A cluster randomised controlled non-inferiority trial to assess the protective effectiveness of sulfadoxine-pyrimethamine plus amodiaquine and dihydroartemisinin piperaquine for seasonal malaria chemoprevention among children 3–59 months, in the context of high parasite resistance, Karamoja region, Uganda

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Background

- Seasonal malaria chemoprevention (SMC) is the intermittent administration of antimalarial medicine to children at high risk of severe malaria living in areas with seasonal transmission.
- SMC involves administering monthly courses of sulfadoxine-pyrimethamine plus amodiaquine (SPAQ) during high transmission periods.
- In 2012, the World Health Organization (WHO) recommended SMC as a safe and cost-effective strategy to complement other control measures, including vector control, prompt diagnosis and treatment of confirmed cases.
- Until 2022, SMC had only been adopted and scaled up in Sahelian countries of West and Central Africa, primarily due to concerns over widespread resistance to SP in East and southern Africa.
- Updated guidelines, published by the WHO in 2022, do not include geographic restrictions on the use of SMC, indicating that SMC might be an appropriate intervention to prevent and treat malaria in other contexts.

Background

- Malaria is public health problem in Uganda that affects almost 100 percent of the population.
- The Karamoja region, where malaria transmission is seasonal, consistently reports the highest prevalence rates.
- The Uganda Malaria Reduction and Elimination Strategic Plan 2021–2025 recommends SMC to accelerate progress towards malaria elimination.
- Modelling conducted by the Swiss Tropical and Public Health Institute suggests SMC would be effective in preventing malaria in the Karamoja region.

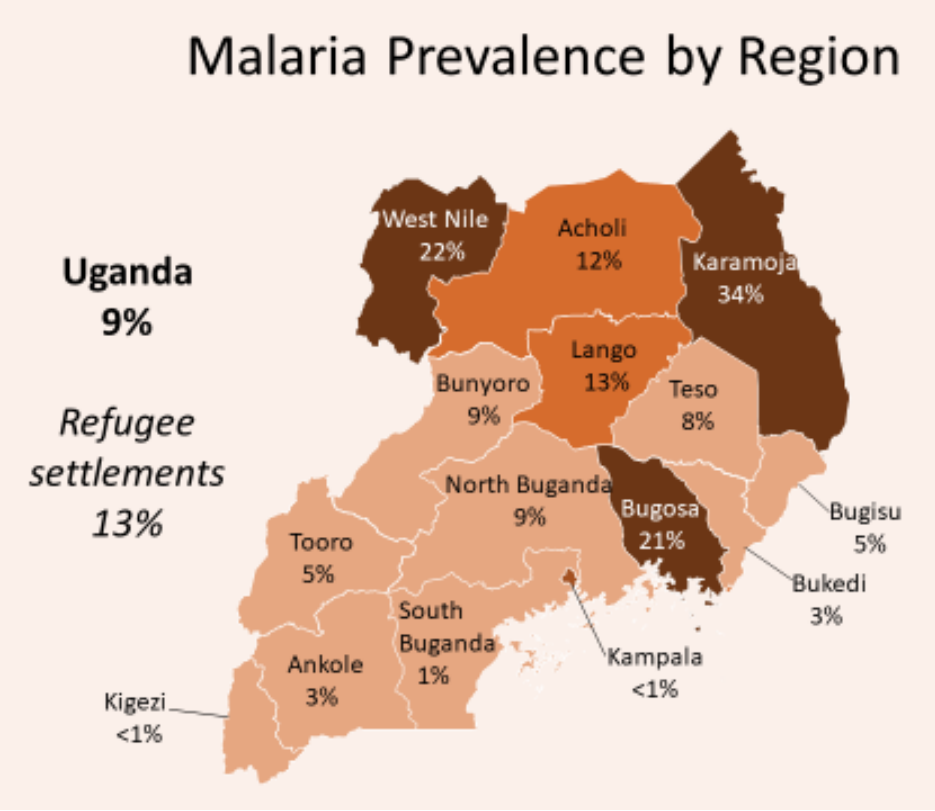

Figure 1: Percentage of children 0–59 months who tested positive for malaria by microscopy

