means, however the following year the coverages verified by card only increased again to levels like those seen in 2017.

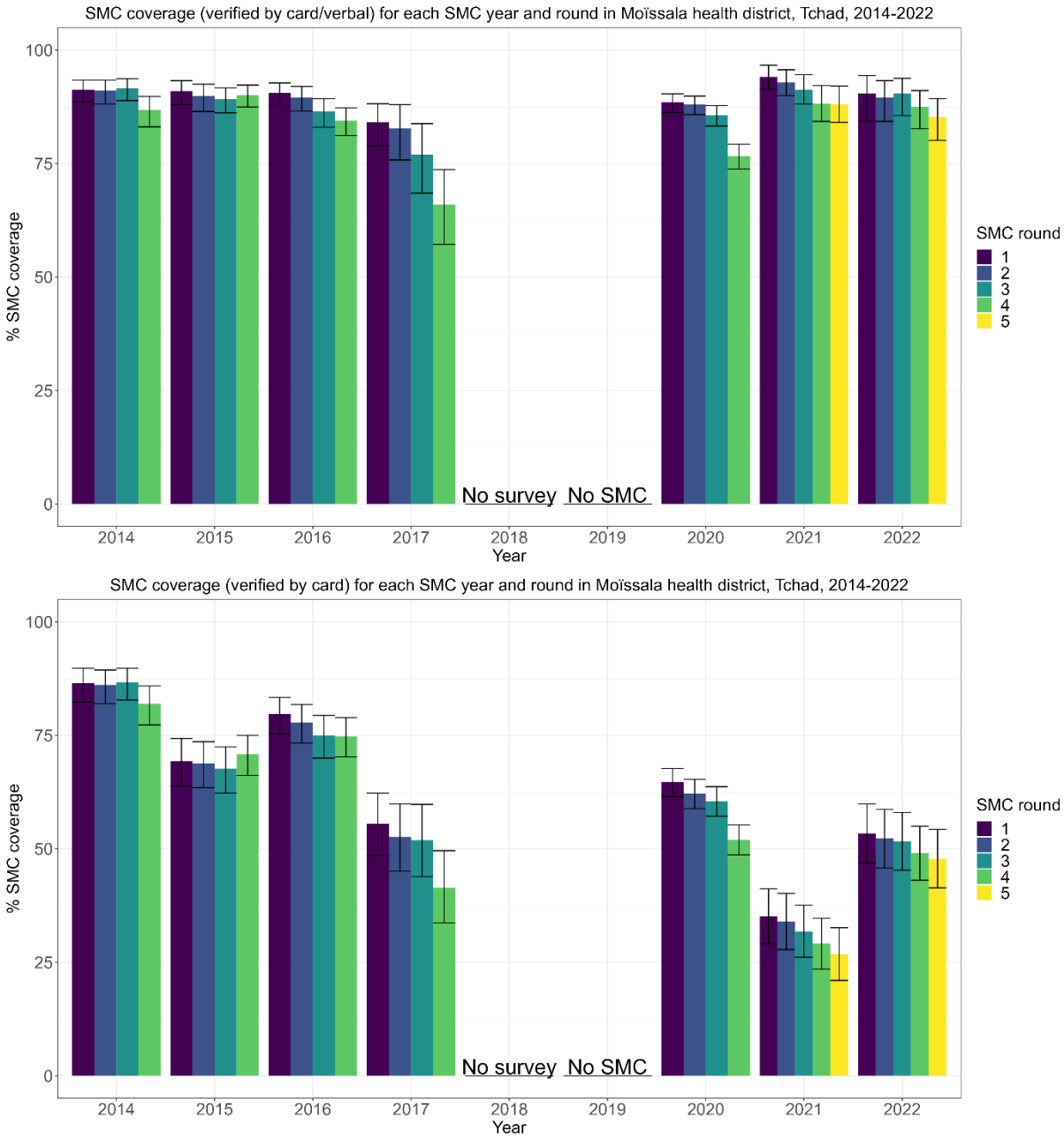


Figure 3 SMC coverages estimated from retrospective surveys by MSF in Moïssala.

6.1.2 Malaria cases and hospitalisations

Figure 4 shows the weekly numbers of malaria cases treated by MSF (upper panel) and hospitalised (lower panel) over time in Moïssala, with coloured bars indicating SMC coverage verified by card. Note that there was no coverage survey conducted in 2018, so coverage values for 2018 were imputed from 2017 data to indicate here that SMC was still distributed in 2018. Gaps in the hospitalisation data between 2014 and 2017 are weeks during which the MSF malaria unit was closed. The number of cases and hospitalisations increased substantially during 2019 when SMC was not authorised for implementation and dropped the following years, when SMC was re-authorised.

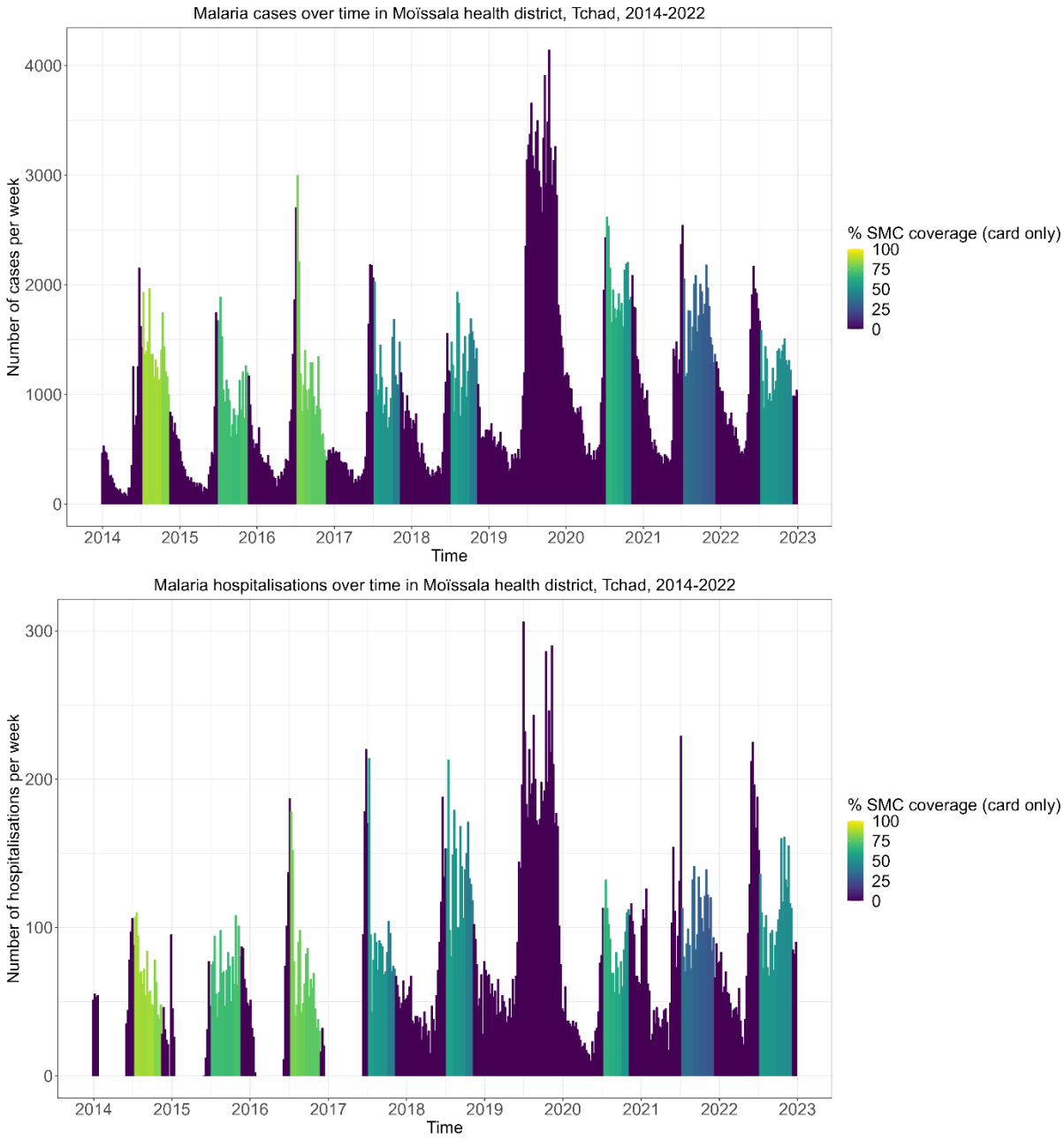


Figure 4 Numbers of weekly malaria cases and hospitalisations in Moïssala.

