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Infectious Diseases

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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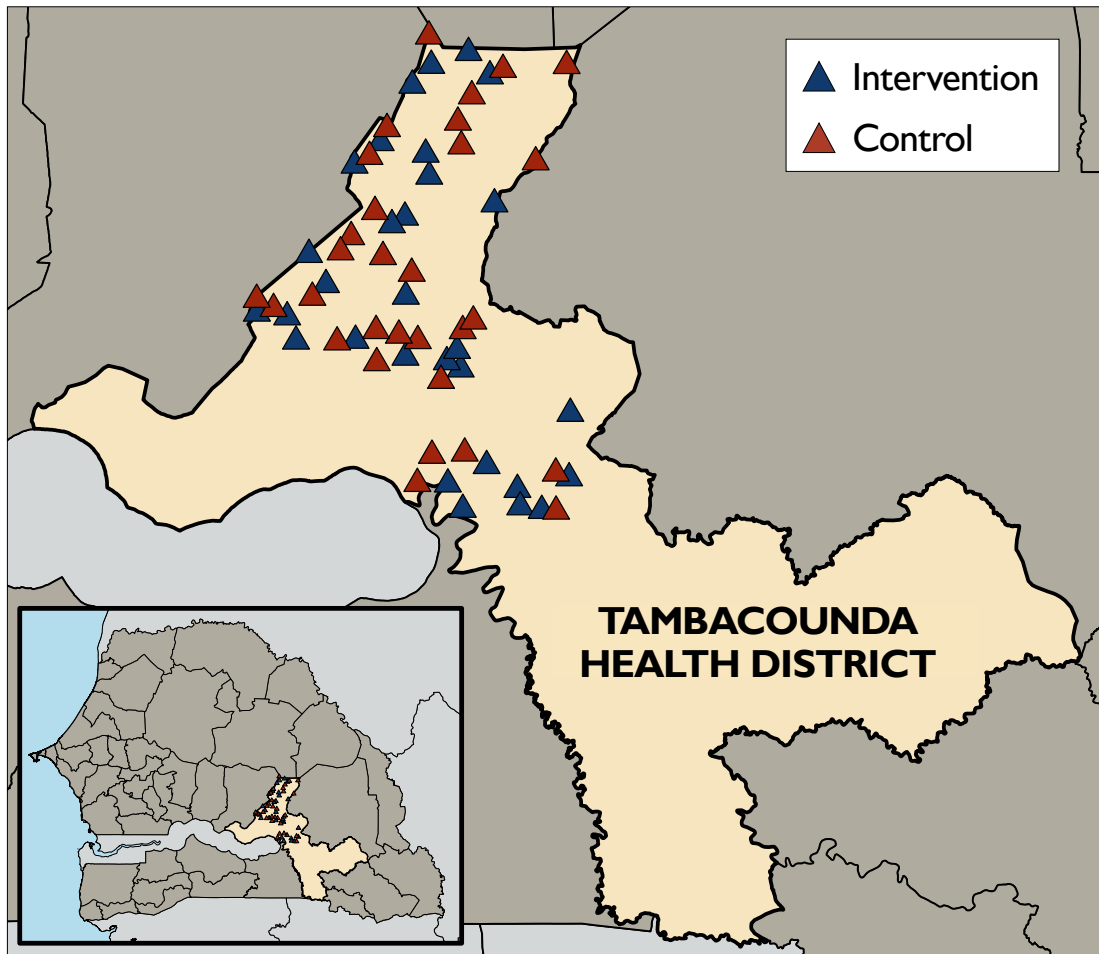
Supplementary Appendix

Supplement to: Ba et al, Mass drug administration to reduce malaria incidence in a low-to-moderate endemic setting: results from a cluster randomised controlled trial in Senegal

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Appendix 1. Map of study site



Appendix 2. Dosing regimens for dihydroartemisinin-piperaquine, single-low dose primaquine, and sulfadoxine-pyrimethamine + amodiaquine

Mass drug administration (intervention arm):

Dihydroartemisinin-piperaquine			
Age	Number of tablets containing 40 mg dihydroartemisinin and 320 mg piperaquine		
	Day 1	Day 2	Day 3
3 to 24 months	0.5	0.5	0.5
2 to 7 years	1	1	1
8 to 10 years	1.5	1.5	1.5
11 to 14 years	2	2	2
15+ years	3	3	3

Primaquine (given on day 1)			
Age	Number of tablets	Dosage (mg)	Volume (ml) of water used to dilute tablets
2 to 4 years	0.5	3.75	3
5 to 7 years	0.75	5.625	5
8 to 10 years	1	7.5	10
11 to 13 years	1.5	11.25	--
14+ years	2	15	--

Seasonal malaria chemoprevention (control arm):

Sulfadoxine-pyrimethamine + amodiaquine (SP-AQ)			
Age	Number of tablets containing 500 mg sulfadoxine and 25 mg pyrimethamine, and 150 mg amodiaquine		
	Day 1	Day 2	Day 3
3 to 11 months	0.5 tablet SP + 0.5 tablet AQ	0.5 tablet AQ	0.5 tablet AQ
12 to 59 months	1 tablet SP + 1 tablet AQ	1 tablet AQ	1 tablet AQ
60 to 120 months	1.5 tablets SP + 1.5 tablets AQ	1.5 tablets AQ	1.5 tablets AQ

Appendix 3. Table of distribution and crude coverage of SMC and MDA campaign during intervention year by cycle and dose.

	MDA (intervention)			SMC (control)		
	≥1 dose	≥2 doses	All 3 doses	≥1 dose	≥2 doses	All 3 doses
Cycle 1						
Overall						
Distribution coverage, % (n/N)	79% (6505/8229)	77% (6360/8229)	74% (6057/8229)	--	--	--
Crude coverage, % (n/N)	73% (6505/8931)	71% (6360/8931)	68% (6057/8931)	--	--	--
<10 years of age*						
Distribution coverage, % (n/N)	85% (2754/3232)	84% (2711/3232)	81% (2618/3232)	93% (3202/3457)	93% (3199/3457)	92% (3187/3457)
Crude coverage, % (n/N)	82% (2754/3353)	81% (2711/3353)	78% (2618/3353)	92% (3202/3492)	92% (3199/3492)	91% (3187/3492)
≥10 years of age						
Distribution coverage, % (n/N)	75% (3750/4996)	73% (3648/4996)	69% (3438/4996)	--	--	--
Crude coverage, % (n/N)	67% (3750/5577)	65% (3648/5577)	62% (3438/5577)	--	--	--
Cycle 2						
Overall						
Distribution coverage, % (n/N)	82% (7125/8673)	81% (6998/8673)	79% (6836/8673)	--	--	--
Crude coverage, % (n/N)	74% (7125/9571)	73% (6998/9571)	71% (6836/9571)	--	--	--
<10 years of age*						
Distribution coverage, % (n/N)	86% (3003/3493)	85% (2966/3493)	83% (2904/3493)	92% (3174/3442)	92% (3171/3442)	92% (3158/3442)

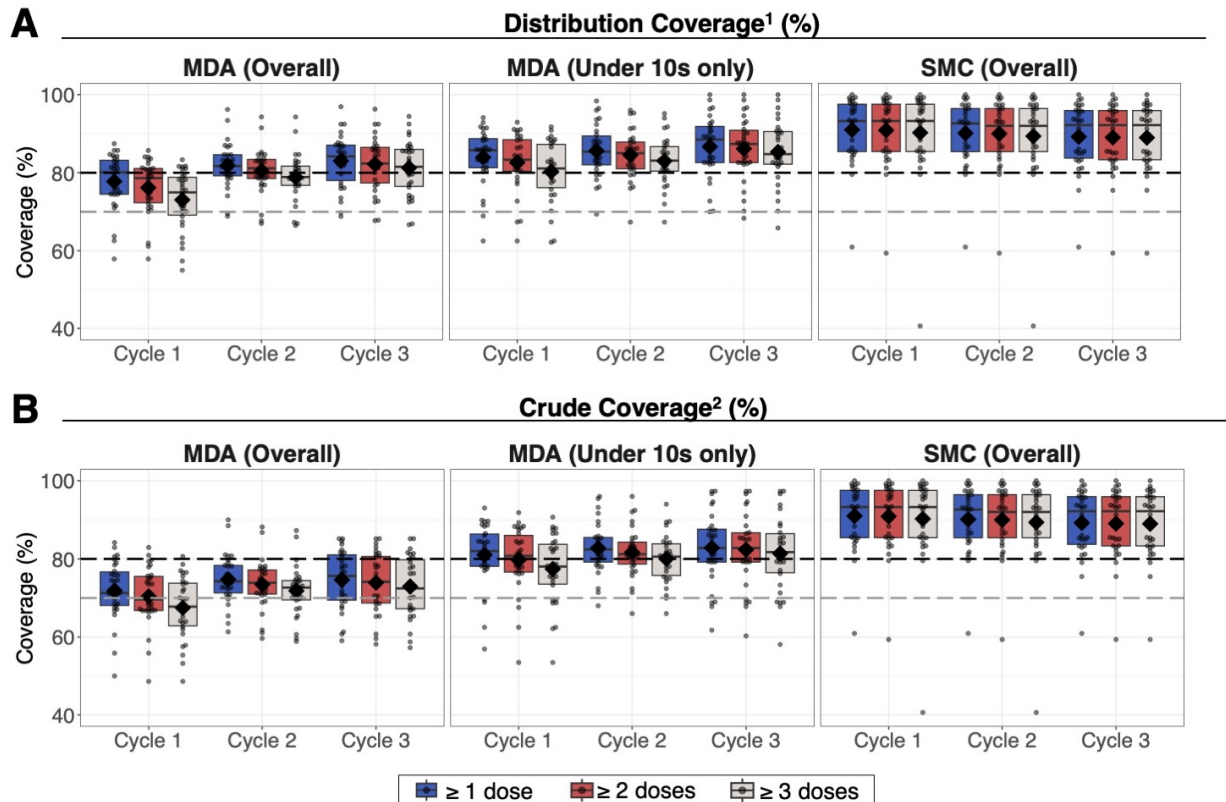
	MDA (intervention)			SMC (control)		
	≥1 dose	≥2 doses	All 3 doses	≥1 dose	≥2 doses	All 3 doses
Crude coverage, % (n/N)	83% (3003/3634)	82% (2966/3634)	80% (2904/3634)	91% (3174/3489)	91% (3171/3489)	91% (3158/3489)
≥10 years of age						
Distribution coverage, % (n/N)	80% (4122/5180)	78% (4032/5180)	76% (3932/5180)	--	--	--
Crude coverage, % (n/N)	69% (4122/5937)	68% (4032/5937)	66% (3932/5937)	--	--	--
Cycle 3						
Overall						
Distribution coverage, % (n/N)	83% (7250/8690)	82% (7169/8690)	81% (7065/8690)	--	--	--
Crude coverage, % (n/N)	75% (7250/9703)	74% (7169/9703)	73% (7065/9703)	--	--	--
<10 years of age*						
Distribution coverage, % (n/N)	87% (3107/3560)	87% (3085/3560)	86% (3046/3560)	92% (3146/3434)	91% (3141/3434)	91% (3139/3434)
Crude coverage, % (n/N)	83% (3107/3732)	83% (3085/3732)	82% (3046/3732)	90% (3146/3487)	90% (3141/3487)	90% (3139/3487)
≥10 years of age						
Distribution coverage, % (n/N)	81% (4140/5127)	80% (4081/5127)	78% (4017/5127)	--	--	--
Crude coverage, % (n/N)	69% (4140/5967)	68% (4081/5967)	67% (4017/5967)	--	--	--

Abbreviations: MDA = mass drug administration; SMC = seasonal malaria chemoprevention

* SMC coverage assessed only among age-eligible children (i.e., 3-120 months).

Appendix 4. Boxplot of distribution and crude coverage of mass drug administration (intervention) and seasonal malaria chemoprevention (control) by village.

Coverage was separately reported for overall population and for those under 10 years of age for comparability of MDA and SMC coverage.



Abbreviations: MDA = mass drug administration; SMC = seasonal malaria chemoprevention

Boxes indicate the interquartile range of village-level coverage; horizontal line in each box indicates median; diamond point represents mean across villages; circle points indicate coverage for each village.

¹ Distributional coverage = # of residents who received study drugs / # of eligible residents targeted for campaign. Denominator includes absences and refusers of the study drugs, but excludes pregnant women (for MDA), persons with a self-reported illness, and persons who emigrated out of study area.

² Crude coverage = # of residents who received study drugs / # of persons targeted for the campaign. Denominator includes those who refused the study drugs, absences, and those who were ineligible to receive MDA due to pregnancy, self-reported illness, but excludes those who emigrated out of the study area.

Appendix 5. MDA and SMC coverage by cycle and by day, including reasons for non-coverage.

Intervention (MDA)	Cycle 1			Cycle 2			Cycle 3		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
Targeted individuals ¹	8931	8931	8931	9571	9571	9571	9703	9703	9703
Received DP	6449 (72.2%)	6310 (70.7%)	6163 (69.0%)	7089 (74.1%)	6986 (73.0%)	6884 (71.9%)	7237 (74.6%)	7162 (73.8%)	7085 (73.0%)
Received SLD-PQ ²	6286/8670 (72.5%)	--	--	6949/9331 (74.5%)	--	--	7199/9521 (75.6%)	--	--
Absent	1649 (18.5%)	1758 (19.7%)	1888 (21.1%)	1419 (14.8%)	1482 (15.5%)	1568 (16.4%)	1311 (13.5%)	1361 (14.0%)	1423 (14.7%)
Refused	121 (1.4%)	125 (1.4%)	129 (1.4%)	146 (1.5%)	161 (1.7%)	169 (1.8%)	131 (1.4%)	135 (1.4%)	140 (1.4%)
Self-reported illness	458 (5.1%)	484 (5.4%)	497 (5.6%)	613 (6.4%)	638 (6.7%)	646 (6.7%)	701 (7.2%)	722 (7.4%)	732 (7.5%)
Pregnant/Breastfeeding	254 (2.8%)	254 (2.8%)	254 (2.8%)	304 (3.2%)	304 (3.2%)	304 (3.2%)	323 (3.3%)	323 (3.3%)	323 (3.3%)
Control (SMC)	Cycle 1			Cycle 2			Cycle 3		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
Targeted individuals	3492	3492	3492	3489	3489	3489	3487	3487	3487
Received SP-AQ	3202 (91.7%)	3187 (91.3%)	3199 (91.6%)	3174 (91.0%)	3159 (90.5%)	3170 (90.9%)	3146 (90.2%)	3141 (90.1%)	3139 (90.0%)
Absent	234 (6.7%)	248 (7.1%)	236 (6.8%)	247 (7.1%)	261 (7.5%)	249 (7.1%)	261 (7.5%)	261 (7.5%)	262 (7.5%)
Refused	21 (0.6%)	22 (0.6%)	22 (0.6%)	21 (0.6%)	22 (0.6%)	22 (0.6%)	27 (0.8%)	28 (0.8%)	28 (0.8%)
Self-reported illness	35 (1.0%)	35 (1.0%)	35 (1.0%)	47 (1.3%)	47 (1.3%)	48 (1.4%)	53 (1.5%)	57 (1.6%)	58 (1.7%)

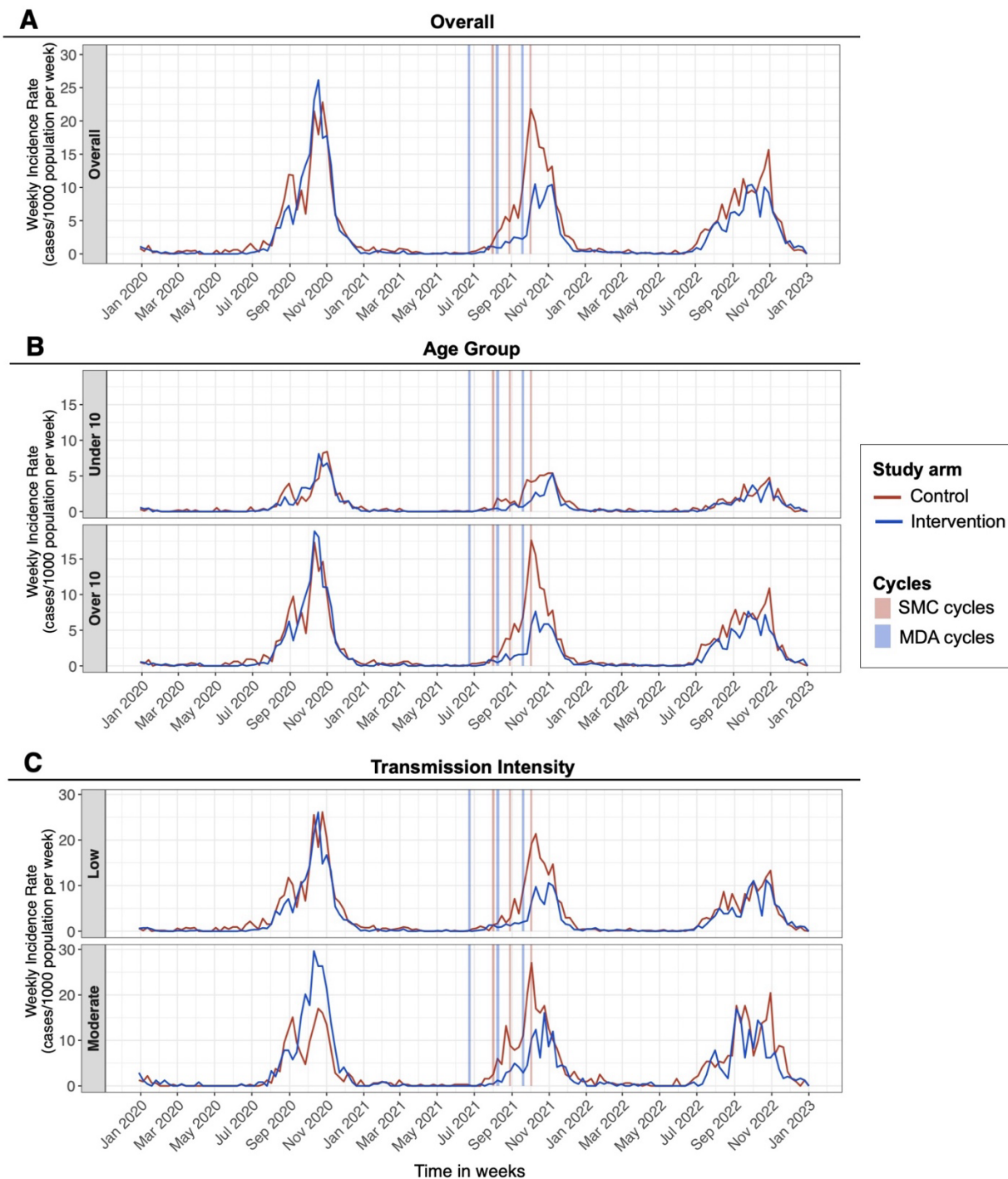
Abbreviations: DP = dihydroartemisinin-piperaquine; MDA = mass drug administration; SLD-PQ = single low-dose primaquine; SMC = seasonal malaria chemoprevention

¹ Targeted individuals includes new and existing residents of the study area, but excludes those that emigrated and deaths.

² % calculated based on PQ eligibility (≥2 years of age).

Appendix 6. Weekly incidence of RDT-confirmed malaria cases during study period.

In the figure below, data are presented by randomised arm based on overall differences (A), by age (B), and baseline transmission intensity (C).



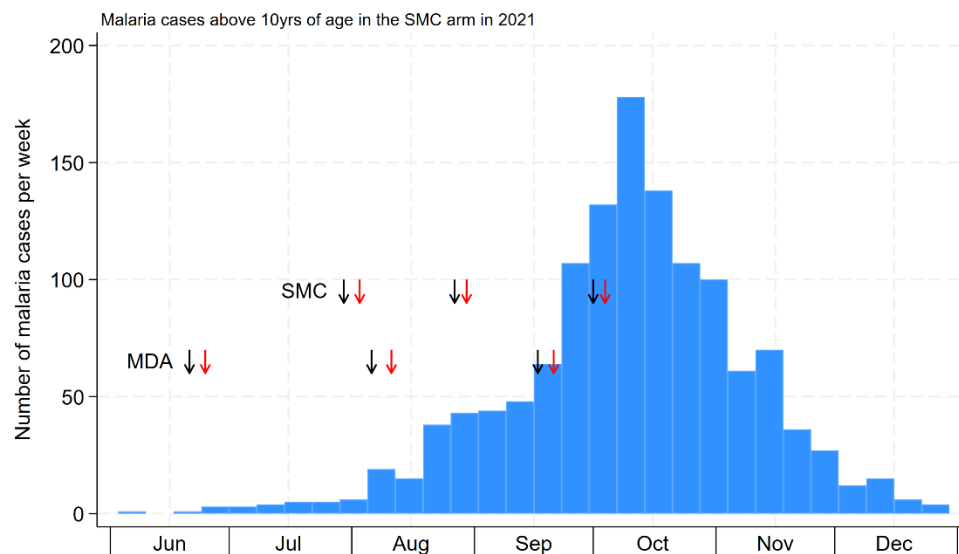
Abbreviations: MDA = mass drug administration; SMC = seasonal malaria chemoprevention

Appendix 7. Sensitivity analyses demonstrating suboptimal timing of SMC.