Background

- A non-randomised study conducted in 2021 suggested SMC with SPAQ was feasible, acceptable and an effective malaria control strategy in the Karamoja region.
- There was a need to explore alternative drug regimens due to concerns about widespread resistance to SP. Dihydroartemisinin-piperaquine (DP) is a potential alternative for use in SMC.
- This cluster-randomised controlled trial (cRCT) was conducted with the aim of generating further evidence regarding the effectiveness of SMC to inform policy decisions.
- The target population consisted of 270,000 children 3–59 months, with the majority receiving SPAQ and approximately 15,000 receiving DP.
- Five SMC cycles were implemented between May and September 2022.
- Village health teams (VHTs) distributed SMC medicines through a house-to-house approach and were supervised by health facility-based health workers.

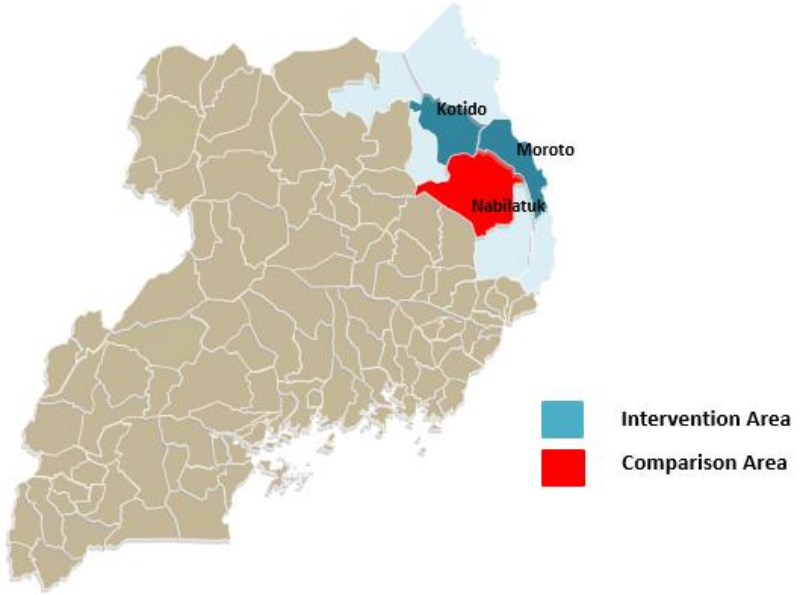

Figure 2: Map of Uganda showing Karamoja region

Background

Overall study objective

- To determine the effectiveness of SMC with DP and SPAQ in reducing the incidence of malaria among children under five.

Ethical clearance

- Ethical approval was granted by Mbale Regional Referral Hospital (reference number: MRRH-2022-168).

- The study was registered by the Uganda National Council of Science and Technology (reference number: HS2212ES).

- The trial was registered on clinical trials.gov (reference number: NCT05323721).

Methods

- This three-arm, open-label, non-inferiority and superiority cluster-randomised controlled trial (cRCT) assessed the effectiveness of SPAQ in children 3–59 months and DP in children 6–59 months, respectively.
- A three-stage random sampling strategy was applied:
  - Villages were randomly allocated to arm one (SPAQ), arm two (DP), or arm three (control).
  - Ten households in each village were randomly selected.
  - One eligible child per household was randomly selected to take part in the study.
- An electronic questionnaire using SurveyCTO version 2.71 was used to collect data.
- Data were analysed using Stata version 16.