To verify that the increase in cases in 2019 could be attributed to the absence of SMC, we assessed other possible explanations such as a larger malaria outbreak in 2019 in neighbouring districts, or heavier season of rainfall, compared with other years. Figure 5 shows the number of monthly malaria cases in Moïssala and the neighbouring districts of Bedjondo, Goundi and Koumra, with coloured bars, again, indicating SMC coverage (verified by card) in Moïssala as described for Figure 4. Moïssala had an increased number of cases in 2019 compared with other years (which is consistent with the MSF data), however the monthly cases in 2019 in each of the neighbouring districts are comparable with those of the past and in the following years). In addition, rainfall was similar in 2019 compared to other years in Moïssala and neighbouring districts, which rules out the role of rainfall in explaining the increase in cases in 2019 (Figure 10).

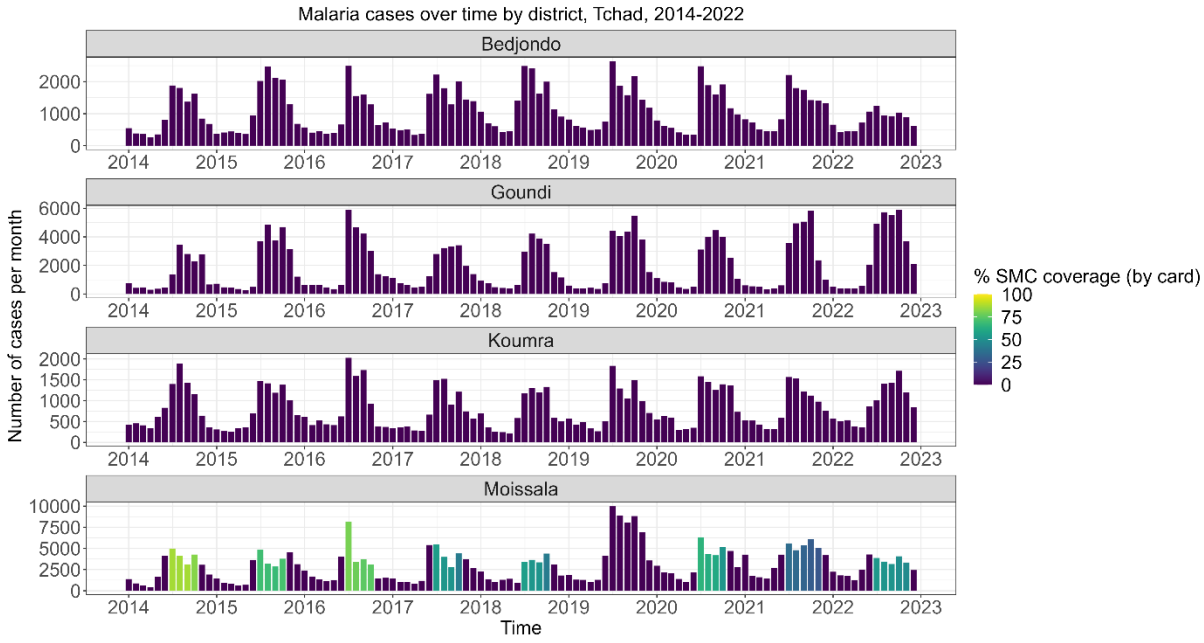


Figure 5 Numbers of monthly malaria cases in Moïssala, Bedjondo, Goundi, and Koumra.

6.1.3 Severity of malaria cases

Having data on both cases and hospitalisations enabled us to investigate the severity of malaria in Moïssala over time, by calculating the proportion of cases that were hospitalised as a proxy. Figure 6 shows the total number of malaria cases during each year in Moïssala (light grey bars for years with SMC, dark grey for years without SMC) alongside the percentage of those cases that were hospitalisations (red line and points). This percentage remained between 5 and 11% throughout the study period, despite large variations in the number of cases in different years.

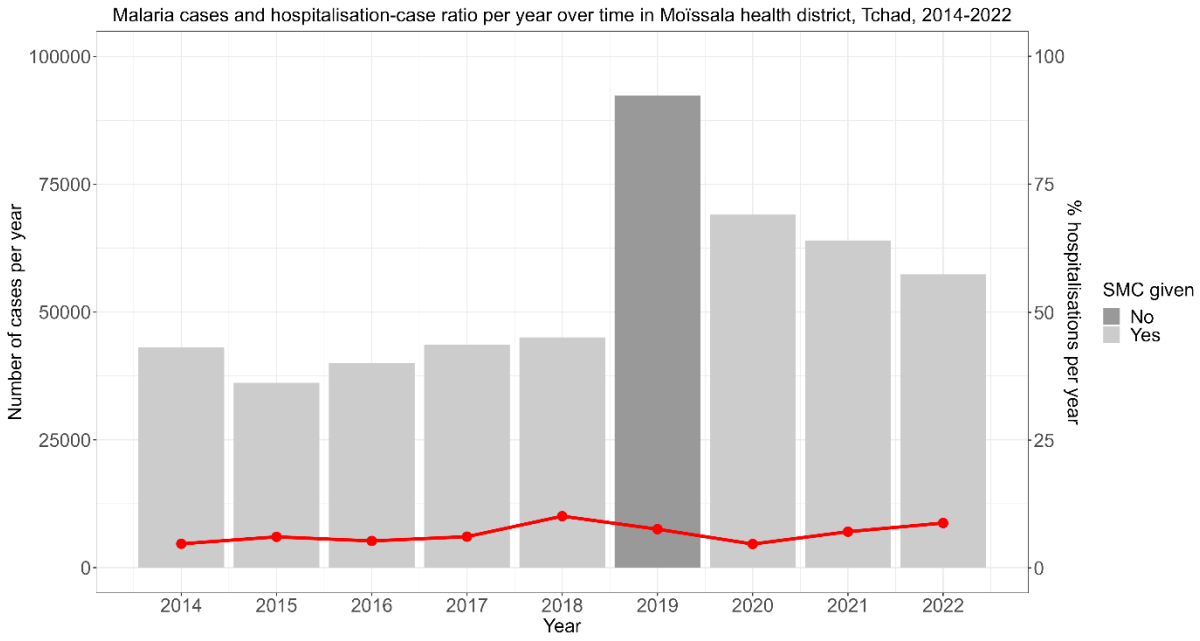


Figure 6 Number of yearly malaria cases and malaria severity over time in Moïssala.

Figure 7 shows the weekly number of malaria cases over time (upper panel) alongside the percentage of those weekly cases that were hospitalisations (lower panel) during each year. More severe cases tend to be observed at the beginning of the transmission season, as the number of cases start to increase. This is followed by a decline in hospitalisations and therefore in severity, during the malaria season.