The study was planned to determine if there would be sustained reductions in transmission. The comparison in the intervention year was to demonstrate that the intervention was working and was not intended as a head-to-head comparison with SMC. SMC was not optimally implemented so this comparison could be misinterpreted.

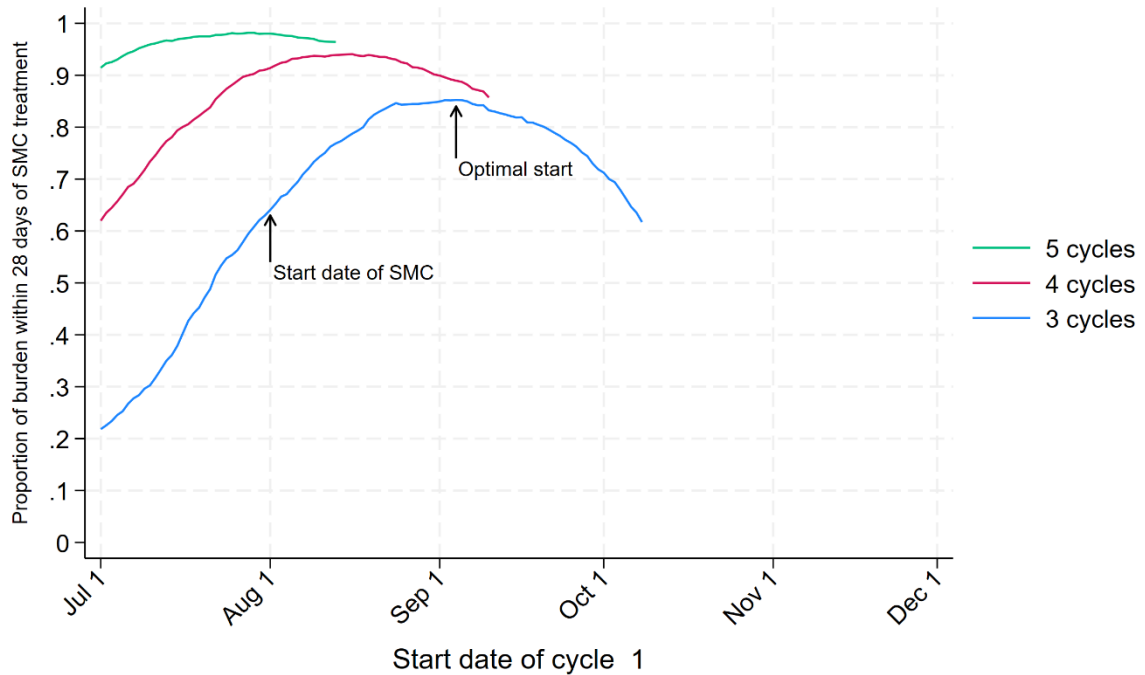
Suboptimal SMC. The first SMC cycle started July 30, 2021. This was too early by about one month. The data for the ≥ 10 years age group in the SMC arm in 2021, show us the seasonal pattern of malaria; data in this group is unaffected by MDA or SMC. In this graph, the first dose of each cycle is shown in black and the last dose of each cycle in red.

The graph below shows that a) SMC was poorly timed, and b) that even so, in terms of prophylaxis, SMC was better timed than MDA (which was deliberately started earlier).



SMC gives a high level of protection for 28 days. By shifting the start of the first SMC cycle by just over one month later, the percentage of the total burden during the months July-December, that falls within 28 days of an SMC treatment, increases from about 65% to about 85%. This percentage would increase to over 90% if four cycles were used.

The graph below shows the % of the July-December burden that falls within 28 days of an SMC treatment, if the first cycle starts on the date indicated and the cycles are 28 days apart. Estimates are provided if SMC was given as 3 cycles (blue), 4 cycles (red) or 5 cycles (green).



If we assume SMC efficacy during 28 days is about 85% (Cairns et al¹) and coverage is as in the trial, about 90%, ‘optimal’ SMC would reduce incidence by about 30% (with 3 cycles) or by about 44% (with 4 cycles), compared to what was implemented. Thus, if SMC had been optimised, we might expect to have seen no difference amongst the under 10s between MDA and SMC.

The number of MDA treatments was 20 887, compared to 9522 SMC treatments. If there were 4 SMC cycles, the number of treatments would come to $9522 \times 4/3 = 12\,696$, 60% of the number with MDA. If the objective is to reduce malaria in the age groups at risk of severe disease (the objective of SMC), MDA would seem an expensive option. MDA has the advantage of reducing incidence in older children and adults, and there is also an advantage in terms of reaching all vulnerable individuals, in that all benefit from indirect effects on transmission not just those treated.

References

1. Cairns M, Ceesay SJ, Sagara I, et al. Effectiveness of seasonal malaria chemoprevention (SMC) treatments when SMC is implemented at scale: Case–control studies in 5 countries. *PLoS Med* 2021; **18**(9): e1003727.

Appendix 8. MDA impact during the full calendar period (January-December) of the post-intervention year.

Study outcomes	Mean village-level incidence per 1,000 (events / population)				2022:2020 Intervention effect, 1-ratio of IRRs [95% CI] ¹	
	Intervention (MDA)		Control		Unadjusted	Adjusted ²
	2020	2022	2020	2022		
Primary outcome						
Incidence among all ages	187 (2120/10745)	93 (924/10745)	211 (1982/9641)	153 (1616/9641)	25% [-19%, 53%]	25% [-18%, 53%]
Subgroup analyses						
Age group						
<10 years old	138 (529/4901)	69 (115/1939)	159 (545/3598)	101 (385/3598)	29% [-14%, 56%]	24% [-22%, 52%]
≥10 years and older	220 (1591/6637)	61 (172/2152)	246 (1437/5991)	186 (1231/5591)	29% [-14%, 56%]	23% [-22%, 52%]
Baseline transmission intensity ³						
Low (<10%)	176 (1538/8316)	115 (994/8316)	236 (1463/6463)	136 (921/6463)	26% [-18%, 54%]	26% [-18%, 53%]
Moderate (≥10%)	223 (582/2429)	180 (389/2429)	152 (519/3178)	192 (695/3178)	23% [-78%, 67%]	23% [-78%, 67%]
DSDOM at baseline ⁴						
Yes	266 (2030/7783)	132 (1075/7783)	285 (1866/7401)	179 (1397/7401)	27% [-18%, 55%]	27% [-18%, 55%]
No	30 (90/2963)	125 (308/2963)	63 (116/2240)	103 (219/2240)	-13% [-257%, 64%]	-15% [-247%, 62%]

Abbreviations: DSDOM = dispensateur de soins à domiciles (community health worker); IRR = incidence rate ratio; MDA = mass drug administration

¹ Intervention effect estimated using mixed effects Poisson regression with village-level random intercepts and robust standard errors

² Adjusted for DSDOM at baseline, village population size of children <10 years of age, distance from health post, baseline parasite prevalence by microscopy, and village population size in 2019, and presence of DSDOM at time of case detection.

³ Transmission intensity was defined as village-level microscopy-confirmed parasite prevalence of <10% for “Low” transmission clusters and ≥10% for “Moderate” transmission clusters. 23 clusters from the intervention arm and 21 clusters from the control arm contributed to “Low” category; 7 clusters in intervention arm and 9 clusters in control arm contributed to “Moderate” category.

⁴ 20 out of 30 clusters in the intervention arm and 20 out of 30 clusters in the control arm contributed to the “Yes” category of the DSDOM at baseline subgroup analyses. 19 out of 20 (95%) clusters without DSDOM at baseline had a baseline incidence <250 cases/1000 population

Appendix 9. Safety outcomes reported through passive surveillance.

Summary. Passive surveillance detected 129 AEs among 67/20 887 (0.003%) participants who received ≥ 1 MDA dose and 4 AEs among 2/9524 (0.0002%) participants who received ≥ 1 SMC dose; all were mild (see table below). The frequency and proportion of participants reporting AEs were higher in the intervention arm compared to control ($p < 0.0001$), with most (74%; 95/129) AEs occurring in participants ≥ 10 years (who do not routine receive chemoprevention). The most common AEs in the intervention arm were gastrointestinal issues (45.7%), headaches (25.6%), and fever (17.1%).

Passive surveillance	Intervention (MDA)	Control (SMC)	p-value
Participants with any AE, n/N (%) ¹			
All cycles	67/20 887 (0.003%)	2/9524 (0.0002%)	< 0.0001
First cycle	46/6506 (0.7%)	0/3202 (0%)	< 0.0001
Second cycle	13/7125 (0.2%)	2/3174 (0.1%)	0.14
Third cycle	8/7256 (0.1%)	0/3146 (0%)	0.062
Frequency of adverse events, n (IR) ²			
All cycles	129 (0.0062)	4 (0.00042)	< 0.0001
First cycle	97 (0.015)	0 (0)	< 0.0001
Second cycle	20 (0.0028)	4 (0.0013)	0.13
Third cycle	12 (0.0017)	0 (0)	0.013
Most common adverse events, n/N (%)			
Gastrointestinal issues	59/129 (45.7%)	3/4 (75%)	0.25
Headache	33/129 (25.6%)	0/4 (0%)	0.24
Fever	22/129 (17.1%)	1/4 (25%)	0.37
Other	15/129 (11.6%)	0/4 (0%)	0.47
Severity of AEs, n/N (%)			
Mild	129/129 (100%)	4/4 (100%)	--
Moderate	0/129 (0%)	0/4 (0%)	--
Severe	0/129 (0%)	0/4 (0%)	--
Any serious AEs, n/N (%)	0/129 (0%)	0/4 (0%)	--

Abbreviations: AE = adverse event; IR = incidence rate

¹ Denominators represent those who received at least one dose of study drug.

² Incidence rate represents events per person-month at-risk. Denominators for incidence rate calculated based on number of persons who received at least one dose of study drug for the time of observation each person was monitored for adverse events.

Appendix 10. Prevalence of drug resistance markers by randomised arm and survey.

Summary. We successfully genotyped 433/597 PCR-positive samples from surveys to determine the prevalence of markers associated with antimalarial resistance (see table below). None of the studied mutations differed in proportions between arms or time periods. Mutations associated with intermediate resistance to sulfadoxine-pyrimethamine (PfDHFR N51I, C59R, S108N and PfDHPS A437G) were seen at high proportions (range: 58%–100%). The prevalence of PfDHFR I164L mutation ranged from 2%–12%. There was no evidence of PfDHPS K540E, PfDHPS A581G, or PfK13 C580Y mutations.

Mutations	Intervention		Control		p-value ¹
	Baseline (n=128)	Endline (n=58)	Baseline (n=141)	Endline (n=106)	
PfK13					
C580Y	0% (0/123)	0% (0/58)	0% (0/135)	0% (0/104)	--
PfDHPS					
K540E	0% (0/128)	0% (0/58)	0% (0/141)	0% (0/106)	--
A437G	82% (96/117)	87% (48/55)	81% (103/127)	87% (86/99)	0.94
A581G	0% (0/128)	0% (0/58)	0% (0/141)	0% (0/106)	--
A613S/T	14% (18/126)	5% (3/57)	16% (23/140)	12% (12/101)	0.33
PfDHFR					
N51I	100% (126/126)	100% (56/56)	100% (139/139)	100% (105/105)	--
C59R	100% (126/126)	100% (56/56)	100% (139/139)	100% (105/105)	--
S108N	75% (88/117)	58% (32/55)	77% (105/137)	60% (61/102)	0.96
I164L	12% (15/128)	2% (1/54)	12% (17/141)	7% (1/101)	0.24
PfCRT					
K76T	38% (48/127)	35% (20/57)	46% (63/138)	44% (46/104)	0.87
PfMDR1					
N86Y	2% (3/128)	0% (0/58)	5% (7/141)	0% (0/106)	0.28
Y184F	67% (80/120)	64% (37/58)	81% (107/132)	64% (68/106)	0.19

Abbreviations: Pf = *Plasmodium falciparum*; K13 = Kelch 13; DHPS = dihydropteroate synthase; DHFR = dihydrofolate reductase; CRT = chloroquine resistance transporter; MDR1 = multidrug resistance 1

¹ P-value computed using Poisson regression with robust standard errors, which compares relative change in prevalence before-and-after intervention between groups.

Appendix 11. CONSORT 2010 Checklist (extended for cluster randomised controlled trials)

Section/topic and Item No.	Standard checklist	Extension for cluster designs	Section
Title and Abstract			
1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	Title
1b	Structured summary of trial design, methods, results, and conclusions.		Summary
Background and Objectives			
2a	Scientific background and explanation of rationale	Rationale for using a cluster design	Introduction
2b	Specific objectives or hypotheses	Whether objectives pertain to the cluster level, the individual participant level, or both	Introduction; Statistical Analysis (Methods)
Methods			
Trial Design:			
3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the cluster	Study design and participants (Methods)
3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		NA
Participants:			
4a	Eligibility criteria for participants	Eligibility criteria for clusters	Study design and participants (Methods)
4b	Settings and locations where the data were collected		Study setting (Methods)
Interventions:			

5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level, or both	Interventions (Methods)
Outcomes:			
6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	Whether outcome measures pertain to the cluster level, the individual participant level, or both	Study outcomes (Methods)
6b	Any changes to trial outcomes after the trial commenced, with reasons		NA
Sample size:			
7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or <i>k</i>), and an indication of its uncertainty	Statistical analysis (Methods)
7b	When applicable, explanation of any interim analyses and stopping guidelines		Study design and participants (Methods)
Randomisation			
Sequence generation:			
8a	Method used to generate the random allocation sequence		Randomisation and masking (Methods)
8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	
Allocation concealment mechanism:			
9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level, or both	Randomisation and masking (Methods)
Implementation:			

10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replaced by 10a, 10b, and 10c	See below
10a		Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	Randomisation and masking (Methods)
10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling)	Procedures (Methods)
10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or both) and whether consent was sought before or after randomisation	
Blinding:			
11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		Randomisation and masking (Methods)
11b	If relevant, description of the similarity of interventions		Interventions (Methods)
Statistical methods:			
12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	Statistical analysis (Methods)
12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		
Results			
Participant flow (a diagram is strongly recommended):			
13 a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 2

13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members	Figure 2
Recruitment:			
14a	Dates defining the periods of recruitment and follow-up		Fig 1
14b	Why the trial ended or was stopped		NA
Baseline data:			
15	A table showing baseline demographic and clinical characteristics for each group	Baseline characteristics for the individual and cluster levels as applicable for each group	Table 1
Numbers analysed:			
16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	Table 1, Fig 2
Outcomes and estimation:			
17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or <i>k</i>) for each primary outcome	Results Section; Tables 2, 3, and 4; Appendix
17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		
Ancillary analyses:			
18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory		Results, Tables 2-3
Harms:			
19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms ¹⁰⁶)		Results, Table 4, Appendix 4
Discussion			
Limitations:			

20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		Discussion
Generalisability:			
21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	Discussion
Interpretation:			
22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence		Discussion
Other information			
Registration:			
23	Registration number and name of trial registry		Summary; Study design and participants (Methods)
Protocol:			
24	Where the full trial protocol can be accessed, if available		Supplementary Materials
Funding:			
25	Sources of funding and other support (such as supply of drugs), role of funders		Summary; Role of funding source (Methods)

Appendix 12. Protocol

Mass drug administration with dihydroartemisinin-piperaquine and primaquine to reduce malaria in a moderate-low transmission setting in Senegal- a cluster randomized controlled trial

Principal Investigator(s):

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Dr Michelle Hsiang

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Dr Julie Thwing

Dr Meera Venkatesan

Dr Sara Zohdy

Funder: U.S. President's Malaria Initiative

Project dates: September 1, 2020 – January 31, 2023

12 *OMB/PRA Information*

13 The principal investigators for this protocol are Dr. Jean Louis Ndiaye (University of Thiès, Senegal) and
14 the Coordinator of the National Malaria Control Program (NMCP) of Senegal (Dr. Doudou Sene).

15 Impact Malaria and its local subcontractors will implement the study, provide technical oversight and
16 collect the data. The NMCP will own the data. Data will be shared with Centers for Disease Control and
17 Prevention (CDC) and other collaborating institutions at the investigators' discretion.

18 CDC is providing technical support to NMCP and Impact Malaria for protocol development, training of
19 staff, data analysis, and report writing. CDC staff may have direct contact with the research subjects and
20 may be able to view identifiable information during the course of monitoring and analysis. DBS samples
21 sent to reference laboratories will not contain personally identifiable information.

22 *Investigator roles and responsibilities*

Name of co-investigators (in alphabetical order per institution):	Professional Discipline/specialty and institutional functions (for NMCP)	Role in the project [Note: All co-investigators will provide critical feedback on the protocol, and associated manuscripts.]
<i>National Malaria Control Program (NMCP), Senegal</i>		
Fatou Ba	Co-Principal Investigator; Malariologist, Head of Research and Vector Control Offices at NMCP	Provide input in study design; nominate study steering committee (represent Senegal NMCP on committee); participate in the selection of local research partners; coordinate liaison(s) between research team and NMCP; provide technical advice to the local research team related to vector control activities and entomological surveillance; provide technical advice with study planning, data analysis, write-up of research findings, and framing of results for programmatic and operational

		implementation
Ibrahima Diallo	Co-investigator; Pharmacist, Head of Procurement and Drug Management Office at NMCP	Lead aspects of the study related to commodities, pharmacovigilance; liaison with local health authorities for any aspect related to supply chain management
Latsouk Gnilane Diouf	Co-investigator; Health Economist, Surveillance, Monitoring, and Evaluation Specialist at NMCP	Provide input in data management, supervision, coordination of NMCP duties
Elhadji Doucoure	Co-investigator; Public Health Physician, Head of Communication and Outreach Office at NMCP	Lead aspects of the study related to community sensitization and mobilization; provide technical advice for qualitative components of the study (e.g. instrument development, training of qualitative team, qualitative data analysis and interpretation); focal point for elimination activities
Seynabou Gaye	Co-investigator; Physician, Head of Case Management, Training and Drug-based Prevention Office at NMCP	Lead aspects of the study related to community health workers and PECADOM+ and case management; liaison (focal point) with local health authorities for any aspect related to community health and case management
Alioune Badara Gueye	Co-investigator; Public Health Physician, Deputy Coordinator at NMCP	Review protocol design and ground truth with current NMCP control and elimination strategies; provide technical advice with planning and study monitoring; lead aspects of the study related to Seasonal Malaria Chemoprevention (SMC); advise on operational

		aspects of MDA administration and cost effectiveness study; liaison with local health authorities as it pertains to chemoprevention issues; framing of research findings for programmatic and operational implementation of MDA
Médoune Ndiop	Co-investigator; Monitoring and Evaluation (M&E) Specialist, Head of the Surveillance, Monitoring, and Evaluation (SME) Office at NMCP	Support data analysis plan development; advise on data collection tools; site selection and data analysis; focal point for routine data management and access at NMCP; lead aspects related to leveraging NMCP SME system
Doudou Sène	Co-Principal Investigator; Public Health Physician; Coordinator of the NMCP	Responsible for overall study oversight and owner of study data; review protocol design; assign project responsibilities within the NMCP; official communication with local health authorities; ensure that the project is framed so that the results will be useful for the Senegalese NMCP
<i>University of Thiès, Senegal</i>		
Jean Louis Ndiaye	Principal Investigator; Epidemiologist	Responsible for overall study implementation and oversight, including national IRB submission; lead the coordination of the study implementation and technical aspects of the study; participate in protocol development, mapping, planning, training, implementation, study monitoring, data analysis, and write-up of research findings.

