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Seasonal malaria chemoprevention effectiveness in Northern Mozambique: Results from a cluster-randomised controlled trial

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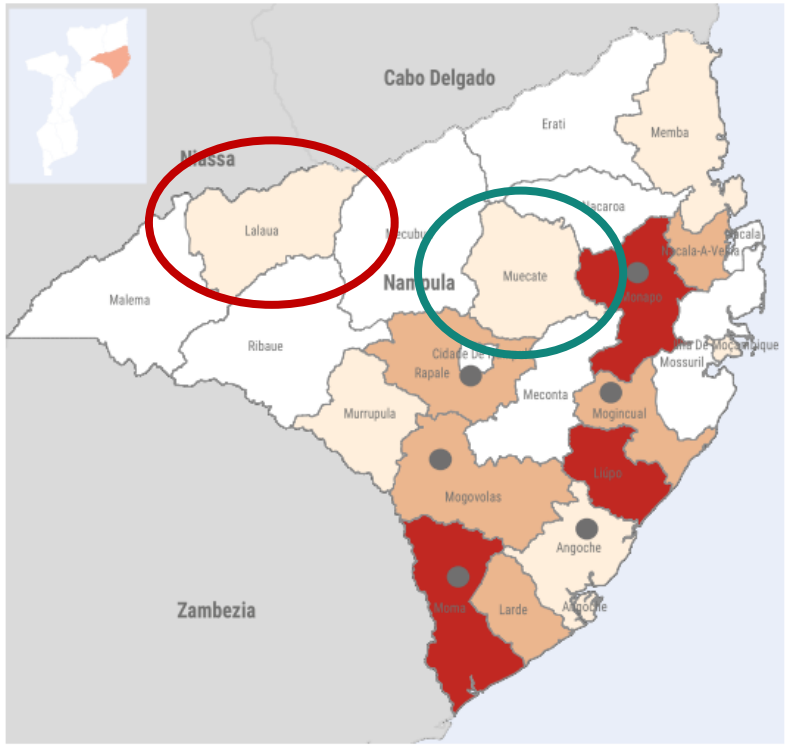
Study site

To assess the effectiveness of seasonal malaria chemoprevention (SMC) with sulfadoxine-pyrimethamine plus amodiaquine (SPAQ) for the prevention of clinical malaria in children aged 3–59 months during the high transmission season, a cluster-randomised controlled trial (cRCT) was carried out. The trial took place in two districts of Nampula province, Mozambique, between January and April 2022.



Eligibility to deploy seasonal malaria chemoprevention

Seasonal malaria transmission:
- 60 percent of malaria cases within four months
- 60 percent of rainfall within a period of four months

Resistance markers profile:
- Existing data on prevalence of molecular markers associated with resistance to S, P and AQ drugs

Potential beneficiaries:
- Children aged 3–59 months

Operational considerations:
- SMC priority in the malaria strategic plan
- Supportive national malaria control programme (NMCP)/ ministry of health (MoH)
- Feasibility of coordinating implementation and drug importation, including security and operational costs.

Methods

Seasonal malaria chemoprevention effectiveness trial design and setting

AIM: To assess the protective effectiveness of SMC with SPAQ in terms of preventing rapid diagnostic test (RDT)-confirmed clinical malaria among children 3–59 months