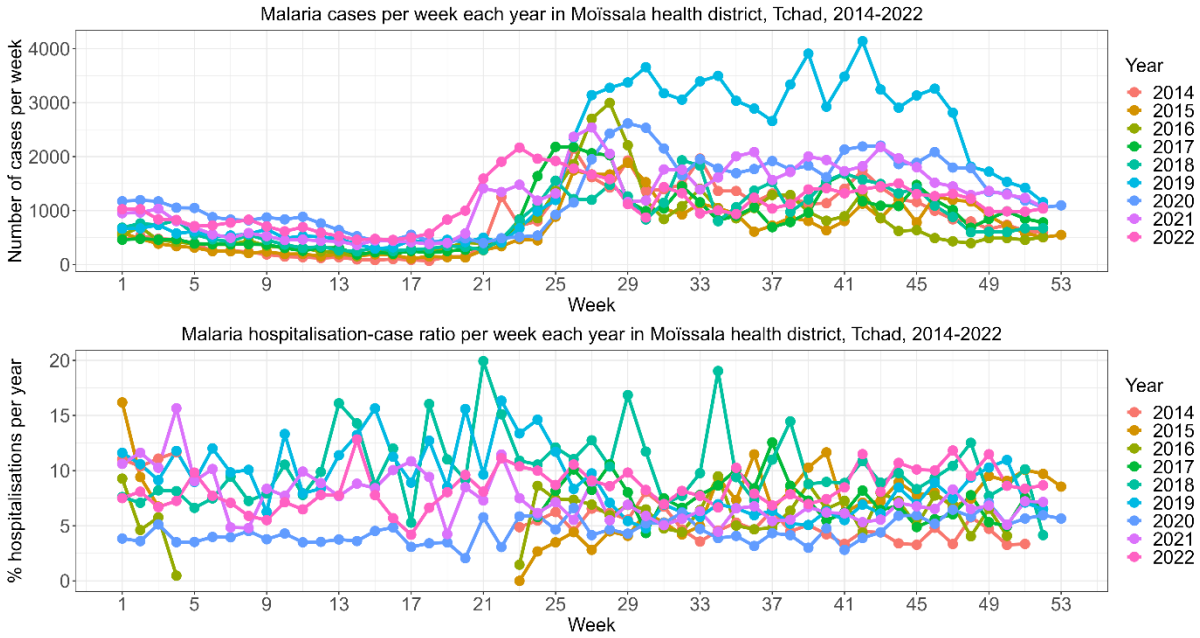


Figure 7 Number of weekly malaria cases and malaria severity in Moïssala during each year.

6.1.4 Trends between SMC rounds

The case and hospitalisation data were also used to investigate whether each round of SMC is providing protection throughout the time intervals between successive rounds of SMC, or whether the incidence increases again before the next round. Figure 8 shows the number of weekly malaria cases (upper panel) and hospitalisations (lower panel) during the SMC period each year, taking the number of cases at the start of each period of each year (upper panel) or the number of hospitalisations at the start of each period (lower panel) as a baseline. Instead of seeing gradually decreasing trends each year over time, the incidences fluctuate.

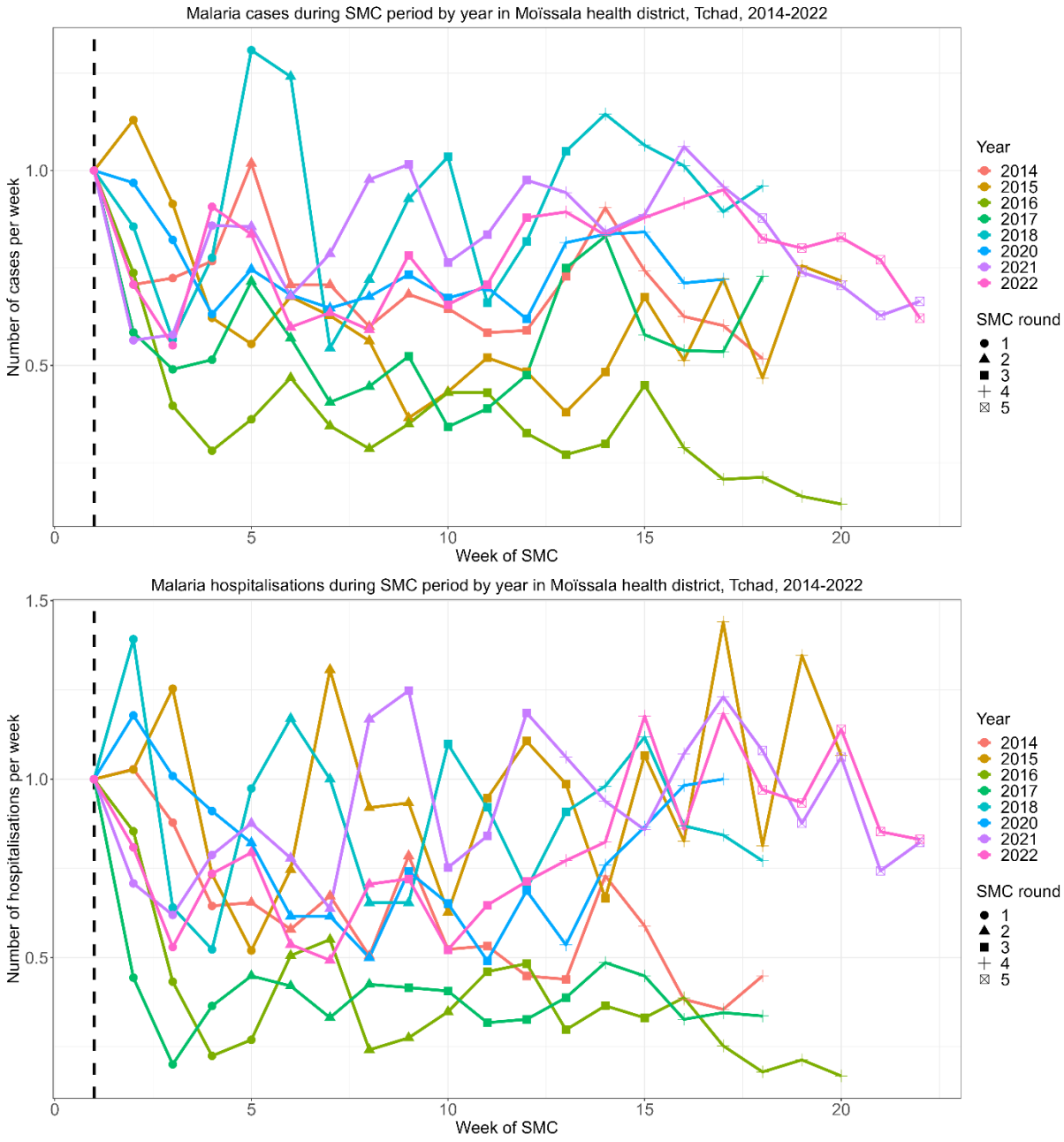


Figure 8 Numbers of weekly malaria cases and hospitalisations during SMC periods each year in Moïssala.

Figure 9 shows the number of weekly malaria cases (upper panel) and hospitalisations (lower panel) between rounds during the SMC period of each year, aligned vertically by the start of each round and taking the number of cases at the start of each round as baseline for the following weeks (up to five weeks after or before the start of the next round, whichever is earlier).

A frequent pattern is observed whereby cases (or hospitalisations) decrease after a round of SMC, as expected, but then increases again towards the end of the time interval between rounds. Sometimes, as often seen following the second and third rounds, the cases can increase to similar or even higher levels than when the previous round was given (as in the third rounds of 2015-2018).

