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Evaluating ASAQ Deployment with Seasonal Malaria Chemo-prevention: A Simulation Study of Resistance and Treatment Outcomes

Sarit Adhikari[1], Kien Trung Tran[1], A. Fabrice Some[2], Issiaka Soulama[3], Noufou Gansore[4], Carter Farinha[1], Aristide Nacoulma[3], Robert Zupko[5], Tran Dang Nguyen[1], Sidzabda Christian Bernard Kompaore[3], Farouk Omar Sana[6], Frederic Nikiema[7], Maciej F. Boni[1]

[1]Temple University, Philadelphia, PA, United States, [2]IRSS-DRO, Hauts-Bassins, Burkina Faso, [3]Ouagadougou, Burkina Faso, [4]SP-PALU, Ouagadougou, Burkina Faso, [5]State College, PA, United States, [6]Clinton Health Access Initiative (CHAI), [7]Houet, Burkina Faso

Abstract

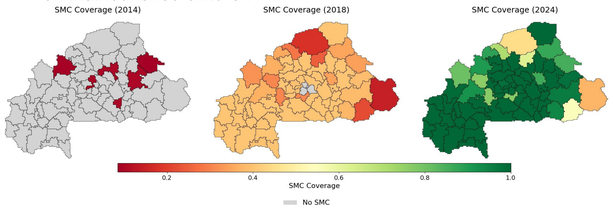
Seasonal Malaria Chemoprevention (SMC) is a highly effective preventive measure where the children at risk (3-59 months) are given antimalarials at monthly intervals during the high transmission season. We model and integrate the SMC process in an individual-based simulation model of malaria transmission to study the combined impact of routine treatment and SMC on malaria-endemic countries like Burkina Faso. We use the WHO-recommended treatment regimen of 1 day of Sulfadoxine-Pyrimethamine and 3 days of Amodiaquine (SPAQ), along with coverage data provided by the national malaria control program of Burkina Faso. We aim to study the potential risk of deployment of artesunate-amodiaquine (ASAQ), currently the highest efficacy ACT in many African countries, along with SMC using SPAQ. We first calibrate the model so that the simulated efficacy aligns with observed SMC effectiveness in field studies. We then evaluate a range of intervention strategies over a ten-year period, both with and without SMC, to assess their relative impact. Switching to ASAQ under SMC is predicted to increase the final *76T* frequency from **21.6%** to **70.1%** compared to the status quo with SMC, while reducing monthly average treatment failures by **32.2%** over the 10-year forecast period (2026–2035). The cycling and MFT strategies that incorporate ASAQ reduce treatment failures by **40.6%** and **39.7%** respectively, when SMC is in place.

Seasonal Malaria Chemoprevention (SMC)

- Preventive administration of full treatment doses of antimalarials at monthly intervals during high transmission season
- Majority of annual cases occur within 4–5 months
- Target population: children 3–59 months in areas with highly seasonal malaria
- Children under five carry the highest burden of morbidity and mortality
- WHO-recommended regimen: Sulfadoxine-Pyrimethamine + Amodiaquine (SPAQ)
- 1 day SPAQ + 2 more days of Amodiaquine
- Different biochemical targets, SP has longer half-life and Amodiaquine ensure that infections are cleared rapidly [3].
- alternative : DHAPPQ, AP, ASAQ
- Without SMC interventions, children slowly develop anti-malarial antibodies, naturally becoming semi-immune
- Directly observed first dose; caregivers administer remaining doses

SMC in Burkina Faso

- Started in 2014 , expanded to most of the districts in 2016
- Has been effective in reducing both uncomplicated and severe malaria burden
- A total of 4101 adverse drug reactions (about 0.1% of children reached) were reported in 2023
- integrated malnutrition screening to prevent administration of SPAQ on malnourished children



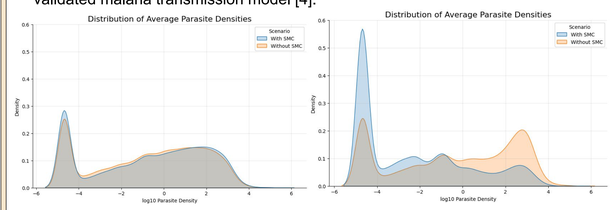
SMC coverage in Burkina Faso in 2014, 2018, and 2024. Data on 2024 SMC coverage and the year of SMC introduction in each health district were provided by the National Malaria Control Program of Burkina Faso. Coverage in preceding years was estimated by applying a 10% reduction for each year before 2024.