STUDY DESIGN: Open-label, cluster-randomised controlled (cRCT) trial

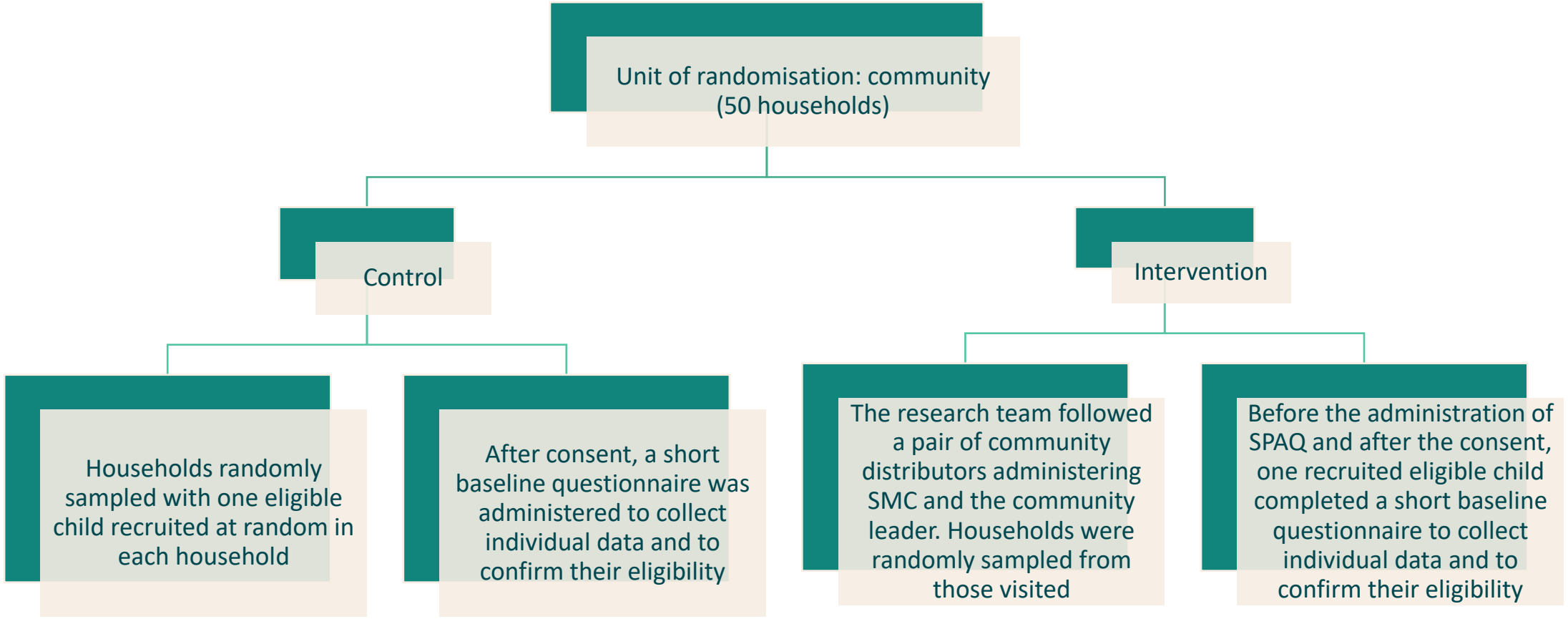
TRIAL SETTING: Most rural community setting with highly seasonal malaria transmission

PRIMARY ENDPOINT: RDT-confirmed clinical malaria cases

SECONDARY ENDPOINT: Caregiver-reported fever episodes

PRIMARY ANALYSIS: Time to RDT-confirmed malaria event (accounting for recurrent episodes) on an intention-to-treat (ITT) basis, accounting for clustering with no assumption of post-infection immunity.