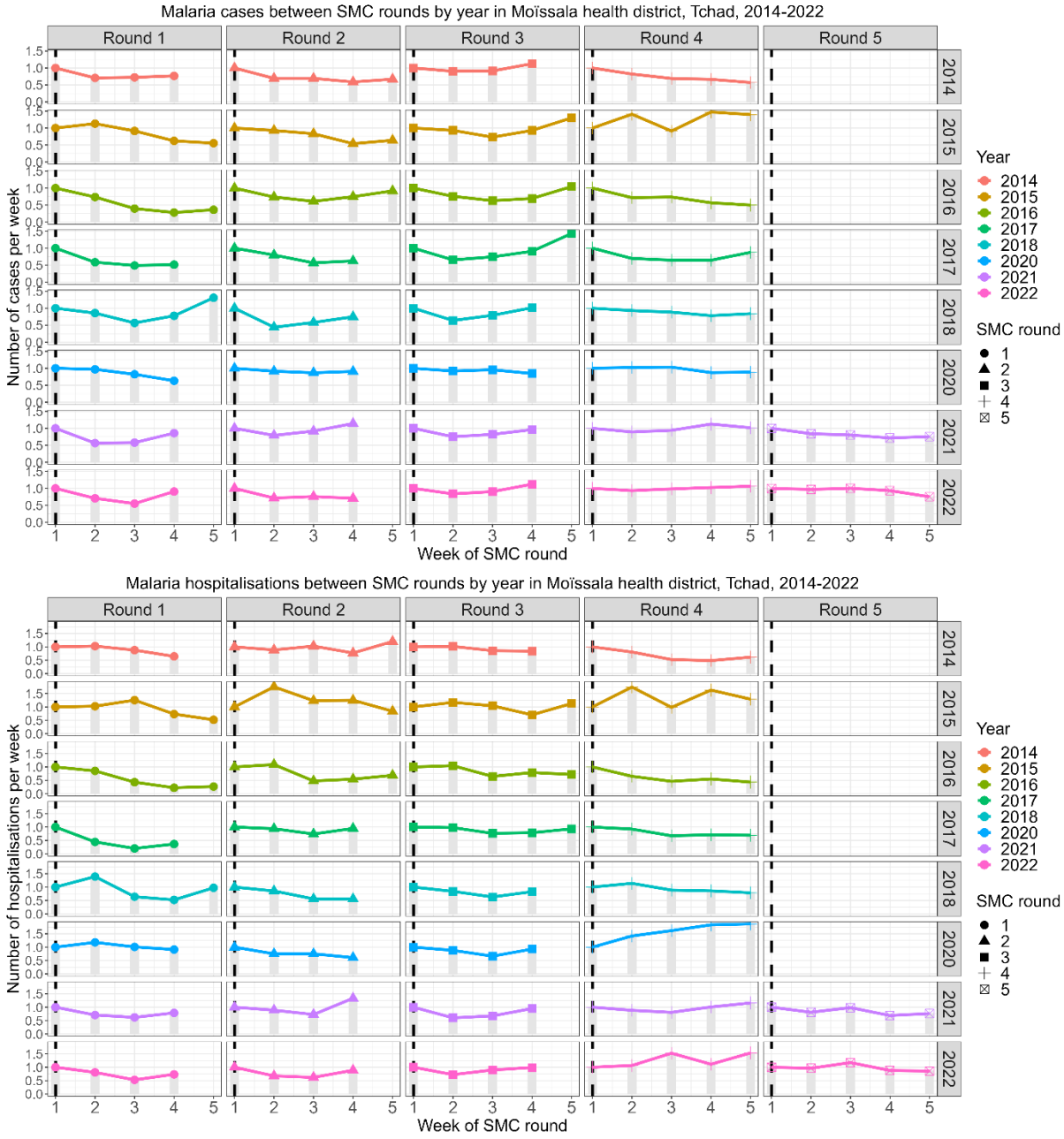


Figure 9 Numbers of weekly malaria cases and hospitalisations in Moïssala between each SMC round each year.

6.1.5 Rainfall and cases

Since malaria cases and hospitalisations increase during the rainy season, data on the amount of rainfall in Moïssala (and the neighbouring districts) were analysed alongside the clinical datasets. First, these data were aggregated by month for each district to investigate whether a season of heavier rainfall in 2019 could explain the increase in cases. Figure 10 shows the amount of rainfall (blue line) alongside the incidence of malaria cases each month (light grey bars for months with SMC, dark grey bars for months without SMC) in each district during the study period. For each district, the annual trends in rainfall are roughly the same (not higher in 2019 than all other years) and these trends are also comparable across the different districts - that is, Moïssala did not experience significantly more rainfall during any season than elsewhere.

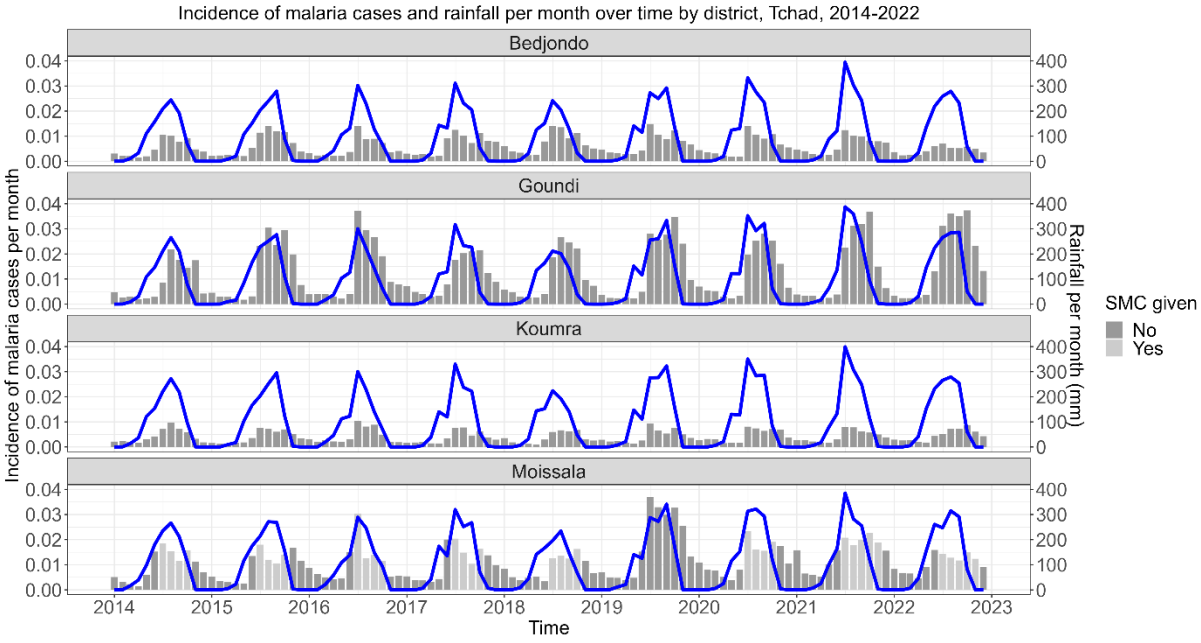


Figure 10 Incidence of malaria cases and amount of rainfall each month in Moïssala, Bedjondo, Goundi, and Koumra.

Figure 11 shows the trends in weekly malaria cases (dark grey bars) and amount of rainfall over past three weeks (blue line) in Moïssala, with the SMC periods indicated for each year it was given (intervals along time axis coloured in light grey). During each year, the increase in rainfall, is closely followed by an increase in the number of cases as expected. It is only once the rainfall reaches its peak period, that SMC begins and starts to curb the number of infections. These patterns are compared between each year in Figure 12, with the trends in weekly cases (upper panel) shown alongside the trends in rainfall over past three weeks (lower panel), vertically aligned by the start of the SMC period each year (dashed line).

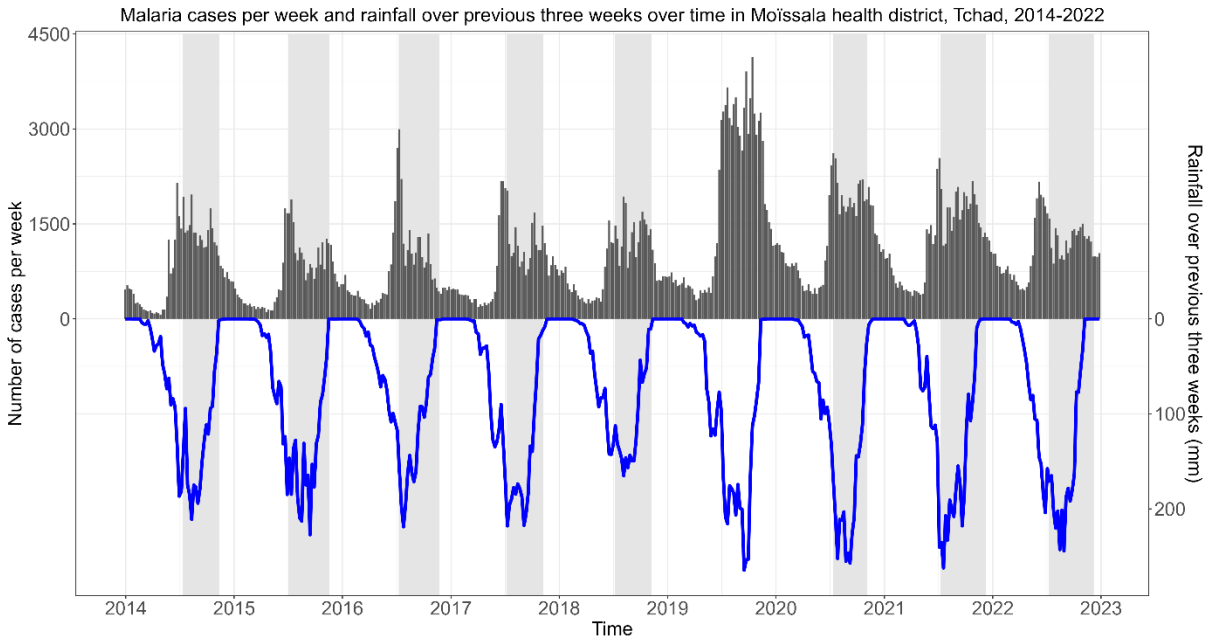


Figure 11 Number of weekly malaria cases and amount of rainfall over past three weeks in Moïssala.

