Quantifying the protective efficacy of seasonal malaria chemoprevention under programmatic implementation in Burkina Faso using routine case data

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Abstract

Background: Seasonal malaria chemoprevention (SMC) therapy was first recommended by the WHO in 2012 for children under 5 years old, who are at highest risk for contracting moderate and severe malaria, and is given throughout the peak malaria transmission period each year. Meta-analysis of clinical trials analyzing SMC efficacy on clinical malaria have found a 75% decrease in disease incidence in the treatment group relative to the control group, although we expect some drop-off when moving to in country intervention campaigns. To analyze the programmatic efficacy of SMC in Burkina Faso, we use routine case data from health facilities, which gives us the ability to assess the protective effect on national scale. The emergence of digitized routine health facility data in sub-Saharan countries with a high burden of malaria presents an opportunity to analyze the changes in malaria incidence using readily available incidence data with national spatial coverage and long temporal resolution. Issues inherent to passively collected malaria data from health facilities brings bias to analysis which fails to control for these imperfections.

Aim: To model the effect of SMC under programmatic implementation, we use routine case data from the Burkina Faso Health Management Information System (HMIS), which, contrary to expectation, shows an increase in raw malaria incidence during the period of SMC deployment.

Methods: Using seasonal trend decomposition, we discover that the apparent increase in raw incidence is driven by increases in treatment seeking, expansions to the HMIS network, and reporting inconsistencies and instead use the malaria share of outpatient visits as our response for intervention efficacy against clinical malaria as this controls for this increase. We quantify the protective efficacy of SMC against clinical malaria in children under 5 years old with generalized linear mixed-models in a difference-in-difference framework accounting for differences between health districts in the random effect components.

Results: There was a significant reduction in the malaria share of outpatient visits correlating with the intervention of SMC, account for a protective efficacy (PE) of 13.1% (95% CI [7.9%, 18.1%]) and 15.3% (95% CI [9.3%, 20.9%]) in the group of districts which initially received SMC in either 2016 or 2017.

Data description

Monthly routine case data from 2,959 health facilities across Burkina Faso from January 2015 to December 2018 were obtained from the Burkina Faso National Malaria Control Program (PNLP) HMIS database. Observations were discarded if the number of all-cause outpatient visits was not specified or was less than the number of confirmed malaria cases, or if the number of confirmed malaria cases was not specified. Data was then aggregated into 70 districts.

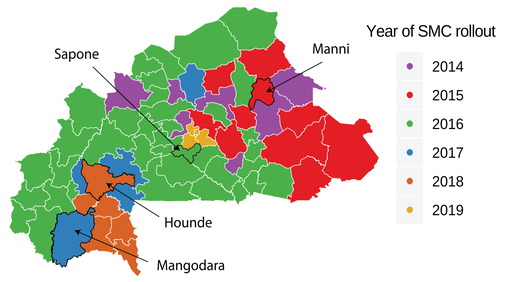

Fig 1. Map of the 70 health districts in Burkina Faso. Districts selected for figure 4 outlined in black. Health districts are colored by the year in which SMC was first introduced.

Despite malaria control efforts, raw incidence is increasing

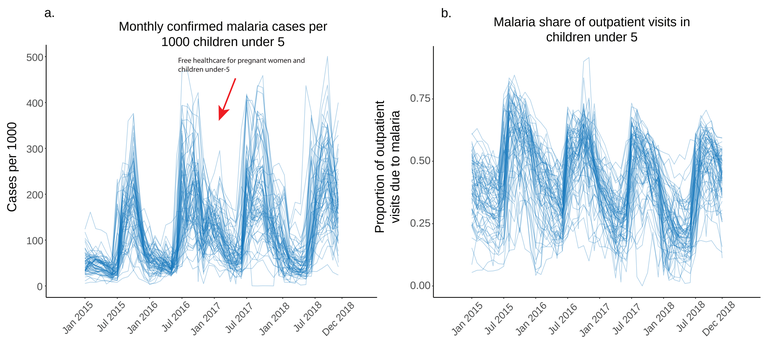

Fig 2. a) Timeseries of raw incidence, the confirmed cases per 1000 children under 5 years old from the 70 health districts in Burkina Faso. Cases are confirmed in health facilities by either RDT or microscopy. b) Malaria share of outpatient visits, the proportion of outpatient visits due to malaria among children under 5 years old in health facilities from the 70 health districts in Burkina Faso. Raw incidence is trending upward when looking at all districts but as a proportion of all-cause outpatient visits, malaria cases are trending downward.