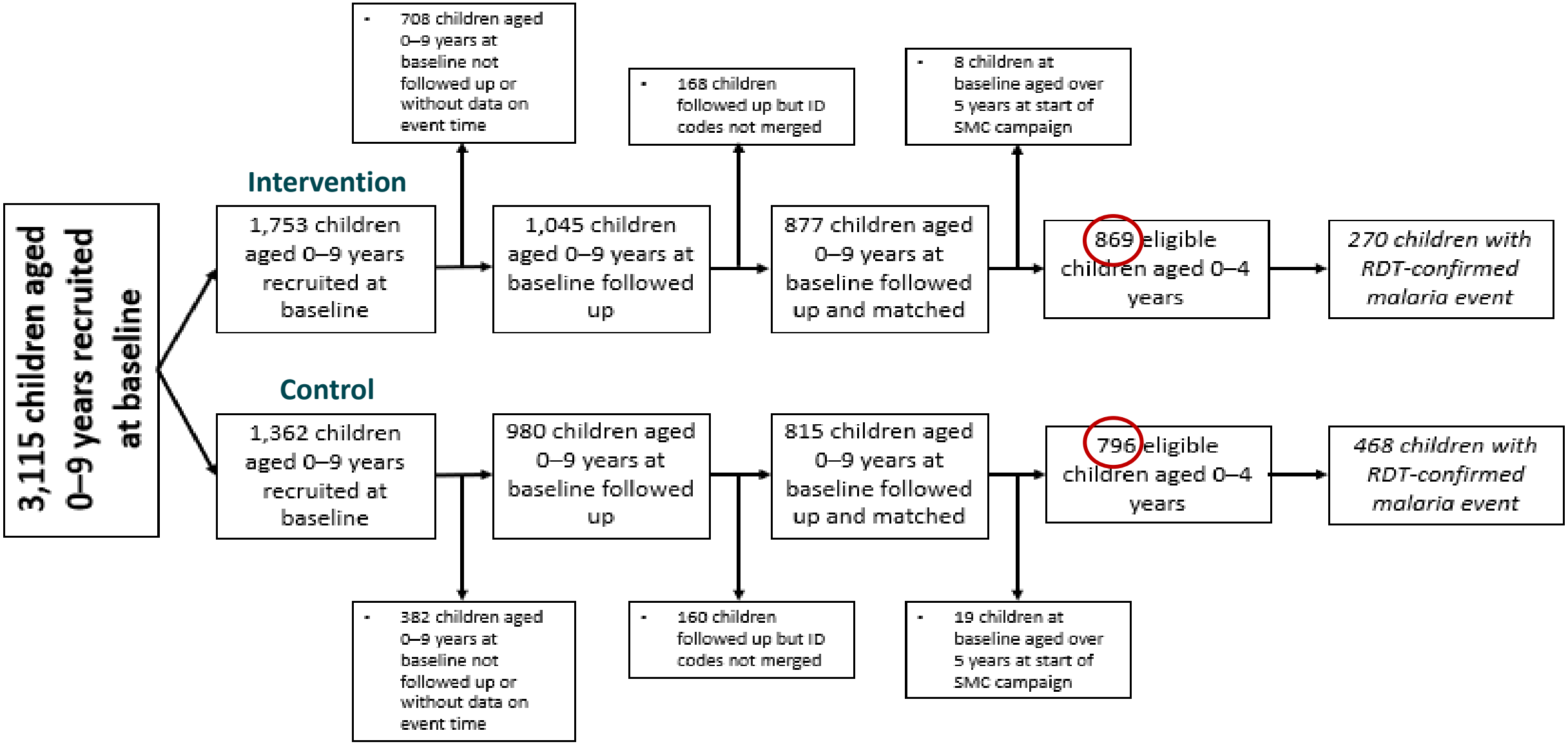
SMC effectiveness trial



After recruitment, in the intervention arm, children presenting at clinics or to community health workers were identified using their SMC record cards; data on suspected malaria cases and results of RDTs were matched to baseline questionnaire data to build a database.

Results

Study population flowchart



Recruitment and follow-up of trial participants

- In total, 3,115 children were recruited through the baseline survey, representing an additional 10 percent above the target. Of those, 1,336 participating eligible children 3–59 months had follow-up for fever outcomes and 1,665 for RDT-confirmed malaria outcomes with 176,480 total child-days of follow-up.
- Sociodemographic characteristics of the children with follow-up were collected during the baseline survey.
- Outcome ascertainment was optimised through passive surveillance.
- Children in the control arm had over twofold greater odds of having an RDT-confirmed malaria fever than children in the intervention arm, odds ratio (OR) 2.19 (95 percent confidence interval [95% CI]: 1.85–2.59, p=<0.001).