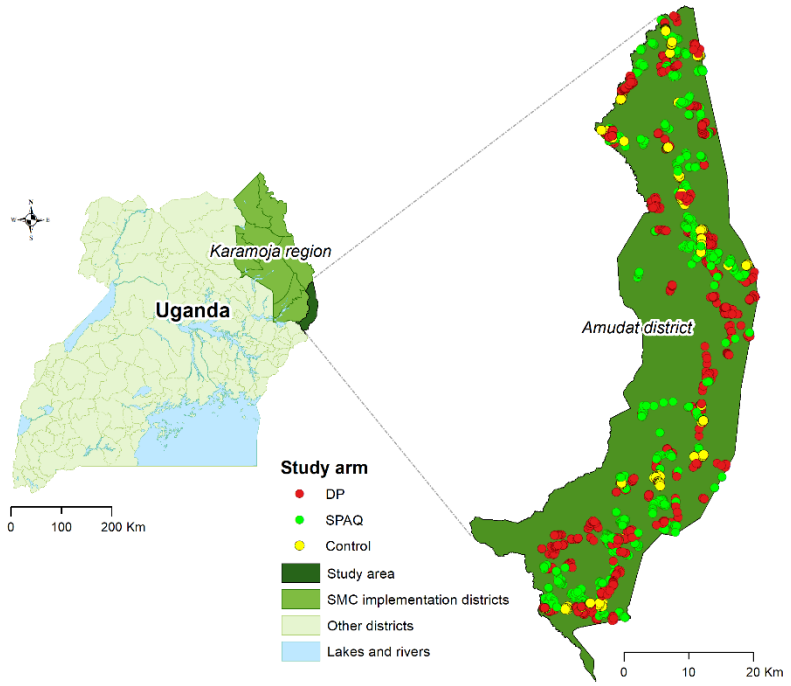

Figure 3: SMC implementation and study areas

Outcome measures

- The primary outcome of this study was the incidence of malaria confirmed by a rapid diagnostic test (RDT) in SMC-eligible children.
- Malaria cases were ascertained through optimised passive surveillance in the three arms.
- The secondary outcome was the occurrence of caregiver-reported fever.
- All children were monitored to determine whether they exhibited a fever since the previous SMC cycle.

Participant follow-up

- Caregivers were asked to respond to a questionnaire at the time of enrolment.
- Research assistants and VHTs conducted monthly visits for five months from May to September 2022.
- Caregivers were encouraged to take children to the VHTs or nearest health facility whenever a child was unwell.
- All health facilities and VHTs were provided with lists of children enrolled in the study for easy identification.
- Children presenting with a history of fever were tested using a RDT for malaria.
    - If positive, children were treated according to national guidelines or referred to the nearest health facility.

Statistical analysis

- Descriptive statistics were used to summarise participants' characteristics across study arms.
- Kaplan-Meier survival plots were used to illustrate the probabilities of occurrence of primary and secondary outcomes over time and across study arms.
- Cox proportional hazard regression models were used to quantify the protective effectiveness of SPAQ and DP relative to control in terms of the primary and secondary outcomes.
- The primary analysis was based on 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.
- Sensitivity analyses considered:
    - Time to RDT-confirmed malaria event (accounting for recurrent episodes) on an ITT basis, but assuming a 21-day period of post-infection immunity or possibility of residual RDT positivity following an infection, and
    - Time to first RDT-confirmed malaria event only on an ITT basis.

Results

cRCT participant enrolment, allocation and follow-up flowchart

- Initially, 3,881 children were considered eligible and were cluster-randomised. Arm one (SPAQ) included 1,755 children. Arm two (DP) included 1,736 children. Arm three (control) included 390 children.
- 132 children were lost to follow-up. This included 57 children in arm one (SPAQ), 69 children in arm two (DP) and 6 children in arm three (control). Children lost to follow-up were not seen in any subsequent post-randomisation follow-up visit.
- The remaining 3,749 children were included in the analysis. This included 1,698 in arm one (SPAQ), 1,667 in arm two (DP) and 384 in arm three (control).
- Data from these children were included in the analysis, contributing a total of 554,155 person-days to the analysis. This included 251,414 in arm one (SPAQ), 249,069 in arm two (DP) and 53,672 in arm three (control).