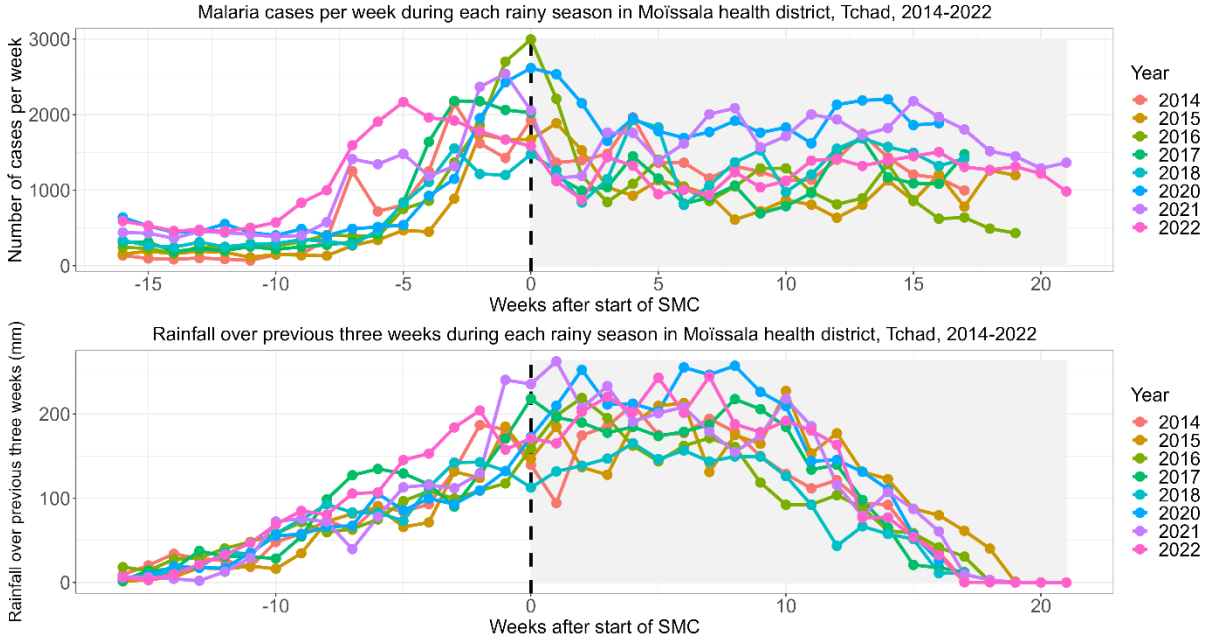


Figure 12 Number of weekly malaria cases and amount of rainfall over past three weeks each year in Moïssala.

6.1.6 Cases and hospitalisations before and after the SMC period

In 2020, the PNLP decided to reauthorise the distribution of SMC and in 2021 they decided to increase the number of rounds from 4 to 5. Analysis of the data available at the time, taking into account logistical constraints, led to the decision to add the 5th SMC cycle at the end of the 4th cycle. In the light of the previous results – showing the high number of cases before SMC starts – the number of cases before and after the SMC period were investigated by calculating the total number of malaria cases

(upper panel) and hospitalisations (lower panel) during the 4 weeks before the start of SMC period (purple bars) and during the 4 weeks after the end of the SMC period (yellow bars), between 2014 and 2020 (except 2019) in Moïssala. These are all the years where 4 rounds of SMC were distributed (before the decision to increase distribution to 5 rounds in 2021). While the totals were closer in 2020, it was frequently the case that the number of cases and hospitalisations before SMC were higher than after SMC. This suggests that starting SMC distribution earlier in the season could have a greater impact on reducing malaria incidence.

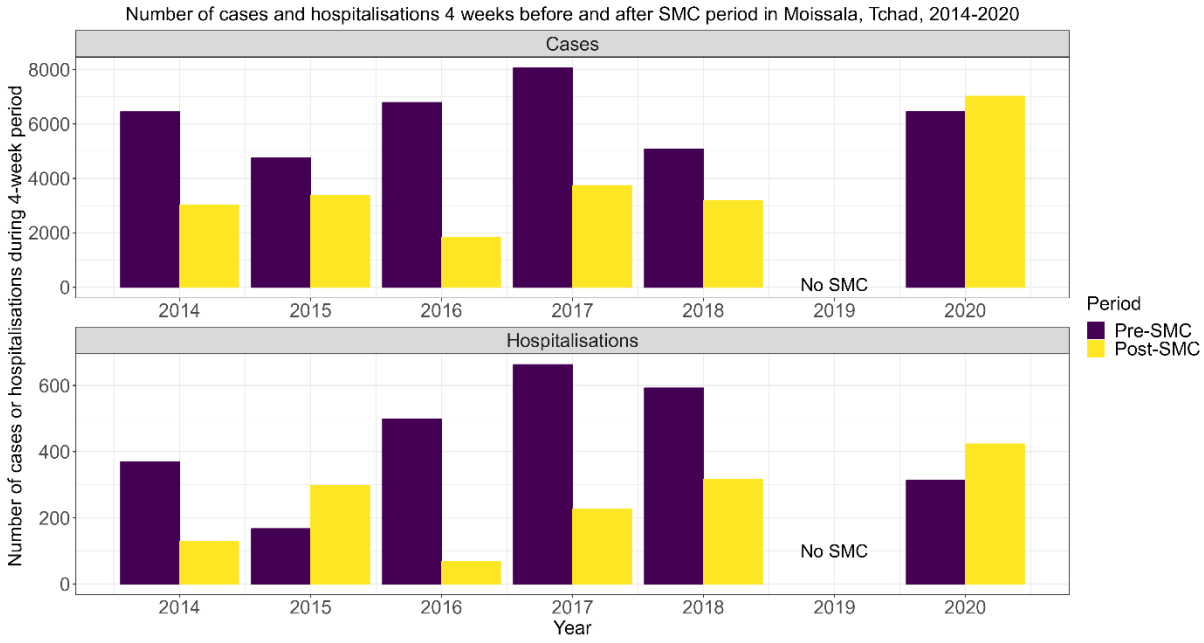


Figure 13 Number of malaria cases and hospitalisations before and after the SMC period each year in Moïssala.

6.2 Mathematical modelling

To investigate the effect of varying the timing of SMC rounds on the number of malaria cases, a mathematical model was used to generate trajectories for the number of new malaria cases each week for different SMC schedules. Details of the model equations and parameters can be found in the appendix.

6.2.1 Calibration to case and rainfall data

The model was calibrated to imitate the evolution of malaria cases in Moïssala by first approximating the number of new infections in the model and the seasonal forcing component to the number of malaria cases and amount of rainfall during 2019, in the absence of SMC campaigns. After selecting suitable parameters relating to malaria transmission and the impact of rainfall, the remaining parameters relating to SMC were calibrated by approximating the number of new infections in the model to the number of weekly cases during 2018. Figure 14 shows both calibration steps. It should be noted that while the model trajectory is fitted to align with the weekly number of cases, the

seasonal forcing curve should only have the same shape as the trend in rainfall over time and not directly overlap the data.