Elhadji Ba	Co-investigator; Epidemiologist/Project Coordinator	Manage day-to-day activities of the project and supervise the field staff throughout the study period; organize all meetings and maintain any project reports; work closely with UCSF Project Coordinator to set up logistical, partnership, and administrative aspects of the study; contribute to the identification of the project's risk and monitor its progress
Abdoulaye Diallo	Co-investigator; Medical Epidemiologist	Contribute to the development of the study protocol; coordinate mass drug administration activities with the Principal Investigator; contribute to the preparation and implementation of the study; contribute to the preparation of the manuscript
Paul Milligan	Co-investigator; Epidemiologist/Statistician	Contribute to the epidemiological design and statistical analysis
Tidiane Ndoeye	Co-investigator; Socio- anthropologist	Responsible for the development and implementation of the qualitative aspects of the study
Ibrahima Seck	Co-investigator; Public Health Specialist	Contribute to the development of the study protocol; assist in the preparation and implementation of the surveys, and write-up of the manuscript
Amadou Seck	Computer Engineer/Data Manager	Responsible for managing all aspects of the quantitative data collected in the study.
<i>Centers for Disease Control and Prevention</i>		
Julie Thwing (CITI Exp 12/11/2021)	Co-investigator; Epidemiologist	Provide technical support with protocol development, planning, training, study

		monitoring, data analysis, and write-up of research findings
<i>US President's Malaria Initiative/CDC</i>		
Jimée Hwang (CITI Exp: 12/27/2021)	Co-investigator; Epidemiologist	Responsible for study conception; liaison with PMI Operational Research Committee; lead CDC Atlanta coordination and technical support with protocol development, planning, training, study monitoring, data analysis and write-up of research findings
Leah Moriarty (CITI Exp: 1/2/2022)	Co-investigator; Epidemiologist	Coordinate partners and budget; provide technical support with protocol development, mapping, planning, training, study monitoring and management, data analysis, and write-up of research findings
Katharine Sturm-Ramirez (CITI Exp: 10/5/2023)	Co-Principal Investigator; Epidemiologist	Lead PMI Senegal coordination and technical support with protocol development, mapping, planning, training, study monitoring, data analysis and write-up of research findings; liaison between PMI and NMCP
Sara Zohdy (CITI Exp 11/13/2022)	Co-investigator; Entomologist	Provide technical support with protocol development, planning, training, study monitoring, data analysis and write-up of research findings as it relates to vector control (e.g. PBO net distribution)
<i>US President's Malaria Initiative/ USAID</i>		
Meera Venkatesan	Co-investigator; Health Science Specialist	Coordinate funding support; provide technical support for protocol development, data analysis, and write-up of research findings

<i>Impact Malaria</i>		
Michelle Hsiang (CITI Exp: 12/21/2023)	Co-Principal Investigator; Epidemiologist	Provide technical support with protocol development, planning, training, study monitoring, data analysis and write-up of research findings; liaison between UCSF and University of Thiès
Roly Gosling (CITI Exp: 3/3/2021)	Co-investigator; Epidemiologist	Provide technical support with protocol development, planning, training, study monitoring, data analysis and write-up of research findings
Adam Bennett (CITI Exp: 4/7/2021)	Co-investigator; Epidemiologist	Provide technical support with protocol development, planning, training, study monitoring, data analysis and write-up of research findings
Michelle Roh (CITI Exp: 11/3/2022)	Co-investigator; Epidemiologist	Provide technical support with protocol development, planning, data quality monitoring, data analysis, and write-up of research findings. Lead selection of villages, mapping, and submission of IRB application for UCSF.
Tabitha Kibuka (CITI Exp: 10/6/2023)	Co-investigator; Surveillance, M&E Advisor	Lead the coordination of Impact Malaria operational research activities and support the coordination and strategic engagement between research collaborators. Provide oversight of study implementation.

23 *Abbreviations*

24	ACT	Artemisinin-Based Combination Therapy
25	AE	Adverse Event
26	AL	Artemether-Lumefantrine
27	API	Annual Parasite Incidence
28	BCC	Behavior Change Communication
29	CDC	U.S. Centers for Disease Control and Prevention
30	CHW	Community Health Worker
31	cRCT	Cluster Randomized Controlled Trial
32	CV	Coefficient of Variation
33	DBS	Dried Blood Spots
34	DHA-PQP	Dihydroartemisinin-Piperaquine
35	DSMB	Data Safety Monitoring Board
36	G6PD	Glucose-6-Phosphate Dehydrogenase
37	GIS	Geographic Information System
38	GPS	Global Positioning System
39	ICC	Intra-cluster Correlation Coefficient
40	IRB	Institutional Review Board
41	LF	Lymphatic filariasis
42	LLIN	Long-Lasting Insecticidal Net
43	M&E	Monitoring and Evaluation
44	MDA	Mass Drug Administration
45	MOH	Ministry of Health
46	NMCP	National Malaria Control Program
47	NTD	Neglected Tropical Diseases
48	PBO	Piperonyl Butoxide
49	PCR	Polymerase Chain Reaction
50	PQ	Primaquine
51	PI	Principal Investigator
52	PMI	U.S. President's Malaria Initiative
53	RDT	Rapid Diagnostic Test
54	SAE	Serious Adverse Event
55	SMC	Seasonal Malaria Chemoprevention
56	SME	Surveillance, Evaluation, and Monitoring
57	SP-AQ	Sulfadoxine-Pyrimethamine and Amodiaquine
58	STH	Soil-transmitted Helminths
59	UCSF	University of California, San Francisco
60	WHO	World Health Organization

Summary

Problem to be studied

Due to scale-up of malaria control measures including access to prompt testing and treatment, long lasting insecticidal nets (LLINs), and seasonal malaria chemoprevention (SMC), much progress has been made in Senegal with 0.4% malaria prevalence in children less than five years of age in 2017. Malaria transmission is heterogeneous in Senegal with lower transmission areas in the north implementing elimination activities and higher transmission areas in the south implementing control interventions including SMC. To rapidly drive down transmission and further shrink the map of high endemicity malaria, additional interventions are needed. Mass drug administration (MDA) with antimalarials has generally been shown to lead to rapid, early reductions in the parasite reservoir, but with eventual decay of impact over time depending on the baseline transmission level [1]. In areas of low transmission with limited importation, sustained impact can be achieved especially with strong case management and surveillance systems. The purpose of this study is determine whether MDA will be able to rapidly reduce malaria incidence in areas of moderate-to-low malaria transmission settings of Senegal where control activities are ongoing so that the program can reorient their malaria strategy to implement elimination interventions in these settings.

Hypothesis. In the context of an optimized malaria control setting (e.g. proactive community case management and distribution of piperonyl butoxide (PBO) LLINs) of a moderate-to-low transmission setting, time-limited MDA with dihydroartemisinin-piperaquine (DHA-PQP) and single-low dose primaquine (PQ) can reduce the transmission of *Plasmodium falciparum* malaria more than the current standard of care (i.e. SMC).

Primary Objective

- To evaluate the effect of three rounds of MDA with DHA-PQP and low-dose PQ on village-level confirmed malaria case incidence compared to standard of care SMC when provided in the context of optimized control (proactive community case management + PBO nets).

Secondary Objectives

- To determine the effect of three rounds of MDA with DHA-PQP and low-dose PQ on parasite prevalence compared to standard of care SMC when provided in the context of optimized control (proactive community case management + PBO nets).

- To determine the cost, coverage, operational feasibility, acceptability, adherence, and adverse events of three rounds of MDA with DHA-PQP and low-dose PQ compared to standard of care SMC
- To determine the impact of three rounds of MDA with DHA-PQP and low-dose PQ compared to standard of care SMC on parasite population dynamics and drug resistance
- To determine the effect of three rounds of MDA with DHA-PQP and low-dose PQ compared to standard of care SMC on malaria burden (number of suspected malaria cases and test positivity rates) evaluated through the routine health facility surveillance systems
- To determine the effect of three rounds of MDA with DHA-PQP and low-dose PQ compared to standard of care SMC on transmission as measured by confirmed case incidence in those <10 and >10 years during the post-MDA period
- To determine whether three rounds of MDA with DHA-PQP and low-dose PQ compared to standard of care SMC leads to reaching a target parasite incidence (e.g. < 5 cases per 1000)
- To monitor the impact of PBO LLIN distribution as well as changes in insecticide resistance in the context of the optimized control efforts

Methods

This study will be a two arm, cluster-randomized controlled trial to determine whether three rounds of MDA using antimalarials (DHA-PQP and PQ) is associated with a greater reduction in confirmed malaria clinical incidence compared to standard of care SMC over a one year follow-up period post-MDA intervention. The study will be conducted in an optimized control setting, where there is ongoing proactive community case management and PBO LLINs have been distributed. Randomization will occur at the village level. Thirty clusters will be enrolled in the comparison arm and 30 clusters enrolled in the MDA intervention arm for a total of 60 clusters (target population of 24,000, assuming an average of 400 persons per village).

Implications

115 This study will inform the Ministry of Health (MOH) on the potential impact of time-limited MDA on
116 accelerating transmission reduction and whether MDA can be an effective tool to transition recent malaria
117 control zones to elimination zones.

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Background

The concept of administering full therapeutic courses of antimalarials to whole communities as mass drug administration (MDA) without prior testing has been applied as a malaria control measure for more than 70 years, particularly during the malaria eradication campaign of the 1950s and 1960s [2]. In the past decade, MDA has garnered renewed interest as a tool to accelerate progress towards malaria elimination.

Although MDA has been used widely for controlling and eliminating the five most highly prevalent neglected tropical diseases (lymphatic filariasis (LF), onchocerciasis, schistosomiasis, soil-transmitted helminths (STH), and trachoma) [3], the role of MDA for malaria has been less clear due to the potential for emergence of antimalarial drug resistance, challenges of reaching high coverage of the entire population, and the varying success of the intervention in sustaining reductions in malaria burden and interrupting malaria transmission. Evidence from published reviews of MDA found that while MDA can be successful at rapidly reducing parasite prevalence, once the activity is stopped, there is a strong tendency for malaria to rebound to previous transmission levels especially in higher transmission settings [1, 4]. A consensus modelling study noted that despite differing effect sizes depending on the transmission model used, all models predicted the percentage reduction in transmission to be temporary [5]. Based on the collective evidence, a 2015 World Health Organization (WHO) Evidence Review Group recommended the limited use of MDA in areas approaching elimination, epidemics and complex emergency settings [6].

To date, only two cluster randomized controlled trials (cRCTs) have been conducted in moderate-high transmission settings: a study in the high transmission setting of The Gambia using a single round of sulfadoxine-pyrimethamine and artesunate which failed to show a lasting impact on malaria transmission [7] and a study from southern Zambia which found two rounds of DHA-PQP showed marked reductions in malaria prevalence and incidence, though large reductions were seen across both control and MDA arms following aggressive efforts to achieve universal coverage of LLINs, indoor residual spraying (IRS), and effective community case management [8]. A more recent uncontrolled study conducted in The Gambia showed that MDA with three rounds of dihydroartemisinin-piperaquine (DHA-PQP) reduced malaria infection and clinical disease during the first months, but these reductions were only maintained in low-transmission areas [9]. There is increasing consensus that population-wide parasite clearance should play a role as an intervention for accelerating toward malaria elimination, but in the context of optimized surveillance systems, effective vector control and case management, and limited importation [10].

In addition to a full therapeutic course of a long-acting artemisinin-based combination therapy (ACT) (e.g. DHA-PQP), recent MDA trials have included or will include additional drugs (e.g. primaquine (PQ) for its gametocytocidal activity or ivermectin for its mosquitocidal effects). Single low-dose PQ (0.25mg/kg) has been recommended by WHO for areas pursuing elimination without the need for glucose-6-phosphate dehydrogenase (G6PD) testing and has been shown to decrease gametocyte prevalence and infectivity to mosquitoes [11]. A review of the published literature and the Uppsala Monitoring Centre adverse events data commissioned by the WHO found a total of 14 deaths attributed to higher doses of primaquine after more than 60 years of use in a large range of age groups (approximately 1 death for every 621,428 patients treated) [12].

Depending on the baseline transmission intensity of the area, a different package of interventions will be needed to approach or reach malaria elimination. In some areas, optimized control interventions comprising of community case management and effective long-lasting insecticidal nets (LLINs) [which in the context of pyrethroid resistance may require a piperonyl butoxide (PBO) treated net] might be sufficient, but in others higher transmission areas, an accelerating intervention such as MDA may be needed.

In Senegal, the National Malaria Control Program (NMCP) adopted a goal of reaching the threshold for pre-elimination (defined by the NMCP as an annual incidence <5 cases per 1000) by 2020 and malaria elimination by 2030. To achieve this goal, the Senegal NMCP has been implementing a tailored set of interventions in different transmission strata based on incidence. In areas of the Sahel and sub-Saharan region of Africa, where malaria is the leading cause of child morbidity and mortality, seasonal malaria chemoprevention (SMC) is implemented as part of the routine malaria control strategy. SMC, as currently recommended by the WHO, involves the monthly administration of sulfadoxine-pyrimethamine and amodiaquine (SP-AQ) to children, during the short, but intense malaria season (i.e. typically lasting 3-4 months) [13]. Studies have shown SMC to be highly cost-effective, safe, and feasible [14] in reducing malaria associated morbidity and mortality. In Senegal, SMC is currently administered to children ages 3 months to 10 years in three southeastern regions, as well as three hot spots in the central zone. In addition to the standard interventions, pre-elimination zones (currently located mainly in the north) are eligible for case investigation and response measures, while malaria control zones with higher transmission (located mainly in the south and central regions) are prioritized for PECADOM+, an active home-based management of fever by community health workers (CHW) who conduct weekly visits during the high transmission months (July-October). Despite the scale-up of all these control interventions, many areas

198 will require an accelerated intervention to allow the program to transition more rapidly to an elimination
199 program and to more aggressively push the elimination margins further south.

200 This operational research study will fill a critical evidence gap for the role of MDA in moderate-to-low
201 transmission settings, which is a key question for the global malaria community and the topic of a recent
202 WHO Evidence Review Group.

203 *Objectives*

204 **Hypothesis**

205 Compared to standard of care SMC, time-limited MDA with DHA-PQP and single-low dose PQ in the
206 context of optimized control (proactive community case management + PBO nets) interventions can
207 reduce the transmission of *Plasmodium falciparum* malaria in moderate-low transmission settings
208 sufficiently so that the program can reorient to elimination-specific strategies.

209 **Primary Objective**

- 210 • To evaluate the effect of three rounds of MDA with DHA-PQP and low-dose PQ compared to
211 standard of care SMC on village-level confirmed malaria case incidence when provided in the
212 context of optimized control (proactive community case management + PBO nets).

213 **Secondary Objectives**

- 214 • To determine the effect of three rounds of MDA with DHA-PQP and low-dose PQ compared to
215 standard of care SMC on parasite prevalence and seroprevalence of malaria infection when
216 provided in the context of optimized control (proactive community case management + PBO
217 nets).
- 218 • To determine the cost, coverage, operational feasibility, acceptability, adherence, and adverse
219 events of three rounds of MDA with DHA-PQP and low-dose PQ compared to standard of care
220 SMC
- 221 • To determine the effect of three rounds of MDA with DHA-PQP and low-dose PQ compared to
222 standard of care SMC on parasite population dynamics and drug resistance
- 223 • To determine the effect of three rounds of MDA with DHA-PQP and low-dose PQ compared to
224 standard of care SMC on malaria burden (number of suspected malaria cases and test positivity
225 rates) evaluated through the routine health facility surveillance systems
- 226 • To determine the effect of three rounds of MDA with DHA-PQP and low-dose PQ compared to
227 standard of care SMC on transmission as measured by confirmed case incidence in those <10 and
228 >10 years
- 229 • To determine whether three rounds of MDA with DHA-PQP and low-dose PQ compared to
230 standard of care SMC leads to reaching a target parasite incidence (e.g. < 5 cases per 1000)

- To monitor the impact of PBO LLIN distribution as well as changes in insecticide resistance in the context of the optimized control efforts

Study endpoints

Primary outcome:

Difference in **village-level malaria case incidence** between arms. Malaria case incidence will be defined as the number of individuals testing positive for malaria through proactive case detection via weekly household screening of individuals with fever by CHWs (PECADOM Plus) and passive case detection of confirmed cases from each village reported at the health facility level. The effect of MDA will be evaluated as the difference in incidence between MDA with DHA-PQP +PQ and the comparison group (standard of care SMC) over a one-year follow-up period. Estimates will be controlled for baseline differences in incidence in Year 1 (pre-intervention period).

Secondary outcomes:

- Difference in **parasite prevalence measured by microscopy, antigen-based multiplex assay, and polymerase chain reaction (PCR)**. Prevalence will be assessed across all age groups from cross-sectional surveys conducted pre- and post-MDA, at the peak/end of the transmission season. Impact will be measured as the difference between MDA and comparison group.
- Difference in **test positivity rates and incidence of suspected cases** detected at health facilities between the MDA and comparison group
- Difference in **parasite diversity and distribution and complexity of multiple-genotype infections** (e.g. multiplicity of infection at pre- and post-MDA surveys) pre and post MDA between MDA and comparison groups
- Difference in **prevalence of drug resistance markers e.g. K13 and plasmepsin copy number** (at pre- and post-MDA surveys between arms)
- Difference in **sero-prevalence** (e.g. seropositivity defined by a cut-off and median fluorescent intensity) **and sero-conversion rates** of recent malaria and *Anopheles* exposure between the MDA and comparison arms.
- Difference in **cost, coverage, adherence, and adverse events** monitored during each MDA round between the intervention and comparison arms.
- Description of **community and health worker perceptions of the desirability, benefits, and challenges around MDA**
- Difference in **cost per case averted** of the MDA vs the comparison arms
- Difference in **insecticide resistance** intensity

Methods

Study Design

This study will be a two arm, cluster-randomized controlled trial to determine whether three rounds of MDA with DHA-PQP and PQ is associated with a greater reduction in confirmed malaria clinical incidence compared to standard of care SMC over a one-year follow-up period. The study will be conducted in an optimized control setting, where there is ongoing proactive community case management (PECADOM+) and PBO nets have been distributed. Villages will be the unit of randomization for the study. Villages will be selected for the study such that there is at least a 2.5 km buffer zone between neighboring study villages, based on geographic information system (GIS) data. This buffer zone will limit cross-contamination by malaria vectors or population contamination.

Districts within Tambacounda Region that meet the district-level inclusion criteria of low-moderate transmission (described below) will be selected. A total of 60 villages from selected district(s) that meet the village-level inclusion criteria (described below) will be randomized using computer-generated randomization to the comparison or intervention arm at a 1:1 ratio. Constrained randomization will be conducted to ensure adequate balance of important covariates that might confound the treatment effect.

Study participants, CHWs, or study field staff will not be blinded to the allocation assignment. However, laboratorians conducting analyses at the reference laboratories will be blinded to the allocation assignment.

Study Location

The region of Tambacounda in southeastern Senegal has an area of 42,706 km² or about 1/5 of the national territory. In 2017, Tambacounda Region reported a parasite prevalence of 1.0% by microscopy and 4.8% by RDT (Figure 1) and the annual parasite incidence (API) was reported as 101 cases/1,000 [15]. Within the seven health districts that make up the region, there is at least one health center and an average of 18 health posts per district (range: 10-27). There is one referral hospital that serves the region of 874,740 people. There are 2-12 private health facilities per district.

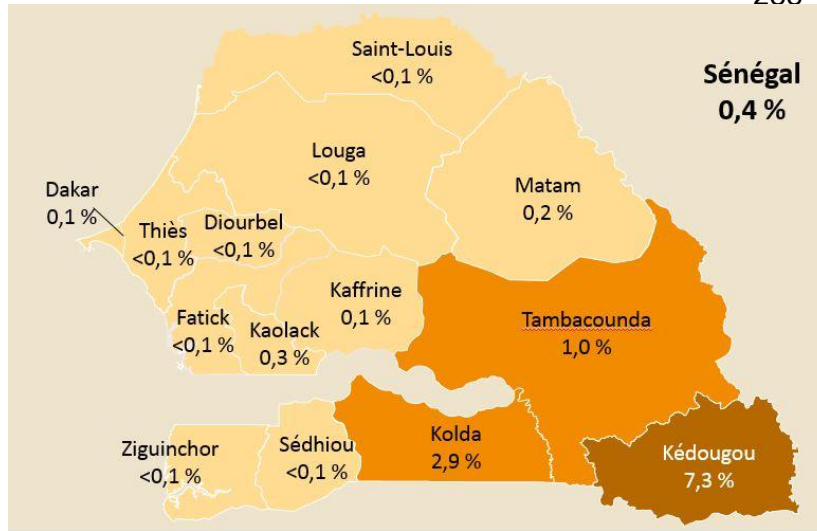


Figure 1: Malaria parasite prevalence by region. Percentage of children 6-59 months who were parasite positive by microscopy (Source: 2017 cDHS)

Table 1. Description of health districts in Tambacounda Region. Data obtained from the Division of Social and Health Information Systems (DSISS) and Ministry of Health and Social Action (MSAS). Malaria incidence averaged across 2016-2019.

Health District	Total Population (2020)	Number of health facilities	Number of CHW (2018)	Number of villages with a CHW (2018)	Average malaria incidence (cases/1000) [2016- 2019]
Bakel	108,561	20	31	41	33.6
Goudiry	93,780	20	47	62	145.6
Koumpentoum	164,409	20	61	96	44.9
Tambacounda	295,018	32	99	148	144.0
Maka Colibantang	90,548	11	45	65	135.1
Dianke Makha	53,216	17	35	47	298.9
Kidira	69,208	20	46	71	190.9
Tambacounda Region	874,740	127	364	530	124.5

Note: P+ = PECADOM+

The region benefits from annual SMC campaigns with three rounds of drug treatment given at least one month apart during the rainy season targeting children aged 3-120 months. In 2017, a total of 235,133 children were targeted in the region and 220,568 were treated (94% coverage). In 2018, the SMC campaign did not take place in Senegal, due to strikes within the health system which prevented its implementation. In addition, in villages far from the health posts, Senegal implements a proactive case management model known as *Prise en charge à domicile* or PECADOM+, where CHWs, known as *dispensateur de soins à domicile* (DSDOMs), conduct weekly household visits to assess fever cases and test for malaria. This currently takes place over 6-7 months (July-Jan) during the highest malaria incidence interval. In the spring of 2019, NMCP conducted a universal LLIN distribution campaign in the region, achieving coverage of one LLIN for every two persons and 72% of sleeping spaces covered. Although there were no IRS activities in Senegal in 2018, the districts of Koumpentoum and Maka Colibantang benefitted from the reintroduction of PMI-supported IRS activities starting in 2020. The IRS campaign took place in May-August 2020. The IRS campaign achieved a 98.3% coverage in Maka Coulibantang health district and a 99.3% coverage in Koumpentoum health district (based on structures found by spray operators) for an estimated total population protected of 276,503 across the two districts.