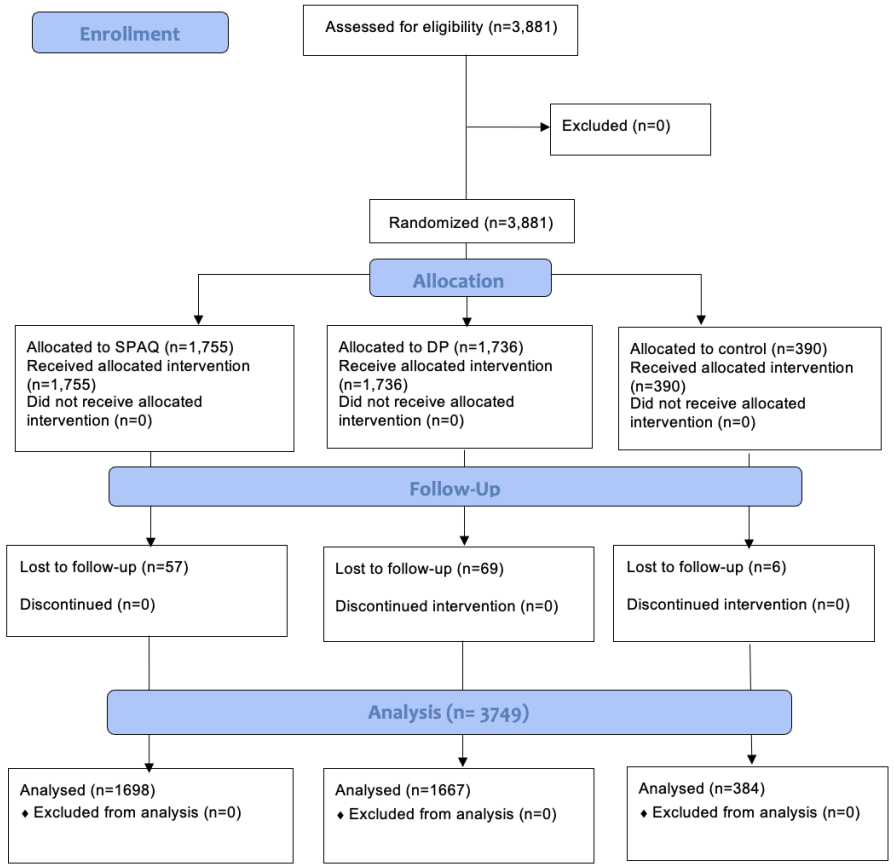

Figure 4: CONSORT flow chart of the trial enrolment, randomisation and follow-up processes

Baseline characteristics of trial participants and variable balancing across study arms

After accounting for attrition, variables were balanced between intervention and control arms among children followed up, except for use of mosquito nets and insecticide spray. These were adjusted for as covariates in the Cox models.

Variable		Category	SPAQ (n=1755)		DP (n=1736)		Control (390)		χ2 test for difference		Total (n=3881)	
			N	%	N	%	n	%	χ^2	p	n	%
Child	**Sex**	Male	852	48.5	835	48.1	184	47.2	0.25	0.881	1871	48.2
		Female	903	51.5	901	51.9	206	52.8			2010	51.8
	Age	< 1 year	247	14.1	230	13.2	42	10.8	28.91	0.315	519	13.4
		1 year	427	24.3	406	23.4	101	25.9			934	24.1
		2 years	398	22.7	429	24.7	96	24.6			923	23.8
		3 years	379	21.6	345	19.9	87	22.3			811	20.9
		4 years	304	17.3	326	18.8	64	16.4			694	17.9
	Net use	Yes	1012	57.7	1107	63.8	244	62.6	14.72	**0.005**	2363	60.9
		No	24	1.4	24	1.4	4	1.0			52	1.3
		Missing	719	41.0	605	34.9	142	36.4			1466	37.8
Caregiver	**Education**	None or informal	1563	89.1	1501	86.5	336	86.2	38.07	0.072	3400	87.6
		Primary	112	6.4	148	8.5	31	7.9			291	7.5
		Secondary or above	70	4.0	77	4.4	22	5.6			169	4.4
		Missing	10	0.6	10	0.6	1	0.3			21	0.5
Household	**Indoor residual spray last 18 months**	Yes	158	9.0	127	7.3	96	24.6	119.1	**<0.001**	381	9.8
		No	1446	82.4	1465	84.4	250	64.1			3161	81.4
		Missing	151	8.6	144	8.3	44	11.3			339	8.7

Table 1: Baseline characteristics of trial participants

Malaria incidence

The incidence rate of malaria was three cases per 10,000 person-days in both SPAQ and DP arms. The incidence rate was 60 per 10,000 person-days in the control arm.