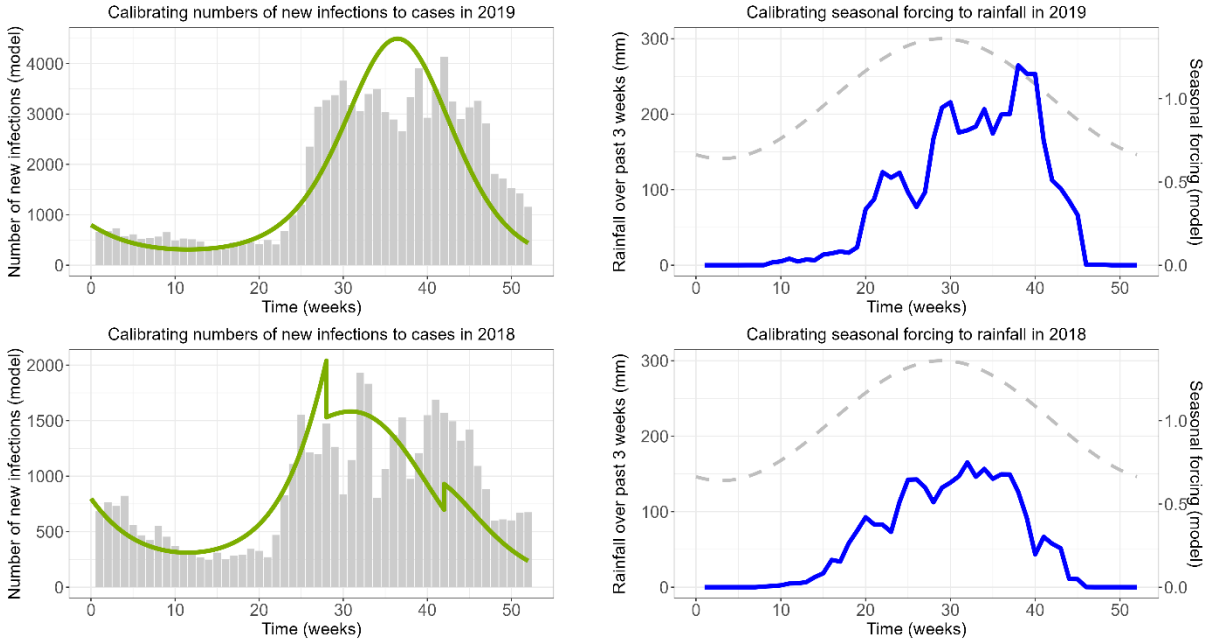


Figure 14 Calibration of the toy model to case and rainfall data from Moïssala.

The weekly number of infections projected by the model (green line) configured to malaria cases (grey bars) in 2019 (upper-left panel), and the seasonal forcing curve (grey, dashed line) configured to amount of rainfall over past three weeks (blue line) in 2019 (upper-right panel). The weekly number of infections projected by the model configured to malaria cases in 2018 (lower-left panel), and the seasonal forcing curve configured to amount of rainfall over past three weeks in 2018 (lower-right panel). Model parameter values are listed in the appendix.

6.2.2 Comparing different SMC schedules

Having obtained a model configured to malaria transmission, rainfall, and the impact of SMC in Moïssala, the model was used to simulate the weekly number of new malaria cases for three different SMC strategies:

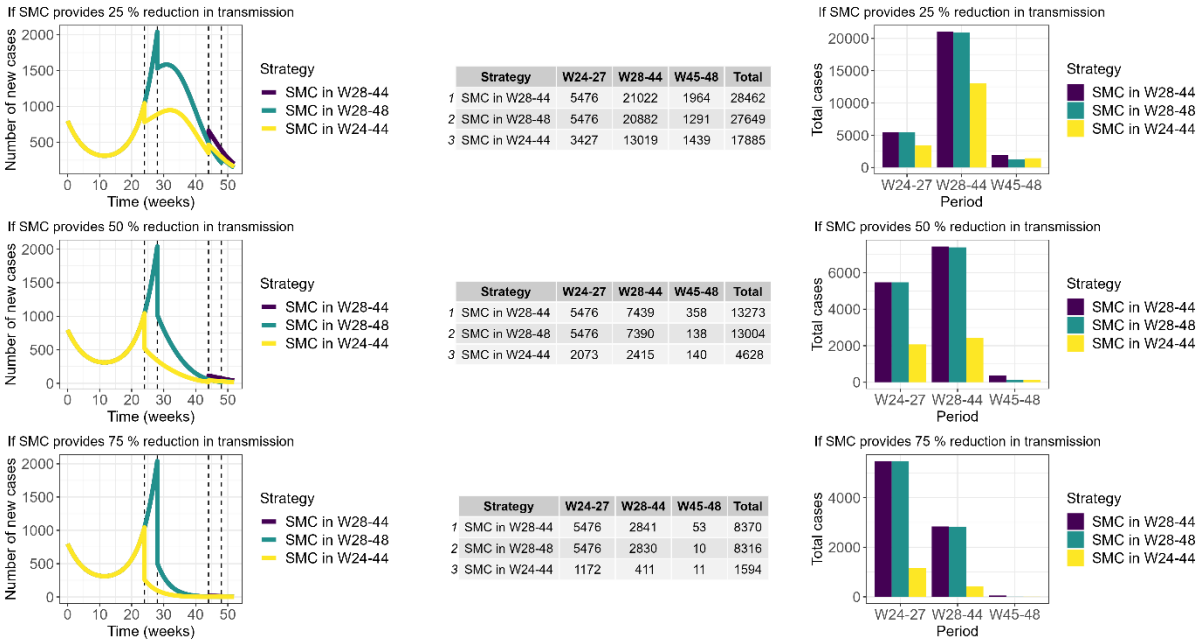
1. SMC is given between the 28th and 44th weeks of the year (similar schedule to four-round distributions in 2014-2018 and 2020)
2. SMC is given between the 28th and 48th weeks of the year (similar schedule to five-round distributions in 2021 and 2022)
3. SMC is given between the 24th and 44th weeks of the year (like the second strategy but started 4 weeks earlier)

This was done to investigate the impact of starting the SMC earlier. The amount by which SMC reduces transmission was also varied at three different levels (25%, 50% and 75%) to test the robustness of the schedules to different degrees of SMC effectiveness.

Figure 15 shows the trajectories for each level of effectiveness and strategy across the year. To compare the impact of the different schedules at different times, the period between the 24th and 48th weeks was divided into three shorter periods of interest:

1. Between the 24th and 27th weeks of the year
2. Between the 28th and 44th weeks of the year
3. Between the 45th and 48th weeks of the year

The number of cases during each period and across all three periods were aggregated and the totals are shown in the tables and bar graphs alongside the overall trajectories. The first strategy with four rounds always gives rise to the highest numbers of cases during any period. The second strategy is at least as good as the first in all periods and the best overall between the 45th and 48th weeks. The third strategy is the best overall during all periods except that between the 45th and 48th weeks, with a slightly higher number of cases here, but overall has far less cases than the other strategies. These results were robust to varying the effectiveness of SMC from 25% to 75%.



	Strategy	W24-27	W28-44	W45-48	Total
1	SMC in W28-44	5476	21022	1964	28462
2	SMC in W28-48	5476	20882	1291	27649
3	SMC in W24-44	3427	13019	1439	17885

	Strategy	W24-27	W28-44	W45-48	Total
1	SMC in W28-44	5476	7439	358	13273
2	SMC in W28-48	5476	7390	138	13004
3	SMC in W24-44	2073	2415	140	4628

	Strategy	W24-27	W28-44	W45-48	Total
1	SMC in W28-44	5476	2841	53	8370
2	SMC in W28-48	5476	2830	10	8316
3	SMC in W24-44	1172	411	11	1594

Figure 15 Number of malaria cases predicted by the toy model for the three different SMC schedules at three different levels of SMC effectiveness.

Assuming SMC provides a 25% (upper row), 50% (middle row), or 75% reduction in malaria transmission: model trajectories for each of the three strategies (left column), table comparing aggregated cases across three periods and overall period for each strategy (middle column), graph comparing aggregated cases across three periods for each of the three strategies (right column). Transmission and seasonal forcing parameters are listed in the appendix.

7. Discussion

Malaria cases increased during in 2019 due to absence of SMC

The increase in cases and hospitalisations in Moïssala during 2019 can likely be attributed to the absence of SMC in Moïssala during 2019. This is because other possible explanations such as a larger malaria outbreak in 2019, or heavier season of rainfall, compared with other years, can be excluded.

Firstly, the number of malaria cases were consistent across the study period in the neighbouring districts of Bedjondo, Goundi, and Koumra. These neighbouring districts would most likely have experienced outbreaks with similar factors to Moïssala, due to their nearby locations, and none of them have ever been authorised for SMC administration. This indicates that the increased number of cases cannot be attributed to a larger malaria outbreak at the regional level during 2019.