Senegal is implementing MDA for LF with ivermectin and albendazole, schistosomiasis with praziquantel, onchocerciasis with ivermectin, and STH with mebendazole or albendazole in selected health districts. Although Tambacounda has also benefited from MDA campaigns for NTD eradication, there are no current plans for ivermectin MDA in Tambacounda District. Nonetheless, input from the NTD program around operational planning, community mobilization, and engaging local community drug distributors will be sought.

Study population

Study participants include all eligible individuals residing in villages eligible for MDA in the Tambacounda Region. Villages selected for randomization will be located in districts of moderate-to-low malaria burden (defined as having an average annual case incidence between 50 to 200 cases per 1000 during the 2016-2019 period) and within the context of an optimized control setting (defined as having had a community-wide distribution of PBO nets and year-round proactive community case management). Further details of the study population, including eligibility criteria of the clusters and individuals within clusters are described below.

Eligibility criteria

334 Study districts, health facility catchment area and villages will be selected from Tambacounda Region
335 according to the following criteria:

336 *District-level:*

- 337 1. District included in implementation zone of annual SMC campaign
- 338 2. Moderate-low burden district (defined as a reported annual case incidence between 50 and
339 200/1000 population, averaged across 2016-2019).
- 340 2. Adequate district-level supervisory capacity and interest/buy-in from health authorities as
341 determined by the NMCP
- 342 3. Moderate population movement as defined by little or no large-scale development or mining
343 activities or cross-border movement
- 344 4. No plans for IRS intervention in the district during the study period

345 *Health Facility Catchment Area-level:*

- 346 1. Health facility catchment area with moderate-to-low burden in their catchment area (defined as
347 reported annual case incidence between 60-160/1,000 population)

348 *Village-level:*

- 349 1. PECADOM+ activities currently instituted or able to be scaled up
- 350 2. Village population size ≥ 200 and ≤ 800
- 351 3. Centroid of village at least 2.5 km from a neighboring study village

352 Upon selection of villages within the study districts, enumeration of all households and all residents will
353 be conducted to obtain a census. In addition, all residents of the selected intervention villages will be
354 screened for MDA eligibility. Eligibility of participants to receive each drug will be assessed
355 independently.

356 Inclusion criteria:

- 357 1. Age ≥ 3 months
- 358 2. Willingness to comply with trial procedures and written informed consent to be obtained at the
359 beginning of the study

360 Exclusion Criteria:

1. Severe illness or self-reported chronic illness (e.g., HIV, tuberculosis, heart/liver/ kidney disease, and severe malnutrition)
2. Known hypersensitivity to study drug

Additional exclusion criteria for DHA-PQP:

1. First trimester pregnancy assessed by history and/or urine pregnancy testing (Will be removed if WHO and national policies have been updated)
2. Concurrent ACT use
3. Taking drugs that influence cardiac function or prolong QTc interval

Additional exclusion criteria for individuals randomized to receive PQ:

1. Pregnancy (any trimester) or currently breastfeeding an infant less than 6 months of age assessed by history and/or urine pregnancy testing
2. < 2 years of age

Sample size calculations

Preliminary modeling as a foundation for hypothesized effect sizes

In order to estimate effect size, models were developed contrasting the effects of MDA against the current standard of care which includes SMC as a drug-based preventive strategy. Preliminary modeling was conducted by Hannah Slater (personal communication) in the Senegalese context. Effect estimates were generated comparing three to four rounds of SMC to three rounds of MDA with DHA-PQP and MDA with DHA-PQP+ivermectin. She concluded the following:

- Compared to three-round SMC, MDA with DHA-PQP alone would have a 53% reduction in clinical incidence in all ages and a 60% reduction in molecular prevalence in all ages after one year of follow-up (Figure 2; comparison of “SMC to under 10s (months 0, 1, 2)” vs. “MDA with DP”).
- The impact of the addition of single, low-dose PQ was not included in this model. Previous modeling showed that single low dose PQ added little to the additional effect of MDA with ACT, though multiple rounds of PQ may enhance the effect and prevent the development of drug resistance [16].

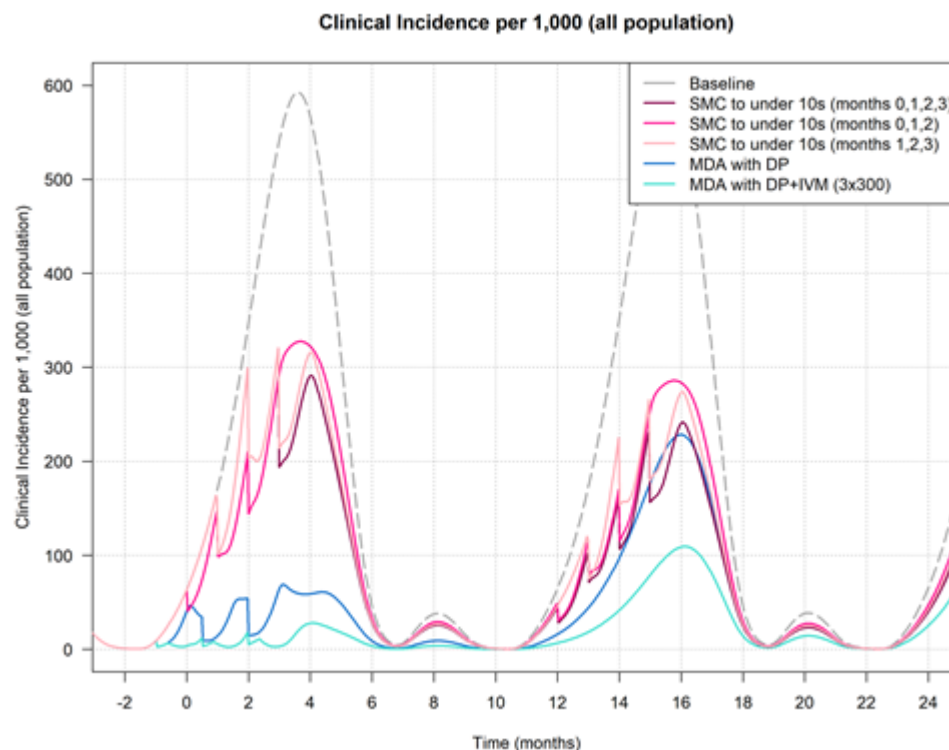


Figure 2. Modeled estimates of clinical incidence per 1,000 in all ages under various SMC and MDA scenarios. Abbreviations: SMC=Seasonal Malaria Chemoprophylaxis; MDA=Mass Drug Administration; DP=Dihydroartemisinin-piperaquine, IVM=Ivermectin

Sample size estimates

The following sample size calculations have been conducted based on the estimated effect sizes generated from Hannah Slater's model. Given budgetary restrictions and limited number of eligible study clusters in Tambacounda, we assumed that only 60 clusters would be available for randomization and the minimal detectable difference were calculated for village-level confirmed malaria incidence (primary outcome) and parasite prevalence by PCR (secondary outcome).

Village-level confirmed malaria incidence (primary outcome)

Sample size calculations were conducted to calculate the minimal detectable difference in cumulative village-level confirmed malaria case incidence between the MDA arm and comparison arm after a one year follow-up period.

Assumptions. For all sample size calculations, we assumed that the distribution of PBO nets, SMC, and proactive case management would decrease malaria incidence by 50% so that in the comparison arm, average cumulative malaria incidence at the end of the study period would be approximately 50 cases per 1000 person-years. Setting the total number of clusters to 60 and an average cluster size of 250 persons, and varying the coefficient of variation (CVs) from 0.1 to 1.0, we estimated the minimal difference we would be able to detect. All calculations were based on 80% power using a two-tailed test with alpha set to 0.05.

Sample size calculation outputs. Based on calculations provided in Table 2, we estimated that with a conservative CV of 0.80, we would have 80% power to detect a 50% relative difference in malaria incidence between the MDA arm and comparison arm.

Table 2. Sample size calculations to estimate the minimal detectable incidence rate ratio in village-level confirmed malaria case incidence based on varied coefficient of variations (CVs). Sample size calculations assumed the following: incidence in comparison arm would be 50 cases per 1000 person-years one year post-intervention, 30 clusters randomized to each arm, 250 person-years observed per cluster, power of 80%, and a two-tailed alpha test.

CV	Minimal detectable IRR	Percent reduction (%): 100*(1-IRR)
0.1	0.79	21%
0.2	0.76	24%
0.3	0.73	27%
0.4	0.68	32%
0.5	0.64	36%
0.6	0.59	41%
0.7	0.55	45%
0.8	0.50	50%
0.9	0.46	54%
1.0	0.41	59%

Note: CV=coefficient of variation; IRR=incidence rate ratio

Molecular parasite prevalence

Additional sample size calculations were performed to calculate the minimum number of persons to sample per cluster in cross sectional surveys to detect differences in molecular parasite prevalence between the MDA arm and comparison arm.

Assumptions. We assumed that by the end of the one-year follow-up post-MDA, parasite prevalence in the comparison arm would be 15% by PCR and 7% in the MDA arm; a relative prevalence ratio of 0.47 (0.07/0.15). We fixed the intra-cluster correlation coefficients (ICC) at 0.10, 30 clusters per arm, 80% power and a two-tailed alpha test.

Sample size calculation outputs. With 30 clusters per arm, an ICC of 0.10, and sampling at least 40 persons per cluster, we would achieve at least 80% power to detect a minimum relative risk ratio of 0.47 (a 53% risk reduction) in parasite prevalence between MDA and comparison arms using a two-tailed test with $\alpha=0.05$. Assuming a median household size of 10 (based on previous household survey data [15]), we would need to sample at least 4 households per cluster, totaling 2,400 persons or approximately 240 households across the 60 villages.

Study procedures

Village selection and randomization

Following selection of the eligible districts based on district-level malaria incidence, supervision capacity and interest of district health officers, health facility level eligibility will be determined based on incidence. Villages from the selected health facility catchment areas will be randomly selected ensuring a 2.5 km buffer zone between each study village. Village leaders and CHWs within villages will be consulted with support from the NMCP to ensure their agreement to participate in the study. Once 60 villages are selected, villages will be assigned to receive either MDA or standard of care (SMC) using constrained randomization (to ensure balance of important prognostic covariates such as distance to health post and village size) and stratified based on whether DSDOMs were present at the time of the baseline survey. Given the small number of clusters ($n=60$), if both constrained and stratified randomization cannot be achieved, constrained randomization will be conducted, taking into account the presence of DSDOMs as an additional covariate requiring balance between arms.

Mapping of study sites and enrollment of participants

Preliminary mapping of the study sites and villages will be performed remotely by using available maps, known GPS locations, satellite images, and OpenStreetMap (OSM) open-source software. Ground

truthing of village mapping will be performed by consulting with local health authorities and in case of discrepancies or doubts about the locations of certain villages, a field staff will collect village GPS coordinates manually. The final map will be used to ensure at least 2.5 km buffer zones between selected villages to prevent contamination of interventions.

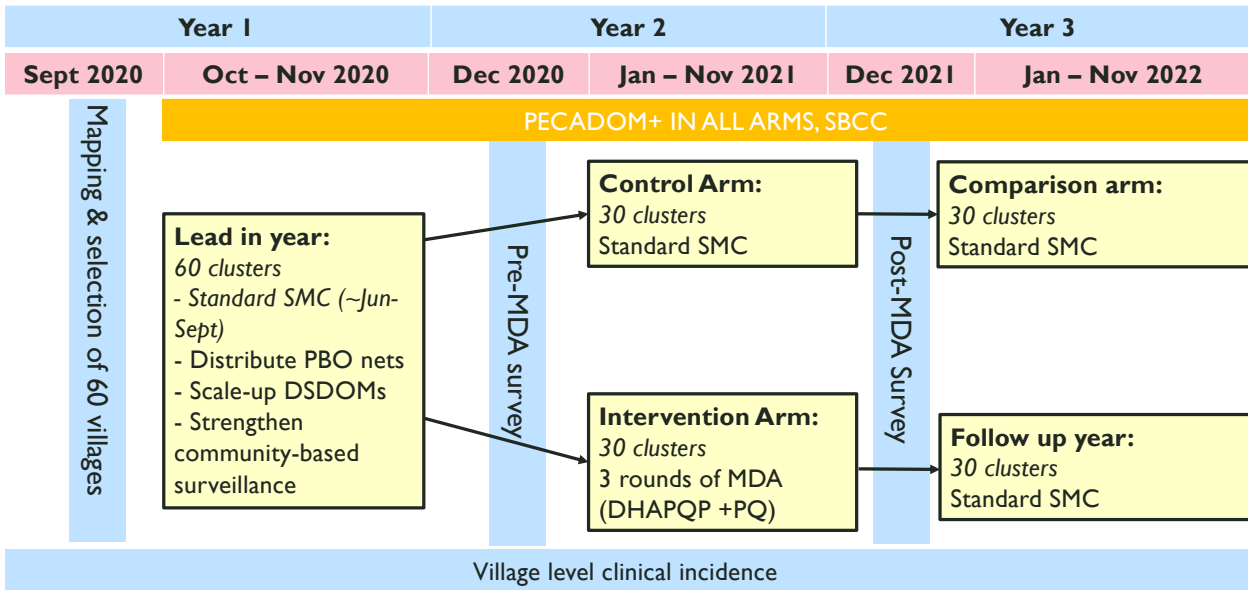
In the selected villages, existing or newly recruited CHWs will receive training to implement proactive community case management procedures year-round and to collect and report the surveillance data on a monthly basis either by paper or smartphone. In addition, they will support the mapping of every building in the enrolled villages. Maps of compounds and a census of the household members within compounds will be generated by field teams with the support of CHWs during PBO net distribution which will occur in October 2020. Individual village maps will be used to enroll all households in the villages for MDA intervention distribution and selection for cross-sectional surveys. All village inhabitants will be enrolled by a field team that will go door to door. Household registration and village inhabitant census will be performed using handheld devices (smartphone or tablet) and data will be entered electronically. A unique study number or scannable QR code will be generated for each participant.

Community mobilization and sensitization

The success of MDA implementation hinges on achieving high coverage. Approaches used successfully in other malaria and NTD MDA campaigns to raise community awareness and encourage participation will be incorporated before and during the campaigns. All community sensitization and mobilization events will be designed and conducted under the leadership of the NMCP and conducted in the selected intervention villages. Key leaders at the district level, including district medical officers, religious leaders and teachers, and at the village-level including the village chief and local CHW will be engaged and their support solicited prior to conducting community sensitization/“town hall” meetings in the villages. Information, education, and communication and behavior change communication (BCC) materials will be developed with the NMCP and BCC partners in the country and pretested in campaign areas in the local language. The community meetings will address the objectives of the MDA intervention to accelerate the community’s transition to elimination activities.

Due to the COVID-19 response, all activities of census, mapping, community mobilization and sensitization, and training will be performed by respecting physical distancing, wearing masks, and physical barriers, where appropriate. Morning health checks will be performed for all fieldworkers and hydroalcoholic gel will be distributed to the research team. Personal protective equipment (e.g. gloves, face shields) will be used where appropriate.

Figure 3. Study Timeline



Intervention

Timeline of interventions is presented above (Figure 3). In year one, three rounds of SMC and optimized control measures will be implemented across the 60 villages enrolled in the study in close coordination with the NMCP.

Optimized control measures will include community-wide distribution of PBO nets and year round proactive community case management will occur in both study arms. PBO nets will be distributed once in all enrolled villages in year one of the study through a community-wide bed net campaign with programmatic assistance from the NMCP and a PMI implementing partner (VectorLink). Proactive community case management will be conducted by CHW(s), whereby each CHW will visit every household within their village catchment area on a weekly basis to test febrile individuals of all ages for malaria by RDT. These services will be expanded from six to eight months as is currently conducted by the NMCP to year-round. CHWs will continue to test all febrile individuals within the household at the time of visit and will treat those with a positive RDT malaria test with AL. If the individual has severe symptoms (of malaria or any other condition), CHW will continue to refer these individuals to a nearby health facility. As part of the current standard intervention packages in the Tambacounda region, SMC with SP-AQ will be administered in three rounds on a monthly basis, from July to September, under the direction of the NMCP. SP-AQ will be given to children between 3 months to 10 years of age.

In year two, the same 60 clusters will be randomly assigned at a 1:1 ratio to one of two arms: optimized control with standard of care SMC or optimized control with the addition of three rounds of MDA with DHA-PQP and PQ for all ages >6 months. Randomization of villages will be computer generated by a UCSF study investigator. MDA will be implemented in three rounds on an approximately monthly basis (4-6 week intervals) initiated before the start of the peak season (no later than the end of June).

Administration of antimalarials

Case management

As per the national malaria treatment guidelines (Annex 2), all suspected cases of malaria (case definition: sick person presenting with a fever) will be tested for malaria by RDT. Confirmed cases will be treated with the first-line antimalarial, artemether-lumefantrine (AL), using age-based dosing as described in the national malaria treatment guidelines. AL is administered twice daily for three days as tablets containing 20 mg of artemether plus 120 mg of lumefantrine in a fixed dose combination. The first dose will be directly observed and subsequent doses will be self-administered or given by the caregiver at home.

Administration of SMC

In year one, children between 3 months to 10 years of age in all 60 villages will receive SMC, as per Senegal's standard of care malaria control policy guidelines, as Tambacounda is a SMC target region. Children will be given SMC at three time points during the rainy season, at monthly intervals, using SP-AQ. The SMC campaign will be implemented by the NMCP as per their routine procedures. As per WHO's recommendation, children with acute clinical malaria at the time of SMC administration will be treated with AL and will not receive SMC drugs during that round but should be included in the next round. In year two, only children between 3 months to 10 years of age allocated to the comparison arm will receive SMC.

Mass drug administration

In villages randomized to receive MDA in year 2, under the coordination of the NMCP, three rounds of MDA (in approximately 4-6 week intervals) will be implemented before the peak transmission (e.g. June-August 2021). All residents in the selected villages will be visited door to door by CHWs accompanied by study team members and offered participation in the study. Written informed consent/assent will be sought from eligible individuals (>6 months of age) as per the inclusion and exclusion criteria.

DHA-PQP will be administered as a 3-day course using age-based dosing according to the manufacturer's instructions and the country's national malaria case management guidelines ([Annex 2](#)). DHA-PQP is a rapidly acting ACT with a relatively long terminal elimination half-life of 20-30 days recommended by WHO for the treatment of uncomplicated malaria [16] and is registered in Senegal. Furthermore, monthly repeated dosing of DHA-PQP is safe, well-tolerated and efficacious for the prevention of malaria [17]. All three doses of DHA-PQP will be directly observed, to be consistent with the NMCP's current guidelines for SMC drug administration.

Single low-dose PQ is part of the national elimination manual for the clearance of gametocytes of *P. falciparum* infection to prevent onward transmission in pre-elimination areas of Senegal [18]. Single low-dose PQ will be given using age-based dosing, directly observed, and administered jointly with the first dose of DHA-PQP.

For participants unable to swallow tablets, such as young children, the tablets may be crushed and mixed in water or juice at the time of administration. If anyone vomits the tablets within 30 minutes of administration, the full dose will be re-administered. If anyone vomits the tablets between 30-60 minutes post administration, half the dose will be re-administered.

All eligible participants will be screened for illness, including fever. As per SMC policy, individuals with any acute illness should not receive MDA drugs during that round and should be referred to the nearest health center or CHW for diagnosis and treatment. Any individual with a fever (temperature $\geq 38.5^{\circ}\text{C}$) will be tested with a malaria RDT and provided AL if positive. Those individuals will not be eligible for DHA-PQP during the current round but should be targeted for inclusion in the following round.

Data Collection

Passive case detection at health facility level

Health facility staff in supporting health facilities will provide the study staff the list of villages they cover and will be asked to record the village in which each patient is resident at each consultation. Health facility data on number of outpatient visits, visits associated with suspected malaria, malaria tests and with positive tests for malaria, as well as all-cause and malaria specific admissions for severe disease will be abstracted monthly by the study team from the registers of primary and referral health facilities supporting the study communities.

PECADOM (Proactive case detection at community level)

Weekly household visits will be conducted year-round by community health workers (CHW). As much as possible, the supervision and monitoring structure for CHWs will reflect the current system which consists of supervision performed weekly by community supervisors, monthly by the head nurse, and quarterly by the district management team. If feasible, all consultations by CHWs in both arms will be recorded using smartphones or tablets to assist in data capture and transmission, including whether the patient was seen in active or passive case detection. Baseline enumeration of households and individuals will provide a patient list in the application so that individuals may be followed through time, with the possibility for the CHW to add to the patient list for births or in-migration, or to document deaths and out-migration. Global Positioning System (GPS) coordinates will be collected by the application for each consultation, and electronic dashboards will be created for supervisors to ensure high quality case management and appropriate implementation of weekly household visits.