Study arm	Participants in the analysis	Person-days at risk	RDT-confirmed malaria episodes	Incidence rate per 10,000 person-days
All children	3,629	554,155	464	8
Arm one (SPAQ)	1,698	251,414	76	3
Arm two (DP)	1,677	249,069	66	3
Arm three (control)	384	53,672	322	60

Table 2: Incidence of RDT-confirmed malaria cases

Protective effectiveness of SMC with SPAQ and DP relative to control

- Children who received SMC using SPAQ had 94 percent lower risk of having an RDT-confirmed malaria episode. Hazard ratio (HR) 0.06 (95 percent confidence interval [95% CI]: 0.04–0.08, p<0.001).
- Children who received SMC using DP had 96 percent lower risk of having an RDT-confirmed malaria episode. HR 0.04 (95% CI: 0.03–0.06, p<0.001).
- The protective effectiveness of SPAQ was non-inferior to that of DP.

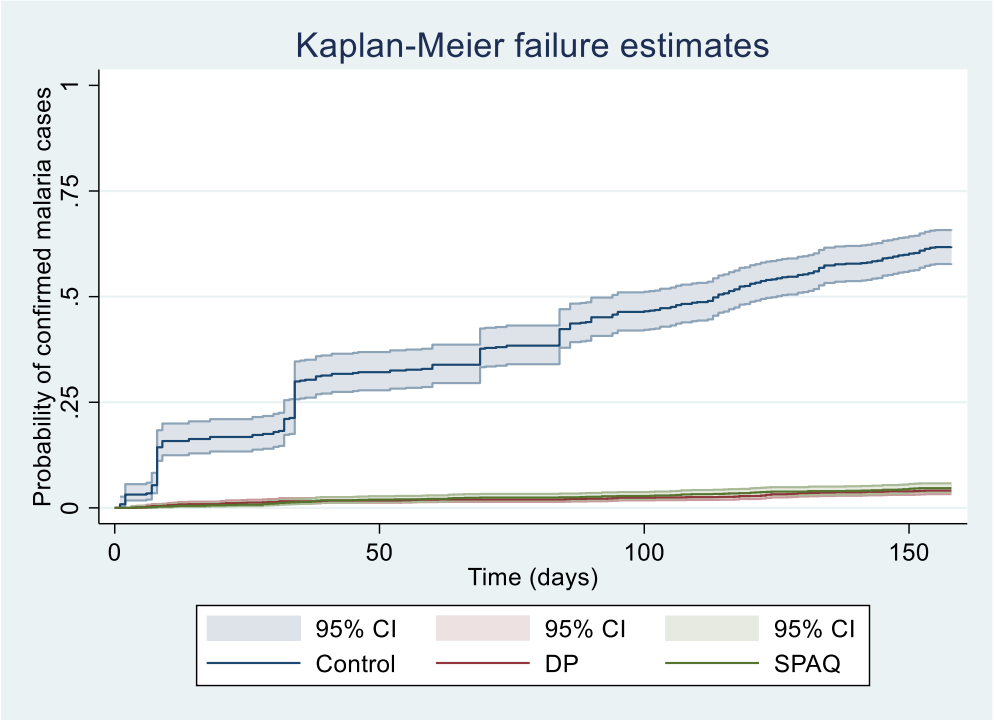

Figure 5: Kaplan-Meier graph showing the probability of RDT-confirmed malaria cases

Probability of fever episodes

Arm one (SPAQ): children had a 79 percent lower risk of having fever episodes.

Arm two (DP): children had an 84 percent lower risk of having fever episodes.

The hazard ratio for the protective effectiveness of SPAQ was non-inferior to that of DP.