	Cases	Controls	Odds ratio	95% CI	
Control	431	197	2.19	1.85	2.59
Intervention	181	531	0.34	0.29	0.4

Test of homogeneity (equal odds): $chi^2(1)=250.89$

$Pr>chi^2=0.0000$

Score test for trend of odds: $chi^2(1)=250.89$

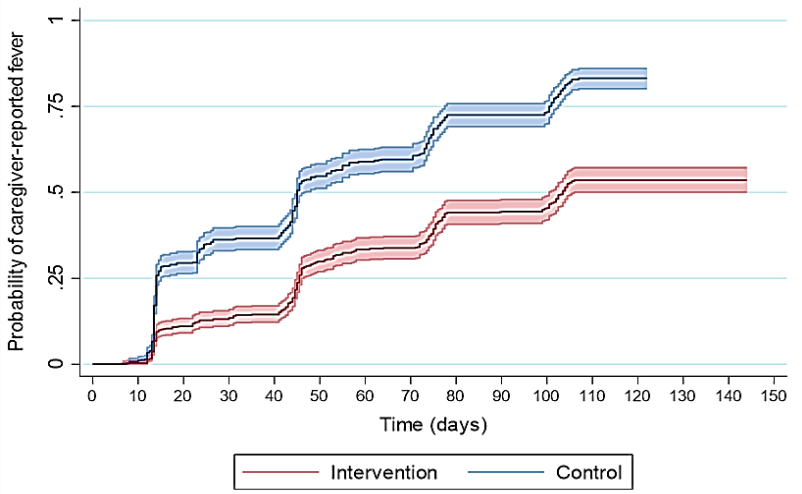
$Pr>chi^2=0.0000$

Advanced statistical analysis

Model 1			Including children in the intervention arm who did not receive a full course of SPAQ in each cycle and children in the control arm who received day 1 SPAQ in any cycle (ITT analysis)			
Outcome	**Model description**	**Covariate adjustment**	**Analytic sample (n)**	**HR**	**95% CI**	***p***
Fever	Time to first incidence of caregiver-reported fever	A: Unadjusted	1,654	0.43	0.38–0.49	<0.001
		B: child age and sex	1,654	0.43	0.38–0.49	<0.001
		C: B, net use and IRS	1,145	0.38	0.32–0.44	<0.001

- In total, 1,145 children were included after accounting for child age, sex and prevention methods used, such as mosquito nets and indoor residual spraying; the hazard ratio (HR) was 0.38 (95% CI: 0.32–0.44), indicating that hazards of fever were reduced by 62 percent in children in the intervention arm compared with those in the control arm.
- All results were statistically significant (p=<0.001) for the difference in risk of fever between arms.

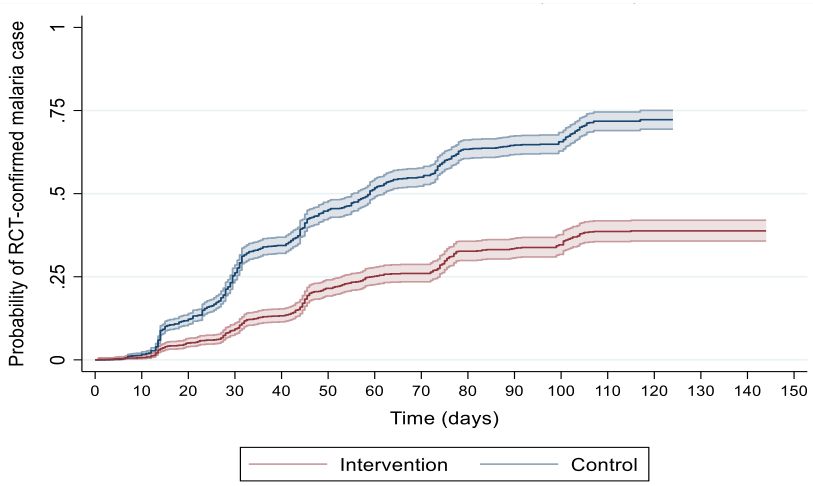
Figure 1: Kaplan-Meier plot of probabilities of caregiver-reported fever across the two study arms



Model 2			Including children in the intervention arm who did not receive a full course of SPAQ in each cycle and children in the control arm who received day 1 SPAQ in any cycle (ITT analysis)			
Outcome	**Model description**	**Covariate adjustment**	**Analytic sample (n)**	**HR**	**95% CI**	***p***
RDT-confirmed malaria case	Random-effects model for time to recurrent incidence of RDT-confirmed malaria cases (caregiver report and logbook record) assuming susceptibility to reinfection immediately after previous case	A: Unadjusted	1,665	0.31	0.26–0.37	<0.001
		B: child age and sex	1,665	0.31	0.26–0.37	<0.001
		C: B, net use and IRS	1,153	0.27	0.21–0.33	<0.001