Cross sectional surveys

Cross-sectional household surveys will be conducted by the study team with support from the CHWs in December each year before and after MDA implementation. A random sample of households will be taken per study village and all members of the household will be asked to participate. Participants will be asked to provide information about their demographic characteristics, malaria risk factors, access and use of vector control tools including LLINs, history of fever in the last two weeks, care seeking behavior, knowledge and attitudes of malaria, SMC, and MDA using a modified Malaria Indicator Survey questionnaire.

Individuals with fever or history of fever will be tested by RDT and treated with AL if found positive by the study team. All participants will be asked to provide a finger prick blood sample. Drops of blood will be collected for blood smear microscopy and on filter paper as dried blood spots (DBS) for subsequent molecular and serological analysis, including estimating malaria parasite prevalence.

Assessment of adherence/coverage to antimalarials

Adherence to the antimalarials used in SMC (SP-AQ) and/or MDA (DHA-PQP+SLD PQ) will be assessed for each individual participant as per the NMCP's SMC procedures. All three doses of antimalarials used in SMC or MDA will be directly observed; adherence will be assessed and documented by the study team or the CHWs.

Biological sample collection and tests

During the cross-sectional surveys, blood samples will be collected by finger prick for testing of malaria by blood smear microscopy and molecular analysis, and for individuals with fever, by RDT. Approximately 6-7 drops of blood will be collected; less than 2 ml of blood or approximately less than half a teaspoon. For individuals with fever or history of fever in the past 48 hours, one drop of blood will be collected for RDT testing. For samples collected for molecular testing, samples will be collected on filter paper, air dried, and stored with desiccant at room temperature for up to two weeks after which they will be stored at -80°C. In a reference laboratory, the DBSs collected on filter paper will undergo multiplex analysis for detection and quantification of antibodies to a panel of malaria and *Anopheles* antigens, as well as ultrasensitive detection and quantification of parasite antigens. In addition, molecular genotyping of parasite population dynamics and drug resistance markers will be conducted. In order to decrease the number of samples for which molecular analysis must be performed, molecular analysis will be conducted on all samples from individuals positive by RDT during the field survey, samples from RDT-negative individuals positive for parasite antigen detected by multiplex bead based assay, and a randomly selected subset (up to 10%) of samples from RDT-negative individuals also negative for parasite antigen in the bead-based assay. Testing will occur at a reference laboratory in Senegal and potentially another laboratory in the United States.

Nucleic acid extraction and quantitative PCR: DNA will be extracted from the DBS punches. Real-time quantitative PCR for parasite detection will be performed by targeting the 18S small rRNA gene using primer and probe sequences described previously [19]. Blood samples in RNA protect buffers will be used for extraction of RNA for gametocyte quantification.

Serology: In the context of lower transmission, seroprevalence estimates will be determined using LUMINEX based multiplex assays as previously described [20]. Age-specific seroconversion and seroreversion rates over the two years will be used to monitor changes in transmission and malaria and *Anopheles* exposure over time. Absence of antimalarial antibodies, particularly among children, will show the success of the interventions.

Antigen Testing: Testing for pan-Plasmodium antigens aldolase and LDH will determine active infection with malaria parasite, and, if the infecting species is *Pf*, by the presence of HRP2 antigen [21]. Any samples found to be positive for any antigen will have total DNA extracted from DBS samples for malaria-specific PCR reactions.

613 **Additional laboratory work:** Additional molecular work as it relates to malaria to assess parasite
614 diversity and distribution and complexity of multiple-genotype infections, drug resistance markers e.g.
615 K13 and plasmepsin copy number may be conducted. Human genetic testing will be limited to genes
616 directly related to malaria or adverse effects/metabolism of MDA drugs (e.g. hemoglobinopathies and
617 liver cytochrome typing).

618 **Qualitative research**

619 Qualitative research will be used to guide refinement of the interventions during the baseline period and
620 to understand both the implementation process and any positive or negative consequences of the
621 interventions beyond those anticipated and measured quantitatively. During the baseline period, a set of
622 consultation meetings with research team members; health post, district, and regional health workers;
623 union leaders; and community representatives will be held to discuss how best to implement the
624 interventions.

625 During the intervention period, the team will use a range of research methods, including structured
626 observations, in-depth interviews, and focus group discussions with 12 community members and health
627 workers (at health facilities and among CHWs) to explore how the interventions are implemented in
628 practice, the factors enabling and constraining implementation, and perceptions of the interventions and
629 their impact. The following questions will be discussed:

- 630 • How do people perceive this dispensation of medication?
- 631 • What are the perceptions about children's health and their ability to protect them from malaria?
- 632 • How are side effects perceived and how does the project team address these issues with the
633 families?

634 In this process, a team of investigators will monitor the side effects over time from the point of view of
635 intra-structure, community management by asking those around them about the perception of side effects
636 and the way of which she represents the administration campaign. Health care providers will also be
637 interviewed to see their perceptions of the intervention, as well as the way in which they face the
638 communities' perceptions of these side effects. Individual and group interviews will be recorded
639 whenever possible with the consent of participants. They will then be transcribed in French and entered in
640 Word format. The transcripts will be imported into N'Vivo software and analyzed for interpretation.

641 **Costing evaluation**

An economic evaluation will be used to assess the costs, affordability, and cost-effectiveness of the interventions. Incremental financial and economic costs to the health system and to households of each of the intervention components (e.g. enhanced surveillance and control activities, MDA, optimized control with SMC, PBO nets, PECADOM+ and treatment at health facilities and by DSDOM) relative to standard malaria surveillance and control measures in the local area will be assessed through a combination of bottom-up and top-down costing. In accordance with the latest guidelines and building on previous economic work in Senegal, we will examine cost variation and cost functions, and use these to model the likely costs of the interventions outside a trial context and in other relevant geographies and to explore the affordability of these interventions in Senegal. The incremental cost-effectiveness of each intervention strategy will be assessed using a decision-tree model. Both cost per case averted and cost per disability-adjusted life-year (DALY) averted will be assessed. DALY estimates will include and compare both the health benefits from reduced malaria transmission and the harms associated with side effects of drug administration. We will use both deterministic and probabilistic sensitivity analyses to explore the robustness of our findings to assumptions, uncertainty, and heterogeneity in costs and outcomes.

Safety assessment and handling of unexpected incidents

Identifying, managing and reporting adverse events

Adverse events are defined as any undesirable experience occurring during the study whether or not it is considered related to the study procedures. The drugs to be used in the study, AL, SP-AQ, DHA-PQP and PQ have been shown to be safe and efficacious and are part of the national treatment guidelines. The common AEs reported for intervention drugs are as below:

- DHA-PQP: prolonged QT intervals, influenza, cough, fever, abnormal cardiac conduction, leukocytosis, neutropenia, thrombocytopenia, hepatitis and seizure
- PQ: nausea, stomach pain or upset, vomiting, loss of appetite, heartburn, abdominal cramps and hemolysis in G6PD deficient patients.

Pharmacovigilance system

The study will set up an active surveillance system among the study team, CHWs, and health facility staff/supervisors to monitor for adverse events. During SMC and/or MDA implementation, either the CHW or study staff will administer all doses of antimalarials of the 3-day dose regimens of SMC and MDA under direct observation. During this time, the study team and/or CHWs will systematically assess for any immediate adverse events and record these into a standardized AE case report form or serious

672 adverse event (SAE) form if they meet the definition. If a participant experiences an immediate severe
673 adverse event, the study team will transport the participant to a local hospital or health facility depending
674 on the severity of the adverse event.

675 In addition, CHWs will passively monitor their respective communities for AEs and refer any potential
676 SAEs to designated health facilities. CHWs administering the medication will inform participants and
677 caretakers of the potential adverse events of the MDA antimalarials. Health workers at relevant facilities
678 will be informed of the program, potential side effects, and report these AEs in an AE case report
679 form. Cases that cannot be treated at health posts will be referred to hospitals. Any treatment related to
680 secondary effects of MDA will be provided free of charge to the patient, in concordance with current
681 SMC guidelines.

682 For each event the following will be recorded: description of the event, date and time of occurrence,
683 duration, severity, relationship to the intervention, action taken, and outcome. Symptoms will be graded
684 as mild (Grade 1: easily tolerated and do not interfere with usual daily activities), moderate (Grade 2:
685 interferes with or limits usual daily activities), or severe (Grade 3: disabling, unable to perform usual
686 daily activities e.g. requiring bed rest). The investigators will also assess the relationship between the
687 intervention and the occurrence of the AEs or SAEs.

688 The investigators will use clinical judgement incorporating knowledge of the patient's medical history,
689 known common AEs associated with each drug, concomitant therapy, other risk factors, and temporality
690 to determine the relationship. The relationship of the AE or SAE to the study procedures can be classified
691 as probable (evidence to suggest a causal relationship; the influence of other factors is unlikely), possible
692 (some evidence to suggest a causal relationship, but other factors may have contributed to the event) and
693 not related (no evidence of causal relationship).

694 **Emergency care:** In the event of any SAE (death, congenital anomaly or birth defect, life threatening or
695 requiring hospitalization like difficulty breathing, convulsions, and change in mental status), the patient
696 will be referred to the health center or hospital for further management. Transportation to the hospital will
697 be provided by the study.

698 **Reporting AEs/SAEs:** SAEs will be reported to all respective institutional review boards (IRB) and the
699 Data and Safety Monitoring Board (DSMB) according to policies on incident reporting and timelines.

SAEs will be reported to the principal investigator(s) within 24 hours of becoming aware of the event. All SAEs resulting in death or are life-threatening will be reported to the IRB within 7 days. All other SAEs will be reported within 14 days after the principal investigator first becomes aware of the SAE.

All AEs will be reported to an independent DSMB at timepoints agreed upon by the DSMB and at least annually to the IRBs.

Data and Safety Monitoring Board

The study will employ a DSMB to ensure that the ethical and safety interests of all participants in the trial are maintained while protecting, as far as possible, the scientific validity of the data.

DSMB Responsibilities. Responsibilities of the DSMB are to:

1. Review the DSMB Charter supplied by investigators, make any recommendations for changes, and agree and sign the Charter;
2. Agree on the type of information needed for review during the study and the presentation format of those data;
3. Review the protocol, informed consent forms, and plans for data safety and monitoring to ensure that it adequately fulfils the needs for the DSMB data review;
4. Identify and evaluate any emergent safety information;
5. Identify and alert the investigators and sponsors of any emergent ethical issues;
6. Make recommendations to investigators and sponsors concerning the continuation, termination, and/or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study. However, DSMB data evaluations and recommendations should not be limited by those predefined criteria.
7. Communicate and discuss the DSMB findings and recommendations with the investigators and sponsor as appropriate.

Composition of the DSMB and Quorum. The DSMB will consist of at least four independent members (i.e. external to the study team and sponsor). A quorum of three committee members is required at scheduled meetings or at phone conferences, and must reach a consensus recommendation, usually by teleconference (i.e. each member must be able to live with the decision made and must be able to support it). The members will be experts in malaria epidemiology, clinical studies, and biostatistics. Study investigators will approve the composition of the DSMBC and appoint the members. Membership will consist of persons completely independent of the investigators who have no financial, scientific, or other

conflict of interest with the trial. Collaborators at the same institutions as the PIs are not eligible to serve in the DSMB. Written documentation attesting to absence of conflict of interest is required.

A Chairperson will be selected by the principal investigator(s) prior to or at the first meeting, this person will be responsible for overseeing the meetings, developing the agenda and summarizing the meeting. The chair is the contact person for the DSMB.

Conduct of DSMB Meetings

Meeting format. The first meeting will take place prior the initiation of the trial to discuss the protocol and to establish guidelines to monitor the study. The Chair will prepare the agenda to address the commencement of the trial, specific stopping guidelines, number of planned interim analyses, etc.

Meetings will consist of open and closed portions. During the initial open portion of a meeting, the investigators and sponsor will be invited to provide an overview of the study results to date and to be available for questions and discussion that may follow. The investigators and sponsor will not attend closed portions of any meeting, unless agreed by the DSMB chairperson.

Data specific to the primary and secondary endpoints will be summarized for the DSMB to review and will include demographic and other baseline data, any available laboratory results, adverse events, and non-adherence. A teleconference will be scheduled to discuss each of these analyses.

The DSMB also may convene an ad-hoc Advisory Committee should it be deemed necessary for review of specific cases/safety concerns. In this case, the investigators and sponsor must be notified prior to the next scheduled meeting and all ad-hoc members must sign a confidentiality agreement that will be provided by the sponsor prior to the meeting. Ad-hoc members would act as consultants with the particular expertise required by the presenting situation but would not participate in the consensus decision. Ad-hoc members cannot be principal/sub-investigators, nor can they knowingly be involved in the medical care of any study participant.

Given the large number of individuals participating in the study, DSMB agreed that investigators will report serious adverse events and immuno-allergic reactions which occurred during the first 7 days after the first round of MDA in a cumulative safety report. Based on this initial safety report, DSMB members will decide on how investigators should report safety data to DSMB in subsequent rounds of MDA.

Protocol violations will be reported to DSMB within 48 hours of awareness which, in turn, may prompt a

758 meeting of the DSMB. Should the DSMB recommend to temporarily halt the trial or to terminate the
759 study due to safety concerns, full vote of the Committee will be required.

760 *Confidentiality of DSMB.* All materials, discussions and proceedings of the DSMB are completely
761 confidential. Members and other participants in DSMB meetings are expected to maintain
762 confidentiality.

763 **DSMB Reports**

764 *Reports from DSMB.* To monitor safety issues with MDA administration, study investigators will provide
765 a report which will include a summary table of serious adverse events and immuno-allergic reactions
766 which occurred in seven days following the first round of MDA, as recommended by the DSMB.
767 Additional reporting of study results will be determined by the DSMB at regularly scheduled meetings.

768 These reports will be emailed. The contents of these reports are determined by the DSMB in collaboration
769 with the Principal Investigators. Additions and other modifications to these reports may be directed by the
770 DSMB on a one-time or continuing basis. Based on the direction of the DSMB, this report may consist of:

- 771 1. Accrual and other general information on study status,
772 2. Efficacy data based on relevant primary and secondary outcomes,
773 3. Safety data (e.g. adverse events and SAE listings)

774 **Response to unexpected rumors (negative) about the interventions**

775 At any time during the intervention period, if a negative rumor about the intervention is identified,
776 additional community sensitization interventions will be conducted, especially through community
777 meetings in collaboration with the local and central health authorities and village leaders.

778 **Entomological Monitoring**

779 Entomological monitoring will be conducted through the PMI VectorLink project with surveillance sites
780 selected corresponding to the study sites. Four villages will be selected for entomological monitoring
781 (two MDA villages and two villages in comparison arm). Monitoring will involve collection of
782 mosquitoes every 4-6 weeks during the transmission season through human landing catches and
783 pyrethrum spray catches. Mosquitoes will be tested for the presence of circumsporozoite antigens by
784 ELISAs while a subset will be tested to determine the species. In addition, larval mosquitoes will be
785 tested from the same villages, reared to the adult stage and tested in WHO tube tests or CDC bottle

bioassays against pyrethroid insecticides (permethrin, deltamethrin and alphacypermethrin) alone or following a pre-exposure to PBO.

Data management and analysis

Data analysis plan

Descriptive analyses

All analyses will be conducted on an intention-to-treat basis. Descriptive analyses will be conducted by comparing baseline group- and individual-level characteristics between arms and assessing for changes in outcomes pre- and post-intervention periods.

Estimation of intervention effect

Primary outcome

Village-level confirmed malaria case incidence data will be analyzed on an intention-to-treat basis. Monthly counts of village-level confirmed malaria cases will be obtained from PECADOM+ and health facility surveillance systems during the pre- and post-MDA implementation periods. Primary effect estimates (for MDA vs control) will be based on village-level cumulative incidence data over the post-MDA period and will be conducted using a Poisson or negative binomial model with generalized estimating equations (GEE; to account for clustered observations at the village level) with an offset term for village level population. Effect estimates will be presented for both (1) analyses adjusted for village-level covariates included in the constrained/stratified randomization scheme (to improve statistical power and achieve the correct type I error rate [22]) and pre-MDA village-level cumulative incidence for the period when DSDOMs were scaled across all villages, and (2) unadjusted analyses. Secondary analyses will be conducted including additional potentially influential covariates such as weather (rainfall, vegetation, temperature) and vector control coverage (LLIN ownership).

Secondary outcomes

1. Effect of MDA on **parasite prevalence** will be analyzed on an intention-to-treat basis. Parasite prevalence by microscopy, PCR, and seroprevalence will be measured during cross-sectional surveys conducted in December, pre- and post-MDA. The analysis will use GEE log binomial or logistic regression models to estimate the absolute and relative risk differences between MDA and optimized control, accounting for clustered observations at the village-level. Models will include the intervention arm (MDA or control), baseline outcome values, and covariates used for

constrained randomization scheme. If GEE models result in estimation problems (e.g. does not converge), a mixed effects model with random intercepts for each village will be used.

2. Effect of MDA on **parasite diversity and distribution** will be analyzed on an intention-to-treat basis using a GEE Poisson or negative binomial model, accounting for clustered observations at the village level. Models will include the intervention arm (MDA or control), pre-intervention outcome values, and covariates used for constrained randomization scheme. If GEE models result in estimation problems (e.g. does not converge), a mixed effects model with random intercepts for each village will be used.
3. Effect of MDA on **the prevalence of drug resistance markers** between MDA and comparison group will be analyzed on an intention-to-treat basis. Prevalence will be compared between the MDA and comparison arms post-MDA adjusting for baseline outcome values and covariates included in constrained randomization scheme. The analysis will use a GEE logistic or log binomial regression model to estimate the absolute and relative risk reduction between MDA and optimized control accounting for clustered observations at the village level. If GEE models result in estimation problems (e.g. does not converge), a mixed effects model with random intercepts for each village will be used.
4. **Cost, adherence, and adverse events.**
 - a. **Costs of MDA and optimized control** will be collected throughout the study period. The primary outcome will be the calculation of the incremental cost-effectiveness ratio (ICER) comparing the cost-effectiveness of MDA to optimized control.
 - b. **Adherence.** Differences in adherence between participants who received SMC versus MDA, adjusting for age, will be analyzed by comparing the prevalence of participants who were directly observed with completing all three doses of either SP-AQ and/or DHA-PQP+SLD-PQ. Statistical testing will utilize a two-tailed χ^2 -test for prevalence differences between arms.
 - c. **Adverse events.** The number of adverse events, assessed through passive and active surveillance, will be compared between MDA and SMC using a GEE negative binomial model, accounting for clustering at the village level. Significance testing will be conducted using a two-tailed alpha test. If GEE models result in estimation problems (e.g. does not converge), a mixed effects model with random intercepts for each village will be used.
 - d. **Description of the community and community health worker's perception of the desirability, benefits, and challenges around MDA** will be conducted during the cross-sectional surveys using a mixed-methods approach. Questionnaires and/or focus group

discussions will be conducted among a random small subset of participants, CHWs, and/or health facility staff. Analyses for these outcomes will mainly be descriptive, but will use simple statistics (χ^2 -tests, Student t-tests, or Mann-Whitney tests) to evaluate differences between arms, when appropriate. For the qualitative study, transcripts and interview notes will be analyzed by thematic content analysis and coding used to identify key themes. N'Vivo software program or similar will be used to aggregate the data by codes and to assist with the findings.

Subgroup analyses

Exploratory subgroup analyses will be conducted to assess whether intervention effects differed between strata that had a DSDOM present/absent prior to the baseline survey and between groups with higher or lower outcomes at baseline.

Data collection

Study Instruments

Study instruments will include structured electronic forms to capture cases seen by CHWs and/or admitted to health facilities (retrospective register abstraction), and a tool to be used during the cross sectional household surveys which will include demographic and illness data (following the format of the DHS/MIS questionnaire). Prior to data collection, these will be translated into French and local languages (if needed).

Data entry, editing, handling, storage, and disposition

Data collection tools will be pre-programmed with validation and logic checks using electronic data collection software. Data will be stored on password-protected laptops, smartphones or tablets, with restricted access to questionnaires and data by study staff and CHWs only. Systematic routines will be developed to check for data entry discrepancies and range and consistency. All discrepancies will be resolved by reference to the original checked data collection forms. The final data set will be transformed to SAS 9.4 or another suitable software for analysis.

Data collection devices (laptops, tablets, and computers) will be handled only by study staff and CHWs and kept in a secure area when not in use. Device access will be restricted by password protection. Personal identifiers collected for the study purposes will be removed upon the completion of the study and only de-identified databases will be maintained.

878 Storage and handling of specimens

879 As described, multiplex bead assays will be performed for malaria antibody response and antigen
880 detection (Plasmodium antigens such as HRP2, aldolase, pLDH etc). The database for laboratory samples
881 will include only the barcode, study ID number, and date of collection, in addition to the laboratory data.

882 Once the study has closed and this information is no longer needed for follow up, the database will be
883 stripped of names and birthdates, though household GPS coordinates will be retained to permit geospatial
884 analysis. At that point in time, samples will no longer be able to be traced back to the participant, and
885 participants will not be able to request to have their samples removed from storage. Filter paper samples
886 may be shipped to the malaria laboratory at the US Centers for Disease Control and Prevention or their
887 partners, if needed.