Many factors could contribute to an increase in crude incidence. Treatment seeking increased in the under-5 population due to changes in healthcare policy in mid-2016. In addition, more health facilities were enrolled in the data collection efforts of HMIS. These two factors would increase the magnitude of reported crude incidence per health facility. It is also possible that there is an actual increase in incidence due to the waning effect of other vector control or preventative interventions. However, we do expect to see a decrease malaria incidence among children targeted by the SMC program.

To account for increases in treatment seeking and an expansion of the HMIS data collection system, we examine malaria share of outpatient visits, which shows an overall decline between 2015 and 2018.

Crude incidence was defined as the number of confirmed malaria cases per 1000 children under 5 years old in the district. The malaria share of outpatient visits was calculated in each health district for each month by dividing the number of confirmed malaria cases by the number of outpatient visits. This is a measure of the rate of visits to health facilities in a district due to malaria. Because of the criterion imposed for each observation coming from a health facility, the malaria share of outpatient visits is a true proportion bound between 0 and 1, representing the proportion of outpatient visits due to confirmed malaria cases.

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Northwestern

Seasonal trend decomposition validates our proposed reponse variable

We use seasonal trend decomposition (STL) to analyze the behavior of 4 representative districts. These districts belong to the different SMC rollout groups which initially began receiving the intervention within our time-period. Both malaria indicators analyzed have been standardized for direct visual comparison.

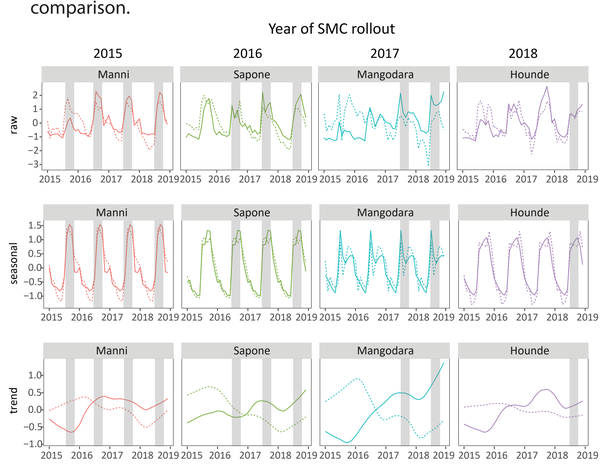

Fig 3. Comparison of seasonal trend decomposition outputs for raw incidence (solid line) and malaria share of outpatient visits (dashed line) variables for 4 districts with different SMC timings. Both variables have been standardized for comparison. SMC rounds are marked by vertical ribbons in grey. The timeseries of confirmed malaria cases trends upwards for all districts however shows a downward trend when analyzing the variable corresponding to the proportion of malaria cases in outpatient facilities.

The pattern observed in the trend component of both variables indicates that while crude incidence at health facilities is rising in all 4 districts, the malaria share of outpatient visits is declining.

Additionally, seasonal components from both variables follow the same pattern. Meaning that in Burkina Faso the seasonality of the malaria share is dominated by the seasonality in malaria rather than other diseases contributing to the number of all-cause outpatient visits.

We visualize the heterogeneity across Burkina Faso by plotting the average trend component for the malaria share of outpatient visits for the 4 months of SMC coverage for each year (Figure 4).

We see large differences between the trend components of the malaria share of outpatient visits for the different districts belonging to each SMC rollout group. The differences between district characteristics and climate variables are a potential driver of the heterogeneity we see here.

Diff-in-diff generalized linear mixed model for SMC efficacy

For each year of SMC rollout, the model compares the districts that received SMC for the first time against those districts that had not received SMC.

Generalized linear mixed models (GLMMs) were used to quantify the effect of SMC on the malaria share of outpatient visits via incidence reduction ratios (IRRs). Modeled malaria share of outpatient visits, describing the rate of visits to health facilities due to malaria, using a log-linear model with a Poisson distribution.

Our analysis for SMC efficacy omits districts that were in the 2014 and 2015 SMC rollout groups as we have no observations from a pre-intervention time-period for these sites. Since each round of SMC is expected to protect against clinical malaria for 28 days, we restrict the analysis to the 4 months during which SMC is administered each year.