- In total, 1,145 children were included after accounting for child age, sex and prevention methods used, such as mosquito nets and indoor residual spraying; the hazard ratio (HR) was 0.38 (95% CI: 0.32–0.44), indicating that hazards of fever were reduced by 62 percent in children in the intervention arm compared with those in the control arm.
- All results were statistically significant (p=<0.001) for the difference in risk of fever between arms.

Figure 2: Kaplan-Meier plot of probabilities of RDT-confirmed clinical malaria across the two study arms



Discussion

1. Model 1 provides an estimate of the incidence of fever, which is a common symptom of malaria and is easily reported by caregivers. However, although fever is a more sensitive measure of malaria outcome, it is less specific, as fever can be a symptom of other illnesses and the information is prone to recall bias of the caregivers.

2. Model 2 introduces a random-effect model that allows a more realistic estimation of the effects of the intervention on the risk of malaria accounting for the possibility of recurrent malaria cases. **This outcome can be interpreted as the headline effectiveness result for Mozambique since it shows the effect SMC had in the study area and in real-life conditions (ITT analysis)**. No assumptions were made about reinfection susceptibility, considering the child is immediately susceptible after a previous case.

Strengths

Randomised controlled trial design: This is the first time an SMC randomised controlled trial (RCT) was implemented in Mozambique. This type of study design has significant strengths since it allows for a high level of control over variables through randomisation and can provide strong evidence of causality.

Large sample size: The trial included a large number of participants, which increased the statistical power and the reliability of the results.

Community engagement: The engagement of communities was a key strength of the trial. By recruiting community leaders and community members as SMC community distributors, we were able to effectively implement SMC at the community level, facilitating not only the delivery of the intervention but also increasing awareness and fostering a sense of ownership among caregivers, enhancing the intervention's success.

Limitations

Generalisability: The trial was conducted in a specific setting in Mozambique. Coverage and quality of delivery may vary in different settings, with different underlying malaria transmission and resistance profiles, health systems, or socio-cultural conditions. These are the reasons the results may not be generalised to other settings.

Loss to follow-up: This study showed 19.7 percent attrition, with notable differences in some caregiver demographic characteristics such as literacy and occupation between children followed up and those lost to follow-up.

Imbalance of variables: An initial imbalance was observed in the age and mosquito net usage of children participating in the study. However, these variables were accounted for in the model and did not impact the effect size substantially.

Dependence on caregiver reports: The trial relied on caregiver reports for fever outcomes, which could be subject to recall or reporting bias.

Conclusions

After adjusting for relevant variables on an ITT basis, SMC with SPAQ effectively prevented clinical malaria in eligible children during the peak transmission season in northern Mozambique. These findings align with a previous non-randomised controlled study conducted in the same area and are consistent with trials in other Sahelian countries.

The extensive use of SPAQ poses a risk for drug resistance, potentially impacting the long-term success of this intervention. To predict its effectiveness in the longer term, it is crucial to consider data from resistance markers and chemoprevention efficacy studies that were conducted in parallel with the cRCT.

Additional research is needed to more comprehensively understand how climatic and environmental factors, such as seasonality, transmission intensity, prevalence of resistance markers and chemoprevention efficacy, may influence the effectiveness of SMC using SPAQ in different geographical settings.

Acknowledgements

We extend our heartfelt gratitude to the communities of Lalaua and Muecate, as well as the respected district authorities, for allowing this project to take place and for greatly contributing to its successful implementation and evaluation. Our deep sense of gratitude also encompasses the dedicated field workers, the clinical officers, field supervisors and data managers who committed their expertise to this study. Lastly, we are immensely thankful to the National Malaria Control Programme and the Ministry of Health, Mozambique, for their support and invaluable guidance.

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