888 The samples and the information without identification will be kept secured and may be used for other
889 tests and research in the future from participants consenting for sample storage for future use. Human
890 genetic testing will be limited to genes directly related to malaria and the use of mass drug administration
891 such as the presence of hemoglobinopathies and liver cytochrome typing.

892 Quality control/assurance

893 Site supervisors will check data collection forms routinely for completeness and accuracy of recording.
894 Regular audits of laboratory performance will be completed by experienced supervisors unrelated to the
895 research study according to standard operating procedures. All DBSs will be stored and transported at the
896 recommended temperatures to test for malaria parasites. Assays for molecular testing and multiplex bead-
897 based assays will be done as per the instructions of the manufacturer and will include the use of negative
898 and positive controls.

899 Bias in data collection, measurement, and analysis

900 This study is attempting to measure whether MDA with DHA-PQP+PQ can reduce the incidence of
901 malaria compared to an optimized set of malaria control measures in the community. As the outcome is
902 objective, it is less likely to be subjected to bias related to knowing the intervention allocation. In order to
903 further prevent the introduction of bias, laboratorians will be blinded to the treatment allocation. Other
904 biases in data collection will be minimized by the use of standardized data collection instruments.

905 Limitations of the study

The primary aim of the study will be to examine the effectiveness of MDA on reducing the incidence of malaria in moderate-to-low transmission settings in Senegal. We believe our study is sufficiently powered to detect a 50% reduction in malaria incidence, but may not be sufficiently powered to detect smaller differences in secondary outcomes, including parasite prevalence that may be low in these settings. A second limitation is that intervention assignment will not be blinded to participants, CHWs, or health/research staff involved in study implementation.

Intermediate reviews and analyses

Data will be analyzed following each cross-sectional survey and post-intervention. Unexpected findings will be discussed with an independent trial steering committee who will assist with any decision making related to the study findings. The DSMB will conduct an interim analysis to assess any safety issues with the study.

Dissemination

Initial meetings will be organized with all partners involved in the research under the leadership of the NMCP to explain the nature and scope of the study. A National Steering Committee will be nominated by the NMCP for advising and monitoring the study implementation. The steering committee will include NMCP staff, the local study coordinator, partners and other researchers. The steering committee will be involved from the protocol review, meet regularly for the duration of the study, and guide the dissemination of the results.

A final dissemination workshop will be organized to present and discuss the results to local district and regional health representatives of the Tambacounda Region and a larger audience involving all national and international organizations involved in malaria control and elimination in Senegal and beyond. Abstract(s) submission to international meetings and publication(s) of the results in peer-reviewed journals are planned.

Ethical Considerations

Approval by the National Ethics Committee

The official approval to conduct this study will be obtained by the Comité National d’Ethique pour la Recherche en Santé (Senegal) before the study begins. The study protocol will also be submitted to the University of California San Francisco for human subjects review. CDC investigators who will actively review data and participate in human subjects research will rely on the UCSF IRB.

Risks

There are minimal physical and psychological risks associated with this study. Participants in the MDA arms might experience drug-related adverse events. The participant may experience a brief moment of physical discomfort and/or fear during the blood drawing procedures. There are minimal social risks associated with this protocol as malaria is a widely recognized disease in Senegal. There are minimal economic risks associated with this study. Due to current COVID-19 pandemic, there will be a risk of exposure to COVID-19.

Methods to minimize risk

During blood draw, blood will be collected by trained staff in sterile technique to minimize the risk of infection, which is rare. Finger pricks may be temporarily painful but will resolve quickly. Medical costs incurred due to management of MDA drug adverse events will be covered by the study. **To minimize COVID-19 risk, all staff and study team members will be trained and required to comply with using personal prevention measures (e.g. face masks, gloves, and physical distancing when appropriate) while in the field. Regular fever checks will be conducted for staff and personnel.**

Anticipated benefits

This study will be of direct benefit to some study participants receiving treatment for unknown malaria infection. This study may also be of indirect benefit, as the findings from the study will assist decision-making to control and eliminate malaria in Senegal.

Risk/benefit ratio

This study has minimal risks and major benefit to the majority of included participants.

Vulnerable populations

The possible vulnerable populations in this study include pregnant women and children.

Non English speaking participants

This study must be implemented in areas in which malaria is endemic, therefore, it is unavoidable that participants will be non-English speaking. All study consent forms will be in French. All explanations of study procedures and clinical findings will be carried out in French and/or the local language of the area (Wolof, Pulaar, etc.) by local study staff.

Informed consent/parental permission process/documentation of informed consent

Assignment to the intervention arm will be randomized at the cluster level. Community consent will be sought from the community leaders, and consent for each individual will be obtained at the time of baseline survey for participation in the survey and storage and future analysis of samples. Consent to participate in the MDA intervention will be obtained by local study staff from individuals and/or parents/guardians residing in MDA intervention arms. Informed consent will also be obtained by local study staff from participants in both MDA and control arms to participate in cross-sectional surveys. All information regarding the participants will remain confidential to the extent allowed by law.

Protection of privacy and confidentiality

Privacy of individual

Interviews and interventions will be conducted to maximize privacy, in the household of the individual being treated or interviewed to the extent possible.

Confidentiality of data

All data collection tools will be kept secured at the site of data collection and data password protected with access limited to authorized study staff. Unique numerical identifiers will be used for data and samples obtained from the study participants as stated above. Publications will contain only aggregate data; no identifying information will be included.

Extra costs to participants

Participants will not incur extra costs through their participation in this trial. All examinations, laboratory testing, and medications will be provided to participants free of charge. In the event of any adverse events, the cost of transport and medical treatment will be paid by the study.

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Annex

Annex 1. MDA Medication Dosing Tables

Dihydroartemisinin-piperaquine

1052 Dihydroartemisinin-piperaquine is manufactured by several companies including Sigma-Tau, Italy, and
 1053 Holleykin, China. It is available as tablets of 320/40mg piperaquine/ dihydroartemisinin per tablet. Full
 1054 treatment course is daily dosing for three days.

Weight (kg)	Age	Number of tablets		
		Day 1	Day 2	Day 3
5–9.9	6 mo–1 yr	1/2	1/2	1/2
10–19.9	2–7 yr	1	1	1
20–39.9	8–13 yr	2	2	2
≥40	≥ 14 yr	3	3	3

1055 *Primaquine*

1056 Primaquine is manufactured by several companies including Sanofi and Remedica, Cyprus and is
 1057 available in various strengths e.g. 7.5 mg or 15mg. Its dosing for *P. falciparum* gametocytocidal dosing is
 1058 a single administration given on the first day of ACT administration.

Body Weight (kg)	Age (years)	7.5 mg tablet
8 – 18	6 months to 4 years	½
19 – 24	5 – 7	¾
25 – 35	8 – 10	1
36 – 50	11 – 13	1 ½
50+	14+	2

1059 *Annex 2. National Case Management Guidelines*

1060 *Translated sections relevant to study*

1061 **Uncomplicated malaria**

1062 1. Case definition

1063 Uncomplicated malaria is considered any case of fever without signs of severity and with biological
1064 confirmation by RDT or microscopy.

1065 2. Medications

1066 WHO recommends the use of artemisinin-based drugs to treat uncomplicated cases of *P. falciparum*
1067 malaria. In Senegal, the different ACTs recommended for the treatment of uncomplicated malaria include
1068 the following:

- 1069 - Artemether + Lumefantrine
- 1070 - Artesunate + Amodiaquine
- 1071 - Dihydroartemisinin-Piperaquine

1072 2.1. Artemether Lumefantrine (AL)

1073 2.1.1. Presentation

1074 These products are available in fixed combination in dispersible (pediatric) tablets containing 20mg of
1075 Artemether and 120mg of Lumefantrine. This combination is available in 4 packages based on the
1076 number of tablets:

- 1077 - **Infant** packages with 6 tablets
- 1078 - **Young child** packages with 12 tablets
- 1079 - **Older child** packages with 18 tablets
- 1080 - **Adult** packages with 24 tablets

1081 2.1.2 Dosing

1082 The recommended treatment is 2 doses per day, spaced 12 hours apart, for 3 days. Dosage is based on
1083 weight or age.

- 1084 - Based on weight
 - 1085 o The recommended dose is 4mg/kg for artemether and 12mg/kg for lumefantrine, 2 times a day for 3
 - 1086 days
- 1087 - Based on age
 - 1088 o Dosage based on age group are summarized in the table below:

1089

Age	1 st day	2 nd day	3 rd day
2-11 months	1 tablet x 2/day	1 tablet x 2/day	1 tablet x 2/day
1-5 years	2 tablets x2/day	2 tablets x2/day	2 tablets x2/day

6-13 years	3 tablets x2/day	3 tablets x2/day	3 tablets x2/day
14 years and older	4 tablets x2/day	4 tablets x2/day	4 tablets x2/day

1090 2.1.3 Side effects

Drug	Side effects
Artemether	- Reduction of reticulocytes, and more rarely leucocytes - Nausea, vomiting, abdominal pain - Transient elevation of transaminases - Bradycardia, first degree atrioventricular block
Lumefantrine	- Trouble sleeping, headaches, dizziness - Palpitations - Abdominal pain, anorexia, diarrhea, nausea, vomiting, itchiness - Asthenia

1091 2.2 Artesunate-Amodiaquine (ASAQ)

1092 2.2.1 Presentation

1093 These products are available in fixed doses in breakable tablet form with different dosages:

Presentation	Artesunate	Amodiaquine
3-tablet blister pack	25mg	67.5mg
3-tablet blister pack	50mg	135mg
3 and 6-tablet blister pack	100mg	270mg

1094 2.2.2 Dosing

1095 This drug is administered based on age or weight.

1096 The recommended treatment consists of administering one dose per day at a fixed time for 3 days. The
1097 dose is 4mg/kg/day of artesunate and 10mg/kg/day of Amodiaquine for 3 days.

Weight intervals/appx. age intervals	Dosing/ACT presentation	1 st day	2 nd day	3 rd day
≥ 4.5kg<9kg (2-11 months)	Artesunate-Amodiaquine (FDC) 25mg/67.5mg <i>Blister pack of 3 tablets</i>	1 tablet	1 tablet	1 tablet
≥9kg<18kg (1-5 years)	Artesunate-Amodiaquine (FDC) 50mg/135mg <i>Blister pack of 3 tablets</i>	1 tablet	1 tablet	1 tablet
≥18kg<36kg (6-13 years)	Artesunate-Amodiaquine (FDC) 100mg/270mg <i>Blister pack of 3 tablets</i>	1 tablet	1 tablet	1 tablet
≥36kg (14 years and older)	Artesunate-Amodiaquine (FDC) 100mg/270mg <i>Blister pack of 6 tablets</i>	2 tablets	2 tablets	2 tablets

1098

2.2.3 Side effects

Drug	Side effects
Amodiaquine	- Minor: Pruritus, urticarial, slate pigmentation, nausea, abdominal pain, eye disorders - Major: hepatitis, agranulocytosis (following prolonged use of Amodiaquine)
Artesunate	- Reduction of reticulocytes, and more rarely leucocytes - Nausea, vomiting, abdominal pain

1099 2.3 Dihydroartemisinin-Piperaquine (DP)

1100 2.3.1 Presentation

1101 This medication is available in fixed dosing in tablet form containing 40mg of dihydroartemisinin and
1102 320mg of piperaquine.

1103 2.3.2 Dosing

1104 This drug is administered based on age or weight. The recommended dose is 4mg/kg/day of
 1105 dihydroartemisinin and 18mg/kg/day of piperazine phosphate, administered once per day at a fixed hour
 1106 for 3 days.

1107 For young children, the tablets can be crushed and diluted in a small amount of water. Dosing consists of
 1108 a single daily dose for 3 consecutive days.

1109 Dose based on age and weights as described in the table below:

Weight	Age	1 st day	2 nd day	3 rd day
5-9.9kg	6 months-1 year	½ tablet	½ tablet	½ tablet
10-20kg	2-7 years	1 tablet	1 tablet	1 tablet
20-40kg	8-13 years	2 tablets	2 tablets	2 tablets
≥40kg	≥14 years	3 tablets	3 tablets	3 tablets

1110 2.3.3 Side effects

Drug	Side effects
Dihydroartemisinin- Piperazine phosphate	- Nausea, diarrhea, anorexia - Pruritus, skin rash - Decrease in reticulocytes and slight increase in liver enzymes

1111 *Annex 3. National Seasonal Malaria Chemoprevention Strategy*

1112 1. Definition

1113 Seasonal Malaria Chemoprevention (SMC) consists of the monthly administration of a full treatment of
1114 sulfadoxine-pyrimethamine (SP) + Amodiaquine (AQ) during the high malaria transmission season to
1115 children between 3 and 120 months to prevent malaria.

1116 **2. Objective**

1117 To maintain therapeutic concentrations of effective antimalarial drugs in the blood during the period of
1118 highest malaria risk in order to prevent and treat malaria.

1119 **3. Strategy**

1120 The SMC strategy consists of administering 3 to 4 rounds of SP+AQ at one-month intervals to children
1121 aged 3-120 months in areas of highly seasonal malaria transmission.

1122 In accordance with WHO strategy, the eligibility criteria for SMC zones include:

- 1123 - More than 60% of malaria cases are within a maximum of 4 months of the year
- 1124 - Malaria Incidence rate is over 10% per season among children under 5 years of age
- 1125 - 60% of annual rainfall is in within 3 months of the year
- 1126 - Proven efficacy of SP+AQ (at least 90%)

1127 In Senegal, eligible zones include Kédougou (4 rounds), Kolda, Sédhiou, and Tambacounda (3 rounds),
1128 that meet these criteria.

1129 **4. Benefits of SMC**

- 1130 - Approximate 75% reduction of malaria cases
- 1131 - Approximate 75% reduction of severe malaria cases
- 1132 - Reduction in child mortality by 1 per 1,000
- 1133 - Reduction in incidence of moderate and severe anemia
- 1134 - Well-tolerated with few adverse events

1135 **5. Medications**

1136 The recommended medications for SMC in Senegal include:

- 1137 - Sulfadoxine-Pyrimethamine (SP): 500/25mg/tablet
- 1138 - Amodiaquine (AQ) 150mg/tablet

1139 **6. SMC Indications**

1140 Target populations: Children aged 3-120 months living in areas with high endemicity with most cases and
1141 rainfall concentrated within 3 to 4 months (July-October)

1142 **7. Dosing of SP-AQ for SMC**

1143 SMC is administered according to the dosing below based on 3 defined age groups:

Age groups	Day 1	Day 2	Day 3
3-11 months	½ tablet SP + ½ tablet AQ	½ tablet AQ	½ tablet AQ
12-59 months	1 tablet SP + ½ tablet AQ	1 tablet AQ	1 tablet AQ
5-9 years	1½ tablets SP + 1½ tablets AQ	1½ tablets AQ	1½ tablets AQ

8. Contraindications

- Children who have received one of these drugs or a combination containing SP or AQ within 9 days preceding the campaign.
- Children with a suspected history of allergic reaction after taking sulfonamides or AQ
- Children with acquired immunodeficiency virus, receiving cotrimoxazole as prophylactic treatment against opportunistic infections

9. Side effects

The drugs used for SMC are effective and safe, but can cause side effects that can be minor, moderate, or severe. The severe reactions described in the literature that must be monitored for and investigated include:

- Dermatological reactions: Lyell's or Stevens-Johnson's syndrome
- Hematological manifestations: leukopenia, thrombocytopenia, megaloblastic anemia
- Hepatitis, agranulocytosis (after prolonged use of Amodiaquine)

10. Specific recommendations

- The first dose under directly observed treatment (DOT)
- It is critical to respect the 30-day time limit between treatment rounds
- The treatment rounds are 3 successive days per month for the 3 to 4 eligible months
- It is critical to implement 3 successive treatment rounds (3 months August, September, October) spaced 1 month apart
- For eligible areas where rainfall occurs earlier, the number of rounds can be increased to 4 (starting in July)

Appendix 10. Statistical Analysis Plan

Statistical Design and Power

TRIAL FULL TITLE	Mass drug administration with dihydroartemisinin-piperaquine and primaquine to reduce malaria in a moderate-low transmission setting in Senegal- a cluster randomized controlled trial
ClinicalTrials.gov Identifier:	NCT04864444
VERSION	1.0
VERSION DATE	3 Jan 2022
TRIAL STATISTICIAN	Ari Fogelson Michelle Hsiang Paul Milligan Michelle Roh Xue Wu
TRIAL PRINCIPAL INVESTIGATOR	Jean Louis Ndiaye
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Abbreviations and Definitions

ACT	Artemisinin-Based Combination Therapy
AE	Adverse Event
AL	Artemether-lumefantrine
aIRR	Adjusted Incidence rate ratio
aPR	Adjusted Prevalence ratio
API	Annual Parasite Incidence
CDC	U.S. Centers for Disease Control and Prevention
CHW	Community Health Worker
cRCT	Cluster Randomized controlled trial
CV	Coefficient of Variation
DBS	Dried Blood Spots
DiD	Difference-in-Difference
DHA-PQP	Dihydroartemisinin-Piperaquine
DSMB	Data and Safety Monitoring Board
G6PD	Glucose 6 phosphate dehydrogenase
GIS	Geographic Information System
GPS	Global Positioning System
ICC	Intra-cluster Correlation Coefficient
IRB	Institutional review board
IRR	Incidence rate ratio
LLIN	Long-lasting insecticide treated net
M&E	Monitoring and Evaluation
MDA	Mass drug administration
MOH	Ministry of Health
NMCP	National Malaria Control Program

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PBO	Piperonyl Butoxide
PCA	Principal Component Analysis
PCR	Polymerase Chain Reaction
PQ	Primaquine
PI	Principal Investigator
PMI	U.S. President's Malaria Initiative
RDT	Rapid Diagnostic Test
PR	Prevalence ratio
SAE	Serious adverse event
SES	Socioeconomic status
SMC	Seasonal Malaria Chemoprevention
SP-AQ	Sulfadoxine-Pyrimethamine and Amodiaquine
UCSF	University of California, San Francisco
WHO	WHO World Health Organization

1 Introduction

1.1 Preface

Mass drug administration (MDA) without prior testing has garnered interest as a tool for low transmission settings nearing malaria elimination. But the role of MDA to accelerate toward malaria elimination in moderate transmission settings is less clear. Evidence suggests that while MDA can be successful at rapidly reducing parasite prevalence, once the activity is stopped, there is a strong tendency for malaria to rebound to previous transmission levels especially in higher transmission settings^{1,2}. At the same time, population-wide parasite clearance, in the context of optimized surveillance systems, effective vector control and case management, and limited importation, may lead to sustained reductions in transmission³. An optimized drug regimen may also further improve the effectiveness of MDA. The addition of a transmission blocking drug to a full therapeutic course of a long-acting artemisinin-based combination therapy (ACT) (e.g. DHA-PQP), recent MDA trials have included or will include additional drugs (e.g. primaquine (PQ) for its gametocytocidal activity or ivermectin for its mosquitocidal effects). Ivermectin remains under evaluation for this use, but single low-dose PQ (0.25mg/kg) has been recommended by WHO for areas pursuing elimination without the need for glucose-6-phosphate dehydrogenase (G6PD) testing and has been shown to be safe and decrease gametocyte prevalence and infectivity to mosquitoes⁴.

The overall objective of our study is to evaluate the effectiveness of MDA as a tool to accelerate toward malaria elimination. We propose an open-label cluster randomized controlled trial (CRCT) in the low-moderate transmission setting of Tambacounda Region, Senegal. Villages or clusters will be randomized to control or MDA. The control arm will receive standard of care SMC for children 3 months to 10 years of age. The treatment arm will receive three rounds of MDA with DHA-PQP and low-dose PQ, for all ages 6 months and above. This study will be conducted in an optimized control setting, where there is ongoing proactive community case management and PBO LLINs have been distributed. MDA will be targeted to consenting and eligible villages, at least a 2.5 km buffer zone between neighboring study villages. MDA will be conducted in 3 rounds, with eligibility to be assessed prior to each MDA round. The outcomes will include: village-level confirmed malaria case incidence, parasite prevalence, parasite diversity, prevalence of drug resistance markers, and cost-effectiveness of MDA.

1.2 Purpose of the analyses

Our hypothesis is that compared to standard of care SMC, time-limited MDA with DHA-PQP and single-low dose PQ in the context of optimized control (proactive community case management + PBO nets) interventions can reduce the transmission of *Plasmodium falciparum* malaria in moderate-low transmission settings sufficiently so that the program can reorient to elimination-specific strategies. To test this hypothesis, our aims are to: 1) evaluate the malaria case incidence, 2) determine the parasite prevalence and seroprevalence of malaria infection, 3) determine the cost, coverage, operational feasibility, acceptability, adherence, and adverse events, 4) determine the

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parasite population dynamics and drug resistance, 5) determine the malaria burden, 6) determine the transmission, 7) determine whether reach a target parasite incidence, and 8) monitor the impact of PBO LLIN distribution as well as changes in insecticide resistance .

2 Study Objectives and Endpoints

2.1 Study Objectives

(ICH E8; 8)

Primary Objective

To determine the sustained effect of three rounds of MDA compared to standard of care SMC, when provided in the context of optimized control (proactive community case management + PBO nets), on village-level confirmed malaria case incidence, during a post-MDA period.