- **Goal** : study the potential risk of deployment of artesunate-amodiaquine (ASAQ), highest efficacy ACT in Burkina Faso and many other African countries along with SMC using SPAQ
  - Use of Amodiaquine in both prevention and treatment might accelerate amodiaquine resistance in pf parasites

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Diagnostics and Calibration

Diagnostic tests are conducted to ensure that the SMC module replicates real-world prophylactic effects and integrates seamlessly with the previously validated malaria transmission model [4].

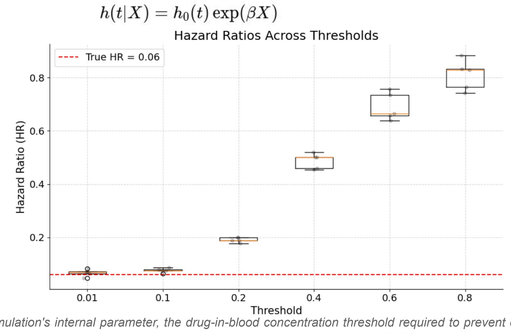


Before SMC

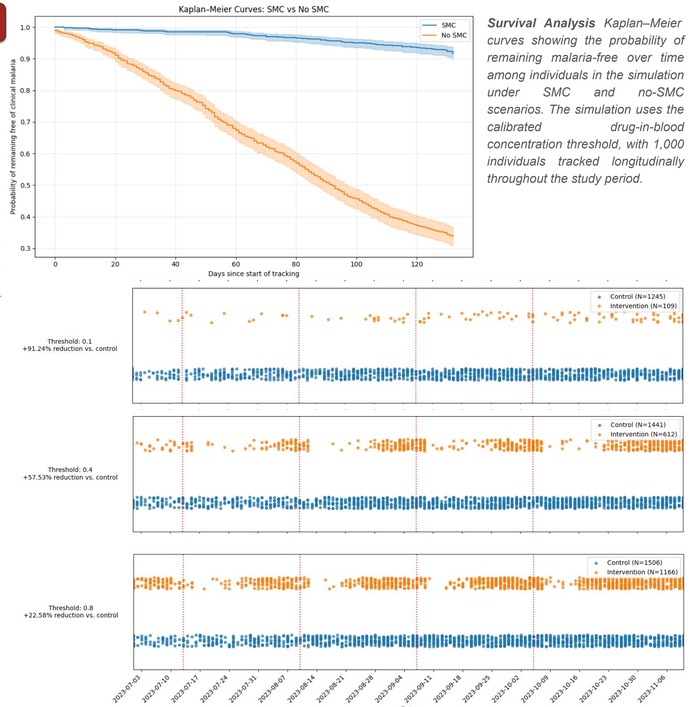
During SMC

Calibration : Cox's proportional Hazards Model

$$h(t|X) = h_0(t)\exp(\beta X)$$



The simulation's internal parameter, the drug-in-blood concentration threshold required to prevent clinical malaria, is calibrated to reproduce the protective effectiveness of SMC reported in a recent cluster-randomized controlled trial in Uganda [5]. Individuals are tracked longitudinally in the simulation, following an approach analogous to that used in the real-world study. A Cox proportional hazards model is used to estimate the hazard ratio for clinical malaria by comparing the SMC and no-SMC simulation scenarios across a range of drug concentration thresholds. The threshold that produces a hazard ratio consistent with the trial-reported estimate is selected for the simulation.