Furthermore, the amount of rainfall was consistent across the study period in each of the four districts, demonstrating that the increased number of malaria cases in Moïssala in 2019 cannot be attributed to a change in rainfall. Thus, it is likely that the increase in cases during 2019 was indeed due to the absence of SMC in that year.

This indicates that SMC would be beneficial in regions with a longer rainy season. The Chadian Ministry of Health recently reported that Sudanian zone health districts account for 60% of the overall reported cases and 62.36% of deaths and argue that broader implementation of SMC would have reduced cases. The results of this study support those of other investigations of the effectiveness of SMC in real-world settings [4-8].

Severity of malaria remains unchanged

The severity of malaria (percentage of cases that were hospitalisations) in Moïssala remained roughly the same across the study period. This was quite a surprising result given the dramatic rise in cases and hospitalisations in 2019 and concerns of whether SMC would continue to be as effective in preventing hospitalisations when SMC was re-authorised in 2020 and scaled up to five rounds since 2021.

The observed trend of a higher hospitalisation rate at the start of the transmission season, followed by a drop thereafter, is frequently observed during epidemics and could be due to changes in people's behaviour with regard to presentation at health centres. Another observation is the lack of data on hospitalisations during the start of 2014-2017 due to the malaria unit being closed during these weeks.

It should be noted that the estimates obtained in this study are only proxy measures which we have obtained from the routinely collected datasets. Results from studies designed to focus on measuring malaria severity over time would be of great importance, both to ascertain trends in severity and to assess whether such proxy measures can serve as valid estimators.

Intervals between SMC rounds may be too long

The fluctuations in cases and hospitalisations, both across the SMC period and between SMC rounds, indicate that the effectiveness of SMC may be waning between rounds. It is currently believed that individuals who adhere to the full three days of SP-AQ during each round can benefit from around 28 days of protection [4], which should mean that they are protected for the entire period until the next round. However, more recent studies have observed a decline in its protective ability before 28 days [19].

Another possible explanation for the trends observed, could be that individuals are not adhering to the full course. The coverage trends indicate that uptake decreases across SMC rounds each year, however no definite relationship between coverage each year and rebounds in cases (or hospitalisations) has been confirmed. Moreover, it is unknown whether individuals adhere to the full 3 days of treatment within an individual round since the latter days of many rounds are taken at home. The ACCESS-SMC Partnership found variation in SMC coverage across areas of west and central Africa [10] and further studies in countries such as Niger have identified decreasing coverage of SMC in children and advocated for strengthening supervision of uptake and improving adherence [20, 21].

Further studies focussing on evaluating SMC effectiveness would be greatly beneficial and MSF is looking to begin studies assessing this and the possible development of resistance to SMC from 2023. Depending on these results, it may be beneficial to reduce the length of time between SMC rounds offered in Moïssala, in the interests of tailoring treatment to the local epidemiology.

Starting SMC earlier may reduce malaria cases

The case and rainfall data together illustrated how during each year, the increase in rainfall is closely followed by an increase in the number of cases, and only once the rainfall and cases have peaked does SMC begin and start to reduce the number of infections. This, along with the frequent observation of more cases before the SMC period than after during years of the study period, prompted the investigation of whether starting SMC earlier could reduce the number of malaria cases across the transmission season.

This was tested by simulating malaria epidemics under different SMC strategies encoded within the toy-model calibrated to the real-world datasets. Of the three strategies simulated, the third strategy, with SMC delivered between the 24th and 44th weeks of the year represented the effect of moving the SMC period forward by four weeks.

Such a strategy was found to be superior to strategies corresponding to those previously used in 2021 and 2022, with significantly less cases across the whole period, despite a slightly increased rebound after the fifth round. Furthermore, this effect was seen when also accounting for different extents to which SMC reduced malaria transmission, either through different levels of coverage, or effectiveness, or both. This suggests that starting SMC up to a month earlier in future years could significantly reduce the number of malaria cases.

Both the real-world data and the model results supported the decision to extend the SMC period to 5 rounds, with the first strategy implemented in the model leading to the highest numbers of cases. Extending the SMC period to 5 rounds has been found to reduce cases and deaths in other regions of

Africa [22]. There have been very few investigations of the impact of timing on cases, however recent studies have investigated the feasibility of adopting an earlier round (in June) in other areas seeing cases increase early in the rainy season [23]. In addition, this study emphasised the need for further studies assessing the cost effectiveness of implementing a fifth round (or further rounds) and such a study would be beneficial here to understand the financial costs associated with health benefits in Moïssala for MSF and the NMCP.

Study limitations

The model developed for this study was a very basic model to roughly simulate the yearly trends in malaria cases. Certain events, such as the delivery of SMC of each SMC round would be more accurately implemented through more detailed equations. Furthermore, the model used was only configured to data from two different years by inspection, rather than through a formal model fitting algorithm which would numerically fit to the entire data from the whole study period. Both the development of a more detailed model and its fitting through a formal process would take a great deal of time and careful consideration, to ensure that the resulting mathematical model is accurately describing the real-world scenario and can be used to make reliable predictions with different strategies.

Another important limitation of the study, which would limit even a more detailed model, is the partial completeness of the data. This is partly due to missing data on hospitalisations, as the malaria unit was only open for six months of the year prior to 2018. In addition, MSF's datasets only contain aggregated data for children under five, meaning that weekly cases in older populations are not captured.

For this study, data on environmental variables, namely rainfall was sourced from outside of MSF and the NMCP. While not essential, a critical gap in the data which would be valuable to better understanding both the evolution of malaria cases and how they are impacted by environmental variables, is the evolution of the vector population. Such data would likely need to be sourced from external studies looking specifically at estimating mosquito numbers, and how many of them are infected, however such studies may not exist or may not be conducted in the Moïssala district.

Finally, it is worth mentioning that understanding the evolution of malaria cases is a highly complex task. Outside of the key factors mentioned, many other processes, such as the migration of humans and vectors, and the impact of other interventions, or use of bed nets, impact malaria transmission and it is a difficult task to determine how many others may be having a significant impact, without overcomplicating the study.

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9. Appendix

9.1 Mathematical model equations

The model equations are

$$\frac{dS}{dt} = -\beta(t)\frac{SI}{N},$$

[Change in number of susceptible individuals = – rate of new infections]

$$\frac{dI}{dt} = \beta(t)\frac{SI}{N} - \gamma I,$$

[Change in number of infectious individuals = rate of new infections – rate of individual recovery]

$$\frac{dR}{dt} = \gamma I,$$

[Change in number of removed individuals = rate of individual recovery]

where

$$N = S + I + R$$

is the total population in the district at any time (constant) and

$$\beta(t) = \beta\delta_T(t)\left[1 - A\cos\frac{2\pi(t-\tau)}{L}\right]$$

is the time-dependent transmission coefficient incorporating the impacts of rainfall and SMC, with

$$\delta_T(t) = \begin{cases} \alpha, & T_{start} \le t \le T_{end}, \\ 1, & \text{otherwise.} \end{cases}$$

If SMC is not to be included in the model (that is, T_{start}, T_{end}, and α do not exist) then $\delta_T(t)$ is simply taken to be always equal to 1.

The interpretations of the constant parameters are shown in the table below. Where appropriate the values of these parameters determined after configuring the model to the case data in 2019 and 2018 are also given. The period of seasonal forcing was chosen to correspond roughly with the length of a year. The start and end times of SMC were chosen to align with the first and weeks SMC was distributed in 2018. The total district population was chosen using the population estimate for Moïssala in 2014 from the NMCP dataset.