Secondary Objectives

To measure the initial effect of MDA compared to standard of care SMC, when provided in the context of optimized control, on village-level confirmed malaria case incidence, during the implementation year.

To determine the effect of MDA compared to standard of care SMC on confirmed malaria case incidence in those <10 and ≥ 10 years, during the implementation year and in a post-MDA period.

To determine the effect of MDA compared to standard of care SMC on *suspected* malaria case incidence evaluated through the routine health facility surveillance systems, in the implementation year and in a post-MDA period.

To determine the effect of MDA compared to standard of care SMC on test positivity rates evaluated through the routine health facility surveillance systems, during the implementation year and in the post-MDA period.

To determine whether MDA compared to standard of care SMC leads to reaching a target parasite incidence (< 5 cases per 1000), during the implementation year and in the post-MDA period.

To determine the effect of MDA compared to standard of care SMC on parasite prevalence, during the implementation year and in the post-MDA period.

To determine the effect of MDA compared to standard of care SMC on serological measures of malaria exposure (sero-prevalence and sero-conversion), during the implementation year and in the post-MDA period.

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To determine the effect of MDA compared to standard of care SMC on the parasite diversity and distribution, during the implementation year and in the post-MDA period.

To determine the effect of MDA compared to standard of care SMC on the prevalence of drug resistance markers (e.g. K13 and plasmeprin copy number), during the implementation year and in the post-MDA period.

To compare the safety of MDA compared standard of care SMC, through monitoring of severe adverse events (SAE), during the implementation year and in the post-MDA period.

To compare the adherence of MDA compared standard of care SMC.

To measure the cost-effectiveness of MDA compared to standard of care SMC.

To assess the acceptability of MDA compared standard of care SMC, by collecting qualitative data on community and health worker perceptions of MDA and SMC, with regards to desirability and risks and benefits.

2.2 Endpoints

(ICH E9; 2.2.2)

3.2.1. Primary Outcome

The primary outcome is malaria defined as fever or a history of fever in the last 48 hours, with a positive Rapid Diagnostic Test. Malaria cases will be those individuals testing positive for malaria through proactive case detection via weekly household screening of individuals with fever by CHWs (PECADOM Plus) and passive case detection of confirmed cases from each village reported either to the CHW or at the health facility.

Health staff are trained to perform RDT only and always in patients with fever or history of fever in last 48 hours. Therefore, the effective case definition will be patients with a positive RDT.

The primary effect measures will be the incidence rate ratio and incidence rate difference between arms, during the post-MDA period

3.2.2. Secondary outcomes and analyses

In secondary analyses, we will compare in incidence between arms during the implementation year, in all age groups combined, and separately in children less than 10 years, and in age groups 10 years or older. We will also compare test positivity rates, and the incidence of suspected cases during the implementation year and in the post-MDA period. Cross-sectional surveys conducted at baseline and post-MDA will be used

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to measure survey secondary outcomes of parasite prevalence, sero-prevalence and sero-conversion rates, complexity of infection, and prevalence of drug resistance markers. Coverage, adverse events, adherence, costs, cost per case averted, and qualitative data regarding acceptability will also be assessed.

Study outcomes and definitions are summarized below in Table 1.

Table 1. Study outcomes

Outcomes	Definition
Village-level malaria case incidence post-implementation (Primary outcome)	Number of individuals testing positive for malaria through proactive case detection via weekly household screening of individuals with fever by CHWs (PECADOM Plus) and passive case detection of confirmed cases from each village reported at the health facility level
Village-level malaria case incidence during initial implementation year	Number of individuals testing positive for malaria through proactive case detection via weekly household screening of individuals with fever by CHWs (PECADOM Plus) and passive case detection of confirmed cases from each village reported at the health facility level
Incidence of suspected cases	Proportion of individuals that are sick person presenting with a fever
Test positivity rates	Proportion of positives among individuals receiving testing by microscopy or RDT in passive and active case detection for fever
Sero-prevalence	Proportion of individuals with seropositivity
Sero-conversion rate	Rate at which the population has converted from seronegative to seropositive
Parasite prevalence	Proportion of individuals with microscopy, antigen-based multiplex assay, and PCR confirmed infection from cross-sectional surveys at the peak/end of the transmission season
Parasite diversity	Expected heterozygosity Complexity of infection Relatedness per Identity by descent methods
Prevalence of drug resistance markers	Proportion of infections with markers of drug resistance
Prevalence of insecticide resistance	Proportion of mosquitos exhibiting insecticide resistance
Cost	Total cost of intervention
Distribution coverage	Coverage of MDA or SMC among eligible population
Adherence	Proportion of individuals completing doses among those in which the first dose is administered
Adverse events	Any undesirable experience occurring during the study whether or not it is considered related to the study procedures
Cost per case averted	Difference in cost between intervention and comparison arms divided by the difference in effect
Description of community and health worker perceptions of the desirability, benefits, and challenges around MDA	Questionnaires and/or focus group discussions will be conducted among a random small subset of participants, CHWs, and/or health facility staff during the MDA implementation period

2.3 General Study Design and Plan

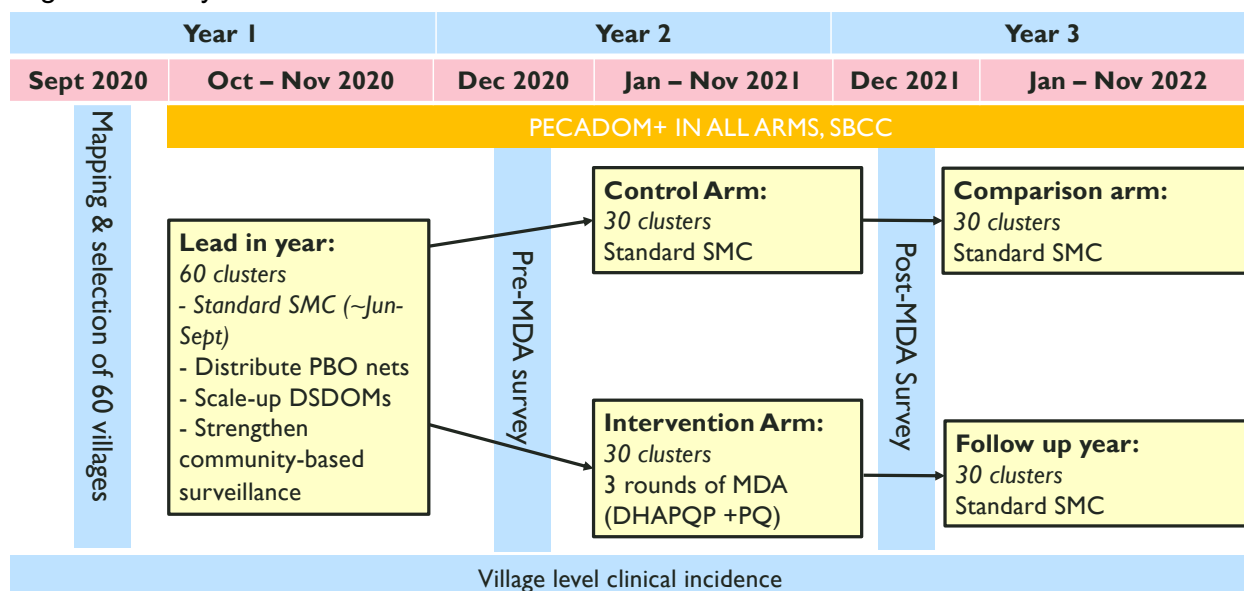
(ICH E3;9)

This study will be a two arm, cluster-randomized controlled trial to determine whether three rounds of MDA with DHA-PQP and PQ is associated with a greater reduction in confirmed malaria clinical incidence compared to standard of care SMC over a one-year follow-up period (Year 3, Figure 1). A preliminary analysis will assess incidence during the implementation period (Year 2). The study will be conducted in an optimized control setting, where there is ongoing proactive community case management (PECADOM+) and PBO nets have been distributed. Villages will be the unit of randomization for the study. Villages will be selected for the study such that there is at least a 2.5 km buffer zone between neighboring study villages, based on

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geographic information system (GIS) data. This buffer zone will limit cross-contamination by malaria vectors or population contamination.

Figure 1. Study Timeline



2.4 Equivalence or Non-Inferiority Studies

(ICH E3; 9.2, 9.7.1, 11.4.2.7. ICH E9; 3.3.2)

N/A - This trial is designed as a superiority trial.

2.5 Inclusion-Exclusion Criteria and General Study Population

(ICH E3;9.3. ICH E9;2.2.1)

Table 2. Inclusion and Exclusion Criteria for receipt of study drugs in the intervention and comparison arm

Inclusion Criteria	Exclusion Criteria
Mass drug administration (MDA) with dihydroartemisinin-piperaquine (DHA-PQP) and primaquine (PQ), and standard of care Seasonal Malaria Chemoprevention (SMC)	
- Age ≥ 3 months old - Willingness to comply with trial procedures and written informed consent to be obtained at the beginning of the study	- Severe illness or self-reported chronic illness (e.g., HIV, tuberculosis, heart/liver/ kidney disease, and severe malnutrition) - Known hypersensitivity or adverse reaction to CQ - Known hypersensitivity to study drug
Addition for Dihydroartemisinin-Piperaquine (DHA-PQP)	
	- Pregnancy (any trimester) by history and/or urine pregnancy testing - Concurrent ACT use - Taking drugs that influence cardiac function or prolong QTc interval
Addition for individuals randomized to receive Primaquine (PQ)	
	- Pregnancy (any trimester) or currently breastfeeding an infant less than 6 months of age assessed by history and/or urine pregnancy testing - < 2 years of age

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All eligible participants to be enrolled into the study must fulfil inclusion criteria listed below (stratified by drug). These will be determined during eligibility screening during each drug administration round. All participants meeting any of the exclusion criteria will be excluded from study participation.

2.6 Randomization and Blinding

(ICH E3; 9.4.3, 9.4.6. ICH E9; 2.3.1, 2.3.2)

There will be 2 study arms:

Control arm:

- standard of care SMC + optimized control (proactive community case management + PBO nets)

Intervention arm:

- three rounds of MDA with DHA-PQP and low-dose PQ + optimized control (proactive community case management + PBO nets)

Based on our sample size calculation (see below), the study will include 60 clusters, in which the target population is ~15000 (mean population ~250 per cluster). Districts within Tambacounda Region that meet the district-level inclusion criteria of low-moderate transmission will be selected. Villages will be randomly selected ensuring a 2.5 km buffer zone between each study village. A total of 60 villages from selected district(s) that meet the village-level inclusion criteria will be randomized using computer-generated randomization to the comparison or intervention arm at a 1:1 ratio. Constrained randomization will be conducted to ensure adequate balance of important covariates that might confound the treatment effect.

Due to the nature of the intervention, study participants, CHWs, or study field staff will not be blinded to the allocation assignment. But, as the outcome is objective, it is less likely to be subjected to bias related to knowing the intervention allocation. In order to further prevent the introduction of bias, laboratorians will be blinded to the treatment allocation. Other biases in data collection will be minimized by the use of standardized data collection instruments. We will internally replicate all analyses to increase reproducibility and reduce confirmation bias.⁵

Table 3a. Study drug information – Rounds 1, 2, 3 (eligible for DHA-PQP)

Weight (kg)	Age	Tablet strength (mg)	Number of tablets		
			Day 1	Day 2	Day 3
5–9.9	6 mo–1 yr	320/40mg base	1/2	1/2	1/2
10–19.9	2–7 yr	320/40mg base	1	1	1
20–39.9	8–13 yr	320/40mg base	2	2	2
≥40	≥ 14 yr	320/40mg base	3	3	3

Table 3b. Study drug information – Rounds 1 (eligible for PQ)

Weight (kg)	Age	Tablet strength (mg)	Number of tablets
			Day 1

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8 – 18	6 mo to 4 yrs	7.5 mg base	½
19 – 24	5 – 7	7.5 mg base	¾
25 – 35	8 – 10	7.5 mg base	1
36 – 50	11 – 13	7.5 mg base	1 ½
50+	14+	7.5 mg base	2

Table 3c. Study drug information – Rounds 1, 2, 3 (eligible for SP-AQ)

Age groups	Tablet strength (mg)	Day 1	Day 2	Day 3
3-11 months	SP: 500/25mg base AQ: 150mg base	½ tablet SP + ½ tablet AQ	½ tablet AQ	½ tablet AQ
12-59 months	SP: 500/25mg base AQ: 150mg base	1 tablet SP + ½ tablet AQ	1 tablet AQ	1 tablet AQ
5-9 years	SP: 500/25mg base AQ: 150mg base	1½ tablets SP + 1½ tablets AQ	1½ tablets AQ	1½ tablets AQ

2.7 Study Variables

(ICH E3; 9.5.1. ICH E9; 2.2.2)

Table 4. Schedule of activities

Study year	1	2				3			
Month	Sept- Nov	Dec- Feb	Mar- May	Jun- Aug	Sept- Nov	Dec- Feb	Mar- May	Jun- Aug	Sept- Nov
Surveys	Mapping, PBO nets	Baseline survey				Endline Survey			
Informed consent for surveys		X				X			
Informed for MDA consent if not previously done				XX	X				
Questionnaire		X				X			
Blood collection by finger prick		X				X			
Control arm SMC administration				X	XX			X	XX
MDA arm MDA administration SMC administration*				XX	X			XX	X
Control arm SMC coverage assessment				X	XX			X	XX
MDA coverage assessment MDA coverage assessment SMC coverage assessment				XX	X			X	XX
Costing data collection						ongoing			
Acceptability assessment				XX	XX			XX	XX
Collect incidence data						ongoing			
Passive monitoring for AEs				XX	X				
Active adverse event monitoring				XX	X				
Prevalence assessment		X				X			
Serologic assessment		X				X			
Genetic diversity assessment		X				X			

*To be determined. MDA may be continued in Year 3 if funding available.

Explanation of participant schedule of events

The primary outcome will be measured throughout the study. Secondary outcomes of prevalence, exposure (serology), and genetic diversity will be measured in an endline survey, though comparisons will also be made to the baseline survey.

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Safety monitoring will be with each MDA round.

Costing data for the economic analysis will be obtained from the program perspective throughout the study, but in a focused effort each April after MDA. Qualitative assessments of acceptability will be assessed with during drug administration campaigns

Table 5. Study Case Report Forms

Survey Eligibility Form
Household Cross-sectional survey Form (baseline, interim, and endline) for control and MDA arms
Individual Survey Form (used for baseline, interim, and endline survey) for control and MDA arms
MDA Eligibility Screening Form
Study Drug Dispensing Form
MDA Day 7 Follow-up Visit Form
AE Form
Severe Malaria form
Hospitalization Admission Form
Subject Death Form
Subject Withdrawal or Study Completion Form

3 Sample Size

(ICH E3; 9.7.2. ICH E9; 3.5)

In order to estimate effect size, preliminary modeling was conducted in the Senegalese context to contrast the effects of MDA against the current standard of care which includes SMC as a drug-based preventive strategy (Figure 2). Based on the estimated effect sizes generated from the preliminary modeling, we assumed that the distribution of PBO nets, SMC, and proactive case management would decrease malaria incidence by 50% so that in the comparison arm, average cumulative malaria incidence at the end of the study period would be approximately 50 cases per 1000 person-years. Setting the total number of clusters to 60 and an average cluster size of 250 persons, and varying the coefficient of variation (CVs) from 0.1 to 1.0, we estimated the minimal difference we would be able to detect. All calculations were based on 80% power using a two-tailed test with alpha set to 0.05. Based on calculations provided in Table 6, we estimated that with a conservative CV of 0.80, we would have 80% power to detect a 50% relative difference in malaria incidence between the MDA arm and comparison arm.

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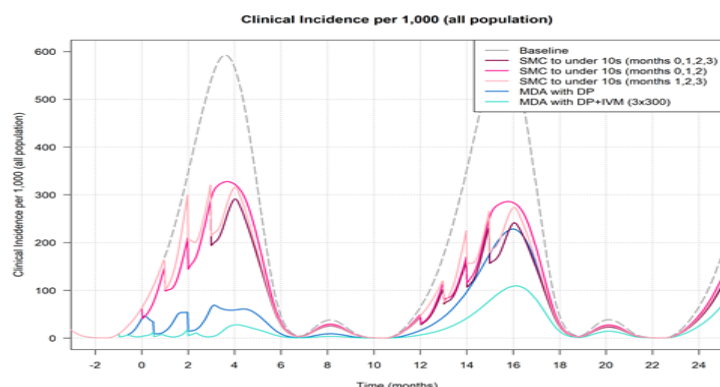


Figure 2. Modeled estimates of clinical incidence per 1,000 in all ages under various SMC and MDA scenarios.

For differences in molecular parasite prevalence between the MDA arm and comparison arm, additional sample size calculations were performed. We

assumed that by the end of the one-year follow-up post-MDA, parasite prevalence in the comparison arm would be 15% by PCR and 7% in the MDA arm; a relative prevalence ratio of 0.47 (0.07/0.15). We fixed the intra-cluster correlation coefficients (ICC) at 0.10, 30 clusters per arm, 80% power and a two-tailed alpha test. With 30 clusters per arm, an ICC of 0.10, and sampling at least 40 persons per cluster, we would achieve at least 80% power to detect a minimum relative risk ratio of 0.47 (a 53% risk reduction) in parasite prevalence between MDA and comparison arms using a two-tailed test with $\alpha=0.05$. Assuming a median household size of 10 (based on previous household survey data ⁶), we would need to sample at least 4 households per cluster, totaling 2,400 persons or approximately 240 households across the 60 villages.

Table 6. Sample size calculations to estimate the minimal detectable incidence rate ratio in village-level confirmed malaria case incidence based on varied coefficient of variations (CVs).

CV	Minimal detectable IRR	Percent reduction (%): $100 \times (1 - \text{IRR})$
0.1	0.79	21%
0.2	0.76	24%
0.3	0.73	27%
0.4	0.68	32%
0.5	0.64	36%
0.6	0.59	41%
0.7	0.55	45%
0.8	0.50	50%
0.9	0.46	54%
1.0	0.41	59%

4 General Considerations

4.1 Timing of Analyses

Data will be analyzed following each cross-sectional survey and post-intervention. An interim analysis of effectiveness will be conducted for Year 1 (Figure 1). Given the large Statistical Design and Power version 1.0: Mass drug administration with dihydroartemisinin-piperaquine and primaquine to reduce malaria in a moderate-low transmission setting in Senegal- a cluster randomized controlled trial

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number of individuals participating in the study, DSMB agreed that investigators will report serious adverse events and immuno-allergic reactions which occurred during the first 7 days after the first round of MDA in a cumulative safety report. Based on this initial safety report, DSMB members will decide on how investigators should report safety data to DSMB in subsequent rounds of MDA. The DSMB will conduct an interim analysis to assess any safety issues with the study. Should the DSMB recommend to temporarily halt the trial or to terminate the study due to safety concerns, full vote of the Committee will be required.

4.2 Analysis Populations

(ICH E3; 9.7.1, 11.4.2.5. ICH E9; 5.2)

An intention-to-treat approach to all analyses will be used, including all randomized clusters where the study intervention occurred and the outcome of interest was measured during the follow-up time. Effect estimates will be presented for both (1) analyses adjusted for village-level covariates included in the constrained/stratified randomization scheme⁷ and pre-MDA village-level cumulative incidence for the period when DSDOMs were scaled across all villages, and (2) unadjusted analyses.

Secondary analyses will be conducted including additional potentially influential covariates such as weather (rainfall, vegetation, temperature) and vector control coverage (LLIN ownership).

4.2.1 Full Analysis Population

- *All clusters that were randomized*
- *All clusters with evaluable data on specific outcomes*

4.2.2 Per Protocol Population

- *No per-protocol analyses are planned*

4.3 Covariates and Subgroups

(ICH E3; 9.7.1, 11.4.2.1. ICH E9; 5.7)

On the cluster level, covariates of interest will include baseline transmission intensity (measured by pre-intervention incidence, infection prevalence, seroprevalence or seroconversion rate, and genetic diversity), coverage of standard interventions, ecological factors, distance to a health facility, distance to the main city, population density, population size.

On the cluster level, sub-group analyses will also be conducted based on categories of baseline transmission intensity, coverage of standard interventions, ecological factors, distance to a health facility, distance to the main city, population density, population size.

4.4 Missing Data

(ICH E3; 9.7.1, 11.4.2.2. ICH E9; 5.3. EMA Guideline on Missing Data in Confirmatory Clinical Trials)

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We will perform a complete-case analysis. Clusters or individual in the trial who prematurely withdraw from the study or are not able to provide data for specific outcomes will be considered un-evaluative and will not be included in the primary trial analysis. At the village level, the most likely reason for withdrawal will be: study fatigue, or adverse event(s). At the individual level, the most likely reasons for withdrawal are participant relocation, study fatigue, or adverse event(s).