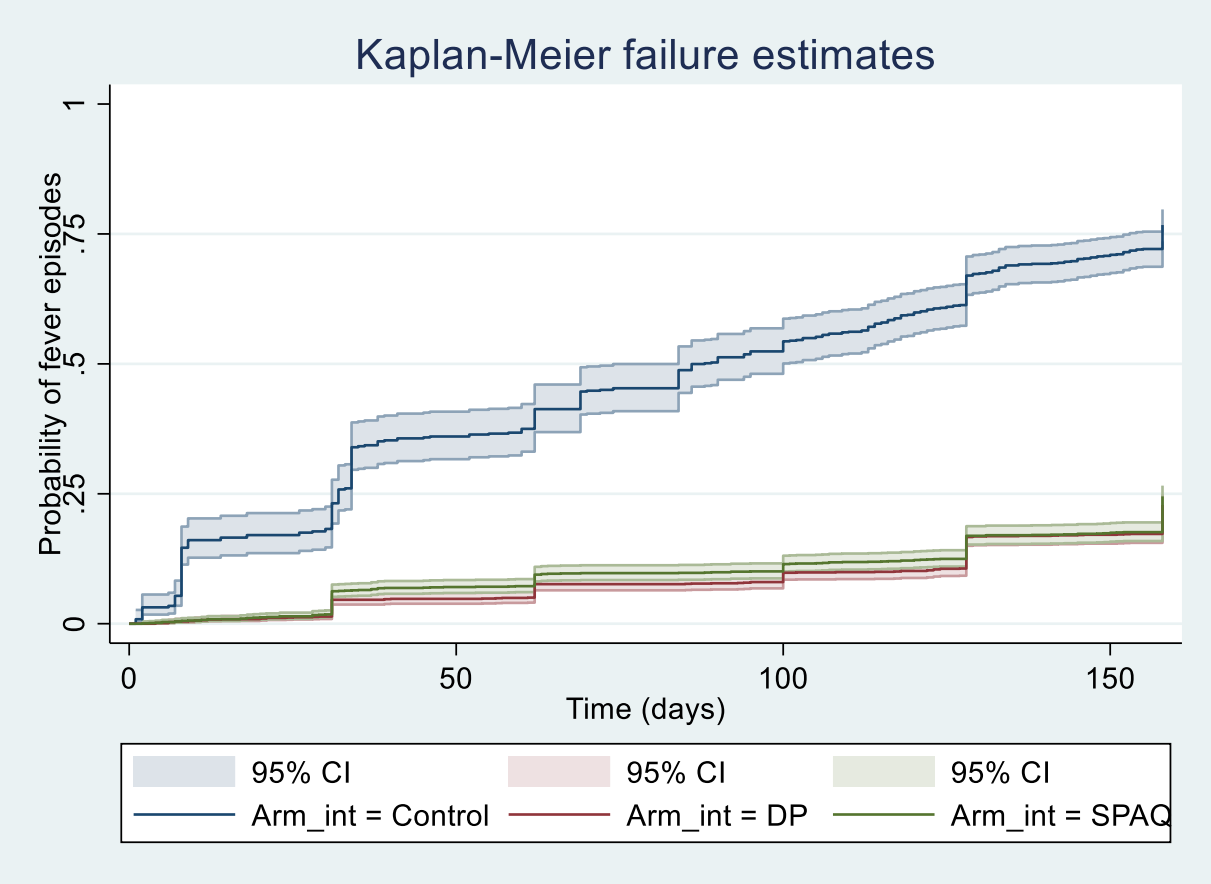

Figure 6: Kaplan-Meier graph showing the probability of fever episodes

Study limitations and mitigation measures

Limitations	Mitigation measures
This study relied on passive surveillance for outcome identification.	Community mobilisation, compensations and incentives.
It was not feasible to make data collectors and health facility workers blind to study arm allocation.	Intensified community engagement.
Respondent bias was present, especially in arm three (control), given that this study was not blinded.	
Language barriers were present with some research assistants unable to speak the local language (Pokot).	Hired local research assistants and field supervisors.
Contamination between study arms may underestimate the true effect of SMC on the observed outcomes.	Intensified community engagement.