Survival Analysis *Kaplan–Meier curves showing the probability of remaining malaria-free over time among individuals in the simulation under SMC and no-SMC scenarios. The simulation uses the calibrated drug-in-blood concentration threshold, with 1,000 individuals tracked longitudinally throughout the study period.*

Clinical episodes (dots) *over time among a sampled population under SMC intervention and control (no-SMC) scenarios. Each panel represents a different value of the calibration parameter (drug-in-blood concentration threshold). Higher thresholds provide stronger protection initially but are followed by an accumulation of clinical episodes as drug concentrations decline and the prophylactic effect wanes. In contrast, lower thresholds provide protection over a longer period, resulting in a more sustained reduction in clinical episodes.*

Future Works

- Apply the framework to other malaria-endemic countries where the deployment of ASAQ alongside seasonal malaria chemoprevention (SMC) is being considered, accounting for country-specific treatment policies and drug-resistance profiles.
- Investigate the potential benefits of DHA-PPQ for SMC, given its longer-lasting prophylactic effect, while assessing the risk of selecting for piperaquine resistance. This is particularly important in countries where DHA-PPQ is used as a first-line treatment, as increased piperaquine resistance could compromise its therapeutic efficacy.

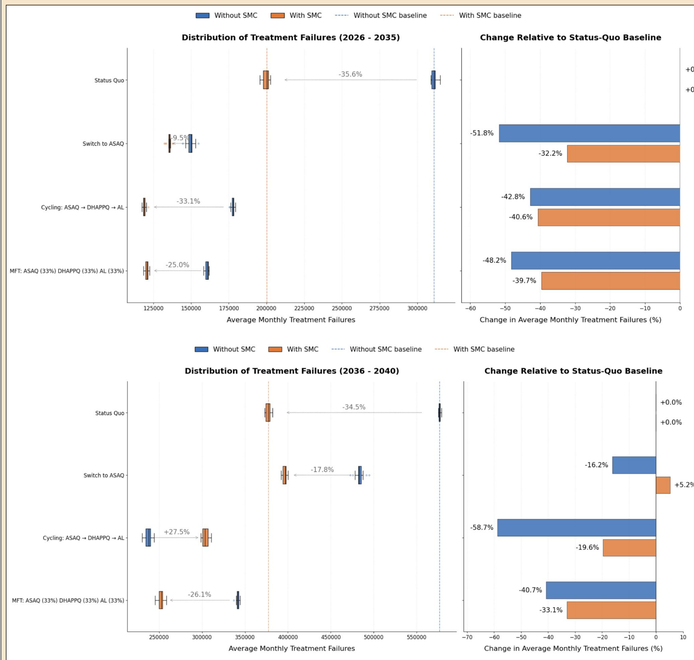
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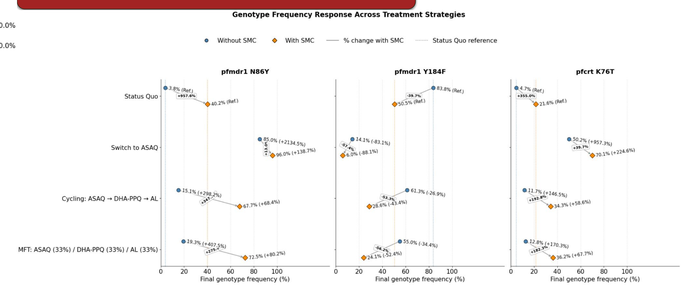
Acknowledgement