Results in 51 districts with each containing 16 observations from 2015 to 2018.

$$\ln[E(Y_{t,s,g})] = \beta_{0,s} + \beta_{1,t^*} + \beta_{2,g} + \beta_{3,s} \ln(1 + X_{t\text{-}1,s}) + \beta_{4,s} \ln(1 + X_{t\text{-}2,s}) + \delta_g \, DiD_{t,g}$$

$Y_{t,s,g}$ is the the malaria share of outpatient visits for date t, district s, and initial SMC rollout group g

β_{1,t^*} represents a year fixed effect for each year t^* to which t belongs

$\beta_{1,g}$ is a group fixed effect, representing each different SMC rollout group g from 2016 to 2018

$X_{t\text{-}1,s}$ and $X_{t\text{-}2,s}$ represent the precipitation of the previous month and 2 months prior to date t

$DiD_{t,g}$ is an indicator variable denoting the dates t of SMC intervention for districts in group g, with the variable equal to 0 before the initial date t of SMC rollout and 1 after

To account for variability accross districts, random effects are introduced to the model through the intercept coefficient ($\beta_{0,s}$) and both lagged precipitation terms, ($\beta_{3,g}$ and $\beta_{4,g}$), and are assumed to be multivariate normal with mean 0. The random effects of the lagged precipitation terms have a compound symmetric variance-covariance structure and are independent of the intercept random effect.

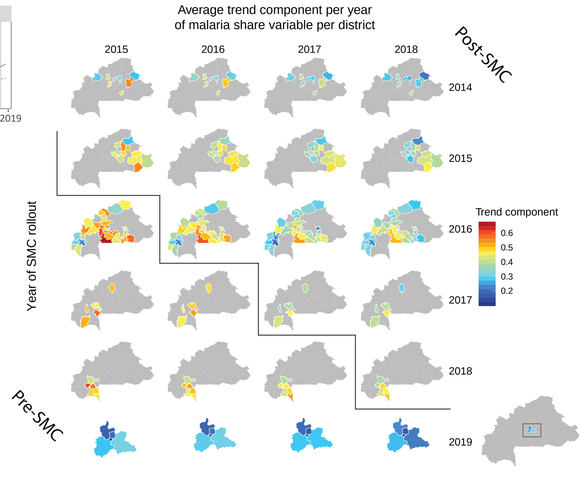

Fig 4. Mapping average trend component for the 4 SMC months per year for each district in Burkina Faso. Each row represents a different rollout group based on the year of SMC introduction. The black dividing line represents when each subgroup gets SMC introduced. The reduction in the malaria share of outpatient visits is evident as we move across each row. The spatial heterogeneity in the trend component points to district level factors influencing the decline in our malaria indicator.

Heterogeneity in districts may also be driven by differences in SMC coverage and the effectiveness of other interventions, such as long-lasting insecticide treated bed-nets (LLINs). The quality of the HMIS data collection efforts and routine case data is also different per district and can affect the trend seen above.

Protective efficacy of SMC from DiD model

The protective efficacy is derived from the model estimate of the IRR and is calculated by (1-IRR)*100%.

In 2016 and 2017, we see about a 13—15% reduction in the proportion of outpatient visits to health facilities due to malaria from children under 5 years old during the peak transmission season in the SMC treated districts relative to the untreated districts attributable to the introduction of SMC.

	Estimate	95% CI
PE_{2016} (treated = 35, untreated = 16)	13.1%	[7.9%, 18.1%]
PE_{2017} (treated = 5, untreated = 11)	15.3%	[9.3%, 20.9%]
PE_{2018} (treated = 6, untreated = 5)	4.8%	[-2.9%, 11.9%]

This is a low PE compared to clinical trials, which found roughly 75% reduction. However, our results are comparable to those of the programmatic PE from a local survey study in Kita, Mali, which found a 15% reduction in incidence (Diawara et al. Malar J., 2017, 16:325).

Future directions

Explore spatial correlation structure with conditional auto-regressive (CAR) model to pool information across neighboring districts.

Find what additional seasonal and economic factors affect the differences in observed SMC efficacy between districts and what drives the drop-off between clinical and programmatic efficacy.