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The impact of seasonal malaria chemoprevention on *Plasmodium falciparum* resistance to sulfadoxine-pyrimethamine and amodiaquine in northern Mozambique

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Monitoring resistance markers is essential as Mozambique expands seasonal malaria chemoprevention and introduces new chemoprevention strategies.

Introduction

Seasonal malaria chemoprevention (SMC) is recommended by the World Health Organization for the prevention of malaria in areas of highly seasonal transmission.[1] SMC employs a regimen of sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ), known as SPAQ. However, resistance to SPAQ may compromise its effectiveness against clinical malaria in children. This study examines resistance marker prevalence before and after one annual SMC round in Mozambique, where resistance has been observed, to improve understanding of the impact of resistance on SMC effectiveness. The study is part of a larger implementation study that involved SMC delivery to 72,000 children in Malema and Mecubúri districts of Nampula province, northern Mozambique, as well as Lalaua district, a control area where SMC was not implemented.

Methods

- Cross-sectional surveys were conducted before (November 2020, baseline) and after (February 2021, endline) one round of SMC to measure resistance to SPAQ in symptomatic children 3–59 months with a positive rapid diagnosis test in selected health facilities in intervention and comparison areas.
- Dried blood samples were collected onto filter papers.
- Analysis of resistance markers included: dihydrofolate reductase (dhfr), dihydropteorate synthetase (dhps), *Plasmodium falciparum* chloroquine resistance transporter gene (pfcrt) and multidrug resistance gene 1 (pfmdr1).

Results

- In total, 1198 dried blood samples were sequenced and genotyped (598 at baseline, 600 at endline).
- Baseline prevalence of pfdhps mutations: Over 60 percent for dhps A437G and K540E SNP in both intervention and control areas.
- In the intervention arm, there was a non-statistically significant trend whereby A437G increased from 85.2 percent to 89.9 percent (p=0.1) and K540E increased from 63.7 percent to 68.3 percent (p=0.3) when comparing baseline to endline.
- The majority of samples in the intervention and control areas had mutations in the pfdhfr gene.
- Single-nucleotide polymorphism (SNP) combinations of relevant Pfdhps-dhfr mutants were notable.
- No mutations were found for I164L, Pfcrt, and mdr1_R1 N86Y.

Conclusion

SP resistance was high, whereas AQ resistance was low in the study area. There was no significant change in resistance after one round of SMC, indicating that SMC introduction was not a contributing factor. Continuous monitoring of SP and AQ resistance markers is crucial as Mozambique scales up SMC and introduces other chemoprevention strategies using the same drugs.

Results

Table 1: Resistance to sulfadoxine-pyrimethamine: pfdhps, pfdhfr, polymorphism frequencies in intervention and control at baseline and endline

Gene	SNPs	Intervention			Control		
		Baseline	Endline	p value	Baseline	Endline	p value
		n (%)	n (%)	p	n (%)	n (%)	
pfdhfr	51I	150	167		171	173	
	Mutated	150 (100)	167 (100)	0.340	171 (100)	173 (100)	0.914
	Wildtype	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
	59R	150	167		171	173	
	Mutated	150 (100)	167 (100)	0.340	171 (100)	173 (100)	0.914
	Wildtype	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
pfdhps	108N	150	167		171	173	
	Mutated	150 (100)	167 (100)	0.340	171 (100)	173 (100)	0.914
	Wildtype	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
	431V	243	254		289	256	
	Mutated	3 (1.2)	2 (0.8)	0.618	2 (0.7)	3 (1.2)	0.558
	Wildtype	240 (98.8)	252 (99.2)		287 (99.3)	253 (98.8)	
	437G	243	257		289	254	
	Mutated	207 (85.2)	231 (89.9)	0.111	258 (89.3)	227 (89.4)	0.971
	Wildtype	36 (14.8)	26 (10.1)		31 (10.7)	27 (10.6)	
	540E	240	252		289	257	
	Mutated	153 (63.7)	172 (68.3)	0.292	188 (65.1)	161 (62.6)	0.559
	Wildtype	87 (36.2)	80 (31.7)		101 (34.9)	96 (37.4)	
	581G	243	255		282	261	
	Mutated	4 (1.6)	2 (0.8)	0.378	1 (0.4)	2 (0.8)	0.518
	Wildtype	239 (98.4)	253 (99.2)		281 (99.6)	259 (99.2)	
	613S	243	255		282	261	
	Mutated	4 (1.6)	2 (0.8)	0.378	1 (0.4)	2 (0.8)	0.518
	Wildtype	239 (98.4)	253 (99.2)		281 (99.6)	259 (99.2)	

Table 2: Mutation combination frequencies in intervention and control areas at baseline and endline

Mutation	SNPs	Intervention			Control		
		Baseline	Endline	p value	Baseline	Endline	p value
		n (%)	n (%)		n (%)	n (%)	
pfdhps double	A437G & K540E	236	250		280	252	
	Yes	148 (62.7)	170 (68.0)	0.221	178 (63.6)	154 (61.1)	0.559
	No	88 (37.3)	80 (32.0)		102 (36.4)	98 (38.9)	
pfdhps triple	A437G, K540E & A581G	234	246		275	250	
	Yes	2 (0.9)	2 (0.1)	0.960	1 (0.4)	0 (0.0)	0.340
	No	232 (99.1)	244 (99.2)		274 (99.6)	250 (100)	
pfdhps double	N51IR & S108N	150	167		171	173	
	Yes	150 (100)	167 (100)	0.340	171 (100)	173 (100)	0.914
	No	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Quintuple	A437G, K540E, N51I, C59R & S108N	142	144		159	153	
	Yes	86 (60.6)	90 (62.5)	0.736	106 (66.7)	88 (57.5)	0.096
	No	56 (39.4)	54 (37.5)		53 (33.3)	65 (42.5)	
Sextuple	A437G, K540E, A581G, N51I, C59R & S108N	141	143		156	153	
	Yes	1 (0.7)	1 (0.7)	0.992	0 (0.0)	0 (0.0)	0.865
	No	140 (99.3)	142 (99.3)		156 (100)	153 (100)	

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Reference

1) World Health Organization. WHO policy recommendation: Seasonal malaria chemoprevention (SMC) for *Plasmodium falciparum* malaria control in highly seasonal transmission areas of the Sahel sub-region in Africa. World Health Organization, 2012.