Potential biases and action measures applied

Question	Actions/Investigation	Results	Discussion	Further actions
Was there underreporting of malaria fevers in the intervention arms?	Comparison of non-malaria fevers in all arms as a proxy for health-seeking behaviour.	~50% less non-malaria fever in SPAQ and DP arms, compared to control arm in Uganda.	Could bias result away from the null: • Possible reduction in reporting due to unblinded nature and community interest in positive results. • Possible antimicrobial impact of SPAQ/DP on all-cause fevers.	• Review non-malaria fevers in non-randomised study and Mozambique study. • Compare results with self-reported fevers and malaria from M&E results.
Was the sample size in the control arm under powered for the target results?	Conducted a post-hoc power analysis.	Sample size in the control arm was able to provide sufficient statistical power for the superiority component of the trial.	No impact on effect size.	No further action.
Was loss to follow-up unequally distributed across the study arms?	Patient record review to conduct comparison of attrition rates in study arms.	Attrition slightly higher in the control than SPAQ and DP arms.	Would likely bias results towards the null.	No further action.

Potential biases and action measures applied

Question	Actions/Investigation	Results	Discussion	Further actions
Could the uneven distribution of other vector control tools across study arms bias the results?	Review self-reported use of vector control for comparison of ITNs and IRS in study arms.	Mosquito net use (SPAQ: 57.7 percent, DP: 63.8 percent and control: 62.6 percent, p=0.005); Use of insecticide spray (SPAQ: 9.0 percent, DP: 7.3 percent and control: 24.6 percent, p=<0.001)	ITN use is approximately equivalent across arms. IRS use is higher in the control, which could bias results towards the null.	No further action.
Were there external influences impacting the ability to conduct the study?	Review of flooding reports and stock-out reports from study team across the study arms.	Flooding and stock-outs effected the study arms equally.	No impact on effect size.	No further action.
Were there differences in malaria transmission intensity across the study arms?	Review geospatial distribution of study clusters.	Ordinarily, randomisation should have ensured a balance in epidemiological and malaria transmission profile across arms. Clusters were in the same district.	Differences in malaria risk unlikely across arms. No impact on effect size.	Review adult malaria cases in study arms, if possible (may not be possible to disaggregate clusters).
Was loss to follow-up unequally distributed across the study arms?	Patient record review to conduct comparison of attrition rates in study arms.	Attrition slightly higher in the control than SPAQ and DP arms.	Would likely bias results towards the null.	No further action.

Contextualisation of findings

Study detail, year of pub	Study design	Setting	Study population	Comparison	Findings
Nuwa et al 2023	Non-randomised study	Uganda	Children 3–59 months	SPAQ vs control	In total, 90.0 percent (361/400) of children did not experience any malaria episodes during the study period, compared to 15 percent (29/200) in the control area. The incidence rate ratio was 0.078 (95% CI: 0.063–0.096), which corresponds to a protective effectiveness of 92% (95% CI: 90.0–94.0) among children in the intervention area.
Taylor et 2022	RCT	Kenya	Children 1–10 years with sickle cell anaemia	SPAQ vs DP vs proguanil	In total, four percent (3/83) of the participants in the SPAQ arm had clinical malaria over a 12-month follow up period. In total, 12 percent (10/83) had parasitaemia (confirmed by microscopy).
Nankabirwa et al 2014	RCT	Uganda	School children 6–14 years	DP vs placebo	DP reduced the incidence of clinical malaria by 96 percent (95% CI: 88.0–99.0, p<.0001) and the prevalence of asymptomatic parasitaemia by 94 percent (95% CI: 92.0–96.0, p<.0001).
Mutabingwa et al 2009	RCT	Tanzania	Pregnant women	SP vs SPAQ vs AQ+AS vs chlorproguanil -dapsone (CD)	By day 28, parasitological failure rates were 15 percent (4/26 [95% CI: 4.0–35.0]) in the SP, 23 percent (18/77 [23%, 95% CI: 14.0–34.0]) in the CD, one percent (1/73 [95% CI: 0.001-7]) in the SPAQ and nine percent (7/75 [95% CI: 4.0–18.0]) in the AQ+AS arms respectively. After correction by molecular markers for reinfection the parasitological failure rates at day 28 were 18 percent for CD, one percent for SP+AQ and 4.5 percent for AQ+AS.