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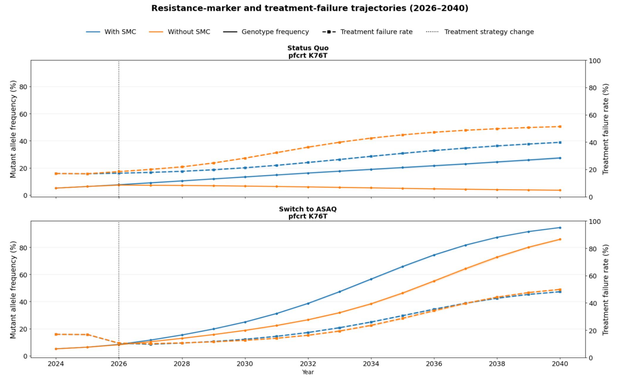
Intervention Studies



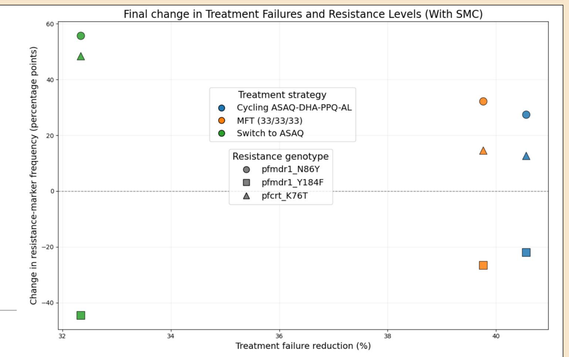
Left panel: *Distribution of average monthly treatment failures across treatment strategies, comparing scenarios with and without SMC. The dotted lines indicate the relative percentage change in treatment failures between the two SMC settings for each strategy.* ***Right panel:*** *Relative percentage change in average monthly treatment failures for each alternative treatment strategy compared with the corresponding Status Quo baseline, evaluated separately under the with-SMC and without-SMC settings. The top figure shows outcomes over the initial 10-year period (2026–2035), during which switching to ASAQ provides a relative benefit over the status quo, even with SPAQ-based SMC. However, extending the evaluation by an additional 5 years (bottom figure) reveals that ASAQ monotherapy as the first-line treatment strategy performs worse than the status quo. This reversal is associated with an increase in the prevalence of the pfcrt 76T mutation. In the absence of SMC, switching to ASAQ continues to outperform the status quo over the extended period.*



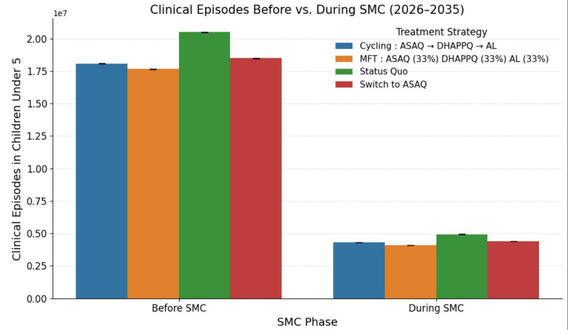
Each panel shows the genotype frequency in 2035 across different treatment strategies and SMC settings. Marker labels indicate the final genotype frequency, with the percentage in parentheses representing the relative change compared with the Status Quo under the same SMC setting. Arrow labels indicate the relative percentage change in genotype frequency with SMC compared with without SMC for each treatment strategy.



Comparison of 76T genotype frequency under SMC and no-SMC scenarios from 2024 to 2040 across status quo and switch to ASAQ treatment strategies. Dotted lines represent trends in treatment failure rates, which is lower under SMC compared with no-SMC for status quo throughout the study period. However, the treatment failure rates under "SMC" and "no SMC" scenarios are very similar for switch to ASAQ treatment strategy.



Comparison between treatment failure reduction and antimalarial resistance-marker frequency change under SMC. The x-axis shows the percentage reduction in treatment failures, and the y-axis shows the change in resistance-marker frequency (percentage points), both relative to the corresponding status quo scenario with SMC. Each point represents a treatment strategy–resistance marker combination.



During the SMC season (June–October), clinical episodes among children under five years of age (the target population eligible for SMC) were substantially reduced across all treatment strategies compared with the period outside the SMC season. This reduction highlights the protective effect of SMC in mitigating the seasonal burden of malaria, regardless of the underlying first-line treatment strategy.