Parameter	*Definition*	*Value*	*Chosen/fitted*
β	Average per capita malaria transmission rate	0.45	Fitted
γ	Average per capita recovery rate	0.4	Fitted
A	Amplitude of seasonal forcing due to rainfall	0.36	Fitted
L	Period of seasonal forcing due to rainfall	52	Chosen
τ	Lag in seasonal forcing due to rainfall	3	Fitted
T_{start}	Week (time) when SMC period starts	28 (or 0)	Chosen

T_{end}	Week (time) when SMC period ends	42 (or 0)	Chosen
α	Factor by which SMC reduces malaria transmission	0.75 (or 0)	Fitted
N	Total population of the district	267922	Chosen
$I(0)$	Initial number of infectious individuals	2700	Fitted

9.2 List of variables contained in original datasets

	Variable
1	Total new cases from all causes
2	Total new suspected simple malaria cases
3	Total new cases of uncomplicated malaria tested by RDT
4	Total new cases of uncomplicated malaria tested by microscopy
5	Total new cases of uncomplicated malaria not tested
6	Total new cases of simple malaria confirmed positive by RDT
7	Total new cases of simple malaria confirmed positive by microscopy
8	Total confirmed uncomplicated malaria cases managed correctly according to national guidelines (ASAQ or AL)
9	Total presumptive uncomplicated malaria cases treated with ASAQ or AL (in case of RDT breakage)
10	Total suspected severe malaria cases
11	Total new suspected severe malaria cases tested by RDT
12	Total new suspected severe malaria cases tested by microscopy
13	Total new severe malaria cases confirmed positive by RDT
14	Total new severe malaria cases confirmed positive by microscopy
15	Total confirmed severe malaria cases referred
16	Total deaths from all causes
17	Total deaths due to malaria
18	Total LLINs distributed
19	Total pregnant women seen in ANC 1
20	Total pregnant women who received IPT 1
21	Total pregnant women who received IPT 2
22	Total pregnant women who received IPT 3
23	Total pregnant women who received IPT 4
24	Community - Total new suspected simple malaria cases
25	Community - Total new simple malaria cases tested by RDT
26	Community - Total new cases of suspected uncomplicated malaria not tested by RDT
27	Community - Total new cases of simple malaria confirmed (positive) by RDT
28	Community - Total confirmed simple malaria cases managed correctly according to national guidelines (ASAQ or AL)
29	Community - Total cases referred to the health centre
30	HOSPITALIZATION/URGENCIES - Total hospitalized cases from all causes
31	HOSPITALIZATION/URGENCIES - Total hospitalized cases with suspected severe malaria
32	HOSPITALISATION/URGENCIES - Total new hospitalized severe malaria cases tested by RDT
33	HOSPITALIZATION/URGENCIES - Total new hospitalized severe malaria cases tested by microscopy
34	HOSPITALISATION/URGENICS - Total new cases of severe malaria confirmed positive by RDT

35	HOSPITALISATION/URGENICS - Total new cases of severe malaria confirmed positive by microscopy
36	HOSPITALIZATION/Urgences - Total hospitalized cases with severe malaria diagnosis properly managed according to national guidelines
37	HOSPITALISATION/URGENCIES - Total deaths from all causes
38	HOSPITALISATION/URGENICS - Total deaths due to malaria

9.3 : Waiver MSF ERB

Time frame: September-December 2022

Exemption criteria:

Address each criterion below:

1. **Studies/articles are based on routinely collected clinical data from pre-existing, established programs.**

Il s'agit d'une étude rétrospective utilisant des données du programme MSF dans le district sanitaire de Moïssala et des données des districts avoisinants fournies par le PNLP. L'étude est basée sur des données cliniques collectées de manière routinière dans le cadre de programmes préexistants et évalue une intervention ciblée (CPS). Aucun identifiant de patient n'est utilisé et les analyses ne sont faites qu'avec des données agrégées

2. **They are either descriptive/evaluative or targeted evaluations.**

Les analyses seront descriptives et évaluatives des campagnes CPS menées depuis 2014 à Moissala ou Tchad.

Ci-dessous un résumé des objectifs :

Décrire l'évolution des cas simples et sévères de malaria à Moïssala avec ou sans CPS entre 2014 et 2021, Région du Mandoul, Tchad.

- Décrire l'évolution des cas au cours de l'année 2019, lorsque la CPS a été suspendue
- Comparer l'évolution des cas dans des districts voisins de Moïssala ou la CPS n'a jamais été déployée
- Etudier les facteurs ayant un impact sur la CPS comme la couverture des cycles CPS et les stratégies mises en œuvre
- Comparaison des ratios cas de paludisme chez les moins de 5 ans et plus de 5 ans de 2014 à 2021

3. **Confidentiality is respected; no individual patient identifiers are revealed or used.**

Il n'y a aucun risque lié à la violation de la confidentialité des patients étant donné que les données sont agrégées et ont été collectées de manière routinière dans les dossiers des patients pour les hospitalisations et les registres des centres de santé sans intervention expérimentale ou rencontre avec le personnel de recherche en dehors des visites médicales de routine. Les données fournies par MSF et PNLP sont agrégées et totalement dépersonnalisées et il ne sera pas possible pour quiconque participant à l'étude d'identifier les patients. Les données seront conservées

en toute sécurité sur des serveurs cryptés aux fins de l'étude et de l'analyse pour une durée maximale de 5 ans, puis seront détruites

4. **Harm is minimal but acknowledged where relevant.**

Non applicable, aucun risque n'est attendu pour les participants

5. **Potential benefits to both the program and the community are described. Since the goal is publication, the relevance to a wider audience is described.**

Il n'y aura pas de bénéfice direct pour les participants, cependant, des bénéfices sont prévus au niveau de la communauté grâce aux résultats fournis par cette étude ainsi que pour les autorités sanitaires afin de fournir des recommandations sur les stratégies de mise en œuvre de la CPS et prévention du paludisme

6. **Collaborative involvement and, if applicable, authorship from a local authority or partner (Ministry of Health, DHO, other NGO) is encouraged. If relevant and applicable, consultation with a body representing the community is desirable.**

Une publication est prévue pour partager les résultats et les effets de la CPS sur l'incidence du paludisme a Moïssala dans le sud du Tchad en collaboration avec les autorités locales et centrales qui ont accepté de partager leurs données et qui participent à la rédaction d'un article. ; les analyses préliminaires ont été partagées avec le PNLP et les autorités sanitaires locales.

Les implications opérationnelles de cette étude sont importantes et cela permettra d'apporter des éléments pour soutenir les efforts continus de la CPS à Moïssala pour réduire la morbidité due au paludisme et pour plaider en faveur d'autres zones du sud qui pourraient en bénéficier en collaboration avec les autorités sanitaires.

7. **If the decision for exemption from review is taken by the respective medical director, the responsibility to ensure that ethical requirements are met lies with MSF. This, however, does not exempt MSF from complying with any relevant regulatory requirements in the country from where the data originate. In some countries, local ethical review may still be required.**

Une dérogation du comité de révision éthique de MSF doit être demandée ainsi qu'une autorisation des autorités nationales et des partenaires conformément aux réglementations locales. Une dérogation sera demandée dans la mesure où le protocole remplit les critères énumérés pour l'examen d'une exemption. L'étude est basée sur des données cliniques collectées de manière

routinière dans le cadre de programmes préexistants et évalue une intervention ciblée (CPS). Aucun identifiant de patient n'est utilisé et les analyses ne sont faites qu'avec des données agrégées. Il n'y a pas de préjudice et l'étude sera bénéfique pour le programme et la communauté et aura des implications opérationnelles.
Il faut également mentionner que le ministère de la santé et ses partenaires (PNLP) seront les co-enquêteurs et qu'ils encouragent la poursuite de l'étude et la documentation de l'impact de la CPS dans le sud du Tchad.

If the above criteria and conditions are met, then the authors can insert into their article the following statement that has been approved by the MSF ERB:

"This research fulfilled the exemption criteria set by the Médecins Sans Frontières Ethics Review Board for a posteriori analysis of routinely-collected clinical data and thus did not require MSF ERB review. It was conducted with permission from Medical Director, Operational Center Paris, Médecins Sans Frontières."

Note: **This exemption is only valid if the protocol has been approved or formally exempted by the Ethics Committee in the study country.**

If challenged by a journal, the authors are responsible for demonstrating that their study meets these criteria, including providing proof of local ethics approval.

Approved: **Claire Rieux (Diretrice Médicale)** **Date:** **4 Novembre 2022**

Epicentre
14-34 av Jean Jaurès, 75019 Paris, France
Association loi 1901

+33(0)1 40 21 55 55

epimail@epicentre.msf.org
www.epicentre.msf.org