Contextualisation of findings

Study detail, year of pub	Study design	Setting	Study population	Comparison	Findings
Clarke et al 2008	Cluster-RCT	Kenya	School children >5 years	SPAQ vs placebo	By the end of the 12-month follow-up period, 4.6 percent and 39·7 percent of the children in the SPAQ and control arms had detectable *P. falciparum* infection, respectively. RR 0·12 (0.05–0·27, p<0·0001)
References 37–41 in Nankabirwa JI et al 2022	Multiple studies, including RCTs	East Africa; multi-country	Adult and paediatric populations	SPAQ vs other antimalarial medicines	This paper highlighted evidence from previous studies (references 37–41) conducted in the early 2000s across locations in East Africa, demonstrating good therapeutic efficacy (parasite clearance) of SPAQ vs other anti-malarial medicines.
Results from routine M&E data 2022–2023	Cross-sectional household surveys	Uganda	Children aged 3–59 months	SPAQ	Generally, caregiver-reported malaria cases in the one month following each SMC cycle are recorded in <10% of children.

Conclusions and next steps

- Overall, the study found both SPAQ and DP to be highly effective in preventing clinical malaria in eligible children during the high transmission season.
- DP was not significantly superior to SPAQ in preventing clinically significant malaria in SMC-eligible children.
- While effect sizes (that of the Karamoja trial in particular) are higher than expected given concerns over widespread resistance to SP in many parts of East and Southern Africa, results are consistent with those of previous studies in Uganda and other locations in East Africa.
- A similarly designed study conducted in Mozambique suggested that SPAQ had a protective effect against malaria infection.
- To predict the longer-term protective effectiveness of SMC using SPAQ and DP in the Karamoja region, results from resistance markers and chemoprevention efficacy studies that have been conducted in Uganda and Mozambique need to be taken into account.

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- Malaria Consortium
- Study respondents

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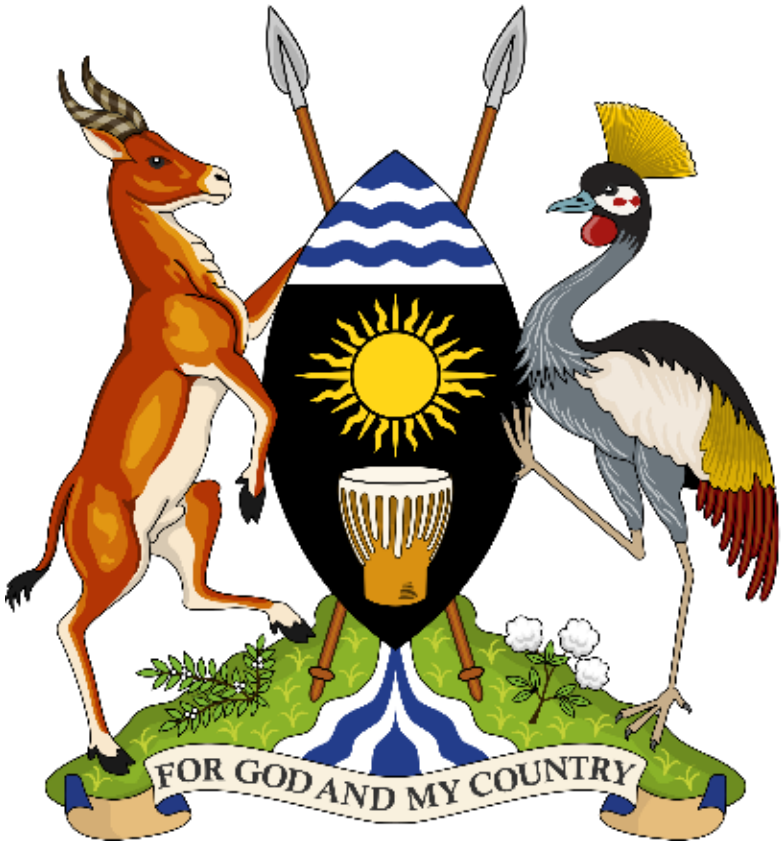

UGANDA NATIONAL MALARIA CONTROL DIVISION

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