Participant relocation is unlikely to result in an imbalance across arms that would bias results. Study fatigue at the village or individual level, could lead to premature withdrawal in the control more than MDA arms if villagers do not see a benefit for their continued involvement. However, due to the enhanced care that control clusters will receive (e.g. malaria testing and treatment in their household if they have fever during subsequent surveys, and likely improvements to standard malaria interventions given the ongoing monitoring and activities), we do not anticipate more withdrawals in the control relative to the MDA arm. Study fatigue could also lead to premature withdrawal in the MDA more than control arm if villagers tire of taking medication with they are not ill. However, from our experience in other MDA trials, the perceived risk of malaria is a motivating factor for participation.⁸ In both arms, ongoing community engagement will also serve to mitigate study fatigue.

4.5 Interim Analyses and Data Monitoring

(ICH E3; 9.7.1, 11.4.2.3. ICH E9; 4.1, FDA Feb 2010 “Guidance for Industry Adaptive Design Clinical Trials for Drugs and Biologics”)

4.5.1 Purpose of Interim Analyses

An interim analysis will be submitted to the DSMB to assess any safety issues with the study. An interim analysis for effectiveness is planned and will include data from Year 2 (Figure 1).

4.5.2 Planned Schedule of Interim Analyses

Given the large number of individuals participating in the study, DSMB agreed that investigators will report serious adverse events and immuno-allergic reactions which occurred during the first 7 days after the first round of MDA in a cumulative safety report. Based on this initial safety report, DSMB members will decide on how investigators should report safety data to DSMB in subsequent rounds of MDA. The DSMB will conduct an interim analysis to assess any safety issues with the study. Should the DSMB recommend to temporarily halt the trial or to terminate the study due to safety concerns, full vote of the Committee will be required. The interim analysis of effectiveness will take place in the early part of Year 3, after incidence data from Year 2 has been collected.

4.5.3 Scope of Adaptations

At the time of any interim analyses, the DSMB may decide to continue, stop, or modify the trial.

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4.5.4 Stopping Rules

The DSMB will determine whether to stop the study for early evidence of intervention safety problems after a thorough review of any submitted interim report and the accompanying meeting with study investigators. The report will provide cumulative enrollment figures and cumulative adverse events (classified according to grade) for the MDA arm, and cumulative episodes of severe malaria for both arms. Brief clinical descriptions of key events will also be provided. The PIs will be responsible for immediately reporting to the funding agency any temporary or permanent suspension of the project and the reason for the suspension.

As an interim analysis for effectiveness or futility is not planned, the trial will not be stopped for futility or achievement of effectiveness. The objective of the study is to evaluate the effect of three rounds of MDA with DHA-PQP and low-dose PQ on village-level confirmed malaria case incidence compared to standard of care SMC when provided in the context of optimized control (proactive community case management + PBO nets), and as such the study is designed to have a 1-year follow-up post-intervention.

4.5.5 Interim Analysis for Sample Size Adjustment

The sample size will not be adjusted based on the results of the interim analysis of safety.

4.5.6 Practical Measures to Minimize Bias

The study will establish and control who will have access to what information at each stage of the trial. Uncontrolled reporting of interim analyses to study investigators responsible for recruiting subjects will not occur.

The following measure will be taken to minimize bias⁵:

- Information will be provided to the sponsor and investigators as per recommendation of the study DSMB.
- Laboratory testing will be blinded.
- We will internally replicate all analyses to increase reproducibility and reduce confirmation bias.
- The analysis will follow the pre-analysis plan, and any deviations from the pre-analysis plan will be clearly labeled in study manuscripts.

4.5.7 Documentation of Interim Analyses

Snapshots of the data available at each interim analysis will be preserved, as will all documentation of analysis plans, programming code and reporting provided at the interim analysis.

4.6 Multi-center Studies

(ICH E3;9.7.1, 11.4.2.4. ICH E9; 3.2)

This is a multi-center study.

4.7 Multiple Testing

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(ICH E3; 9.7.1, 11.4.2.5. ICH E9; 2.2.5)

This study has a primary outcome and multiple secondary outcomes. No formal adjustment of p-values and confidence intervals will be made for the comparison of multiple a priori outcomes.

5 Summary of Study Data

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. All summary tables will be structured with a column for each study arm and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

5.1 Trial Profile

The overall study profile will be presented as a figure following CONSORT guidelines. This profile will include all clusters enrolled. Clusters excluded due to potential lack of intervention implementation or and unmeasured primary outcome will also be shown. On the individual level, the profile will include total estimated population. For the MDA arm, the profile will show people eligible for the study intervention, excluded during screening (including criteria for exclusion), and enrolled. The numbers of villages and people enrolled in each arm and followed through each stage of the trial profile are presented in skeleton Table 7 below.

Table 7. Trial profile

		Arm			
		Control		Intervention	
Clusters					
Enrolled		##		##	
Completed follow-up		##		##	
Individuals					
Total population		####		####	
	MDA Round 1			SMC Round 1	
	Eligible to receive MDA		#	Eligible to receive SMC	#
			(%)		(%)
	Screened		#	Screened	#
			(%)		(%)
	Received MDA		#	Received SMC	#
			(%)		(%)
	Did not receive MDA	#	Did not receive SMC	#	
		(%)		(%)	
	Reason		Reason		
	Absence	#	Absence	#	
		(%)		(%)	
	Refused	#	Refused	#	
		(%)		(%)	
	Illness	#	Illness	#	
		(%)		(%)	
	Pregnancy	#	Pregnancy	#	
		(%)		(%)	

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Other	#	Other	#		
	(%)		(%)		
	#		#		
	(%)		(%)		
	#		#		
	(%)		(%)		
MDA Round 2				SMC Round 2	
Eligible to receive MDA			#	Eligible to receive	#
			(%)	SMC	(%)
Screened			#	Screened	#
			(%)		(%)
Received MDA			#	Received SMC	#
			(%)		(%)
Did not receive	#	Did not receive	#		
MDA	(%)	SMC	(%)		
Reason		Reason			
Absence	#	Absence	#		
Refused	(%)	Refused	(%)		
Illness	#	Illness	#		
Pregnancy	(%)	Pregnancy	(%)		
Other	#	Other	#		
	(%)		(%)		
	#		#		
	(%)		(%)		
	#		#		
	(%)		(%)		
MDA Round 3				SMC Round 3	
Eligible to receive MDA			#	Eligible to receive	#
			(%)	SMC	(%)
Screened			#	Screened	#
			(%)		(%)
Received MDA			#	Received SMC	#
			(%)		(%)
Did not receive	#	Did not receive	#		
MDA	(%)	SMC	(%)		
Reason		Reason			
Absence	#	Absence	#		
Refused	(%)	Refused	(%)		
Illness	#	Illness	#		
Pregnancy	(%)	Pregnancy	(%)		
Other	#	Other	#		
	(%)		(%)		
	#		#		
	(%)		(%)		
	#		#		
	(%)		(%)		

5.2 Baseline Characteristics

Skeleton table of all baseline variables collected on the day of enrollment that will be presented are provided in Tables 8a and 8b below.

Table 8a. Baseline characteristics of clusters randomized

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Characteristic	Control	Intervention
Mean annual incidence in year prior to study (cases/1 000 population)		
Bednet coverage, mean (95% CI)		
Village population size, mean (SE)		
Distance to nearest neighboring study village, meters, mean (SE)		
Distance to nearest health facility, km, mean (SE)		
DSDOMs were present at the time of the baseline survey (yes/no)		
Mean monthly rainfall in year prior to study, mm, median (range)		
Intervention coverage pre-trial		
Bednet coverage (%)		
IRS coverage (%)		
SMC coverage (%)		
Enhanced vegetation index (EVI), median (range)		
Elevation, m, median (range)		
Daytime Land Surface Temperature in year prior to study, °C, median (range)		

Table 8b. Baseline characteristics of study participants randomized

Characteristic	Control	Intervention
Age in years, mean (SD)		
Age category, n (%)		
≤10 years		
>10 years		
Female, n (%)		
Slept away from home in past 15 days, n (%)		
No		
Yes		
Education, n (%)		
Total years of formal schooling by caretaker		
Total years of Koranic schooling by caretaker		
Occupation (for age ≥18 years), n (%)		
Farmer		
Herdsman		
Fisherman		
Shopkeeper/ Retail		
Business		
Nurse		
Childcare		
Domestic Help		
Student		
No Occupation		
Civil Servant		
Other (Specify		
Assistance from outside household		
No		
Yes		
If Yes, how much monthly assistance?, mean (SE)		

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Socioeconomic status (SES)*, n(%)
Low
Average
High
Bednet typically used, n (%)
None or Non-PBO
PBO
Long-lasting insecticide-treated net (LLIN)
Indoor residual spraying (IRS), n (%)
House sprayed in the past year
Not sprayed in the past year
Self-reported receipt of SMC by round in year prior to trial (for age <10 years of age)
SMC in August
SMC in Sept
SMC in Oct
Fever, n (%)
No
Yes
Illness in the last 4 months, n (%)
No
Yes
If Yes, spent overnight in a health facility
No
Yes
Laboratory values
Current or recent infection (antigen testing)
Pan-Plasmodium aldolase, n (%)
LDH, n (%)
HRP2 antigen, n (%)
Infected, n (%)
<i>P. falciparum</i>
<i>P. ovale</i>
<i>P. malariae</i>
<i>P. vivax</i>
Mixed infection
Parasite density among infected, mean (SD)
Recent or past exposure, n (%)
Seropositive
Seronegative
Molecular markers of resistance
K13, n (%)
Plasmepsin copy number, mean (SD)

*To be based on principal component analysis of questions regarding SES

5.3 Treatment Adherence

People in each arm will be given treatment regimens in each round, depending on age and other criteria.

Treatment regimen in intervention arm for MDA Rounds 1, 2, 3:

Single-low-dose PQ +3 day DHA-PQP

Treatment regimen in control arm for Rounds 1, 2, 3:

Single dose SP + 3 day AQ

Each treatment will be given as a single dose per day. All doses of study drugs will be pre-packaged by a study pharmacist and administered by a study personnel. Administration will not be blinded. All doses will be administered by directly observed therapy (**DOT**). If a study participant vomits the study drug within 30 minutes of administration, the drug will be re-administered. If participants report that they will not be present for subsequent doses, they will receive instructions on self-administration. These participants are anticipated to be few. Measures of treatment adherence are summarized in skeleton Table 9 below.

Table 9. Measures of treatment adherence, separate tables will be made for each drug and each MDA/SMC Round

	Control			Intervention		
	1	2	3	1	2	3
At the level of each person receiving at least one dose of study drugs						
At least one dose of study drug held for adverse event	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Missed at least 1 course of study drugs (all doses)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
At the level of each scheduled dose of study drug						
Study drugs (all doses) held for adverse event	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Study drugs (Day #) held for adverse event	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Study drugs (all doses) missed						
Study drugs (Day #) missed						

6 Analyses

6.1 Outcomes

Definitions and criteria used to generate estimates of all primary and secondary outcomes are presented in Table 10 below.

Table 10. Primary and secondary analyses

Outcome	Category	Type of measurement	Timing of measurement	Numerator	Denominator	Missing data	Imputation
Difference in village-level malaria case incidence post-MDA vs baseline (Primary outcome)	Primary analysis	Incidence	Post-MDA period (y3) vs baseline (y1)	Number of confirmed malaria case via weekly household screening by CHWs and reported at the health facility level	Population*	Surveillance records incomplete	None
Difference in village-level malaria case incidence during implementation year vs baseline	Secondary analysis	Incidence	During implementation period (y2) vs baseline (y1)	Number of confirmed malaria case via weekly household screening by CHWs and reported at the health facility level	Population*	Surveillance records incomplete	None

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Difference in village-level malaria case incidence in post-MDA and implementation year vs baseline	Secondary analysis	Incidence	Post-MDA and during implementation period (y2+3) vs baseline (y1)	Number of confirmed malaria case via weekly household screening by CHWs and reported at the health facility level	Population*	Surveillance records incomplete	None
Difference in village-level malaria case incidence by age category	Secondary outcome	Incidence	1. y3 vs y1; 2. y2 vs y1; 3. y2+3 vs y1	Number of confirmed malaria case via weekly household screening by CHWs and reported at the health facility level among age <10 and age ≥10 years	Population among age <10 and age ≥10 years*	Surveillance records incomplete	None
Difference in test positivity rates	Secondary outcome	Proportion	1. y3 vs y1; 2. y2 vs y1; 3. y2+3 vs y1	Number of individuals testing positive by microscopy or RDT in passive and active surveillance	Number of individuals tested by microscopy or RDT in passive and active surveillance	Surveillance records incomplete	None
Difference in incidence of suspected cases	Secondary outcome	Incidence	1. y3 vs y1; 2. y2 vs y1; 3. y2+3 vs y1	Number of individuals who had an RDT performed	Population*	Surveillance records incomplete	None
Difference in parasite prevalence	Secondary outcome	Proportion	Baseline and endline surveys	Number of individuals tested by microscopy, antigen-based multiplex assay, and PCR during cross-sectional surveys	Population tested	No blood sample available	None
Difference in a Plasmodium antigenemia	Secondary outcome	Proportion	Baseline and endline surveys	Number of individuals	Population tested	No blood sample available	None

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				testing positive			
Difference in sero-prevalence rate	Secondary outcome	Proportion	Baseline and endline surveys	Number of individuals with seropositivity	Population tested	No blood sample available	None
Difference in sero-conversion rate	Secondary outcome	Rate	Baseline and endline surveys	calculated from age-stratified prevalence of antibody responses		No blood sample available	None
Difference in parasite diversity	Secondary outcome	Proportion	Baseline and endline surveys	Complexity of infection, Expected heterozygosity, identity by descent	All positive samples	No blood sample available	None
Difference in markers of drug resistance	Secondary outcome	Proportion	Baseline and endline surveys	Number of samples with markers of drug resistance	All positive samples	No blood sample available	None
Difference in cost	Secondary outcome	Incremental cost effectiveness ratio (ICER)	Implementation period (y2)	Total costs	3 different denominators : number of MDA rounds, number of individuals receiving intervention, and	No documentation of expense	None
Difference in distribution coverage (by round)	Secondary outcome	Proportion	With each round of MDA or SMC	Number of individuals receiving first dose of MDA or SMC	Population in MDA or SMC arms that is eligible	Withdrawn or not present prior to timepoint of measurement	None
Difference in distribution coverage (across rounds)	Secondary outcome	Proportion	With all rounds of MDA or SMC	Number of individuals receiving at least first dose of MDA or SMC in 1, 2, or 3 rounds	Population in MDA or SMC arms that is eligible	Withdrawn or not present prior to timepoint of measurement	None
Post-implementation coverage (by round)	Secondary outcome	Proportion	Endline survey	Number of individuals receiving MDA or SMC	Population in MDA or SMC arms that is eligible	Withdrawn or not present prior to timepoint of measurement	None
Post-implementation coverage (across rounds)	Secondary outcome	Proportion	Endline survey	Number of individuals receiving MDA or SMC	Population in MDA or SMC arms that is eligible	Withdrawn or not present prior to timepoint of measurement	None

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Difference in adherence	Secondary outcome	Proportion	On day of last planned dose	Number of individuals that took 1, 2, or 3 doses in a round.	Number of individuals for which the 1 st dose of a round was administered.	Withdrawn or not present prior to timepoint of measurement	None
Complete adherence to study drugs	Secondary outcome	Proportion	On day of last planned dose	Number of courses with any dose missed	Number of total courses started	Withdrawn or not present prior to timepoint of measurement	None
Difference in adverse events	Secondary outcome	Incidence	Ongoing	Number of individuals reported adverse events	Population received SMC or MDA	Withdrawn or not present prior to timepoint of measurement	None
Difference in cost per case averted, per DALY	Secondary outcome	Incremental cost effectiveness ratio (ICER)	Ongoing	Difference in cost between MDA and control arm	Difference in the effect	No documentation of expense	If cost data not available, will impute based market prices or government rates
Description of community and health worker perceptions of the desirability, benefits, and challenges around MDA	Secondary outcome	Qualitative data	Implementation period (Year 2) and in baseline and endline surveys	Interviews and/or focus group discussions will be conducted among study participants, CHWs, an health facility staff		No documentation of questionnaires and/or discussions	None

*For calculations of incidence, 2020 census data will be used for the population denominator for 2020 (year 1), and 2021 census data will be used for the population denominator for 2021 and 2022 (years 2 and 3). Population includes residents that have lived or plan to live in the residence for 6 months.

6.2 Coverage

Per WHO guidelines, coverage will be assessed as distribution coverage and post-implementation coverage.

Village-level SMC (SP-AQ) and/or MDA (DHA-PQP+SLD PQ) distribution coverage will be assessed with each round of drug administration during the implementation year and village-level SMC (SP-AQ) coverage will also be assessed with each round of drug administration during the follow-up year. Population estimates will be based on household census information obtained prior to the trial, and then updated with subsequent visits. For these estimates, an individual is considered covered in a

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particular month if at least one dose of SMC or MDA is administered. Because all doses of antimalarials used in SMC or MDA will be directly observed; coverage regarding proportion of the population that received 1, 2, or 3 doses per round will also be measured.

Post-implementation coverage of SMC or MDA during the implementation year will be assessed in an endline survey that will be administered in a sample. Participants will be asked about number of rounds where they received at least one dose of SMC or MDA. Participants will also be asked about receipt of 1, 2, or 3 doses in the most recent round. Thus, coverage regarding proportion of the population that received 0, 1, 2, or 3 doses in the last round will also be measured.

Table 11. Coverage of SMC or MDA

	SMC n=30	MDA n=30
SMC or MDA (Implementation year)		
Round 1		
Distribution coverage (Percentage receiving at least 1 dose), mean % (95% CI)	## (##-##)	## (##-##)
Percentage receiving at least 2 doses	## (##-##)	## (##-##)
Percentage receiving at least 3 doses	## (##-##)	## (##-##)
Post-implementation coverage (Percentage receiving at least 1 dose), mean % (95% CI)	## (##-##)	## (##-##)
Round 2		
Distribution coverage (Percentage receiving at least 1 dose), mean % (95% CI)	## (##-##)	## (##-##)
Percentage receiving at least 2 doses	## (##-##)	## (##-##)
Percentage receiving at least 3 doses	## (##-##)	## (##-##)
Post-implementation coverage (Percentage receiving at least 1 dose), mean % (95% CI)	## (##-##)	## (##-##)
Round 3		
Distribution coverage (Percentage receiving at least 1 dose), mean % (95% CI)	## (##-##)	## (##-##)
Percentage receiving at least 2 doses	## (##-##)	## (##-##)
Percentage receiving at least 3 doses	## (##-##)	## (##-##)
Post-implementation coverage (Percentage receiving at least 1 dose), mean % (95% CI)	## (##-##)	## (##-##)
Post-implementation coverage (Percentage receiving at least 2 doses), mean % (95% CI)	## (##-##)	## (##-##)
Post-implementation coverage (Percentage receiving at least 3 doses), mean % (95% CI)	## (##-##)	## (##-##)
All rounds		
Distribution coverage (Percentage receiving at least 1 dose in 1 round), mean % (95% CI)	## (##-##)	## (##-##)
Distribution coverage (Percentage receiving at least 1 dose/round in 2 rounds), mean % (95% CI)	## (##-##)	## (##-##)
Distribution coverage (Percentage receiving at least 1 dose/round in 3 rounds), mean % (95% CI)	## (##-##)	## (##-##)

Table 12. Coverage of SMC in Year 3

	SMC n=30	MDA n=30
SMC		
Round 1		
Distribution coverage (Percentage receiving at least 1 dose), mean % (95% CI)	## (##-##)	## (##-##)
Percentage receiving at least 2 doses	## (##-##)	## (##-##)
Percentage receiving at least 3 doses	## (##-##)	## (##-##)
Post-implementation coverage (Percentage receiving at least 1 dose), mean % (95% CI)	## (##-##)	## (##-##)
Round 2		
Distribution coverage (Percentage receiving at least 1 dose), mean % (95% CI)	## (##-##)	## (##-##)
Percentage receiving at least 2 doses	## (##-##)	## (##-##)
Percentage receiving at least 3 doses	## (##-##)	## (##-##)
Post-implementation coverage (Percentage receiving at least 1 dose), mean % (95% CI)	## (##-##)	## (##-##)
Round 3		
Distribution coverage (Percentage receiving at least 1 dose), mean % (95% CI)	## (##-##)	## (##-##)
Percentage receiving at least 2 doses	## (##-##)	## (##-##)
Percentage receiving at least 3 doses	## (##-##)	## (##-##)
Post-implementation coverage (Percentage receiving at least 1 dose), mean % (95% CI)	## (##-##)	## (##-##)
Post-implementation coverage (Percentage receiving at least 2 doses), mean % (95% CI)	## (##-##)	## (##-##)
Post-implementation coverage (Percentage receiving at least 3 doses), mean % (95% CI)	## (##-##)	## (##-##)
All rounds		
Distribution coverage (Percentage receiving at least 1 dose in 1 round), mean % (95% CI)	## (##-##)	## (##-##)
Distribution coverage (Percentage receiving at least 1 dose/round in 2 rounds), mean % (95% CI)	## (##-##)	## (##-##)
Distribution coverage (Percentage receiving at least 1 dose/round in 3 rounds), mean % (95% CI)	## (##-##)	## (##-##)

6.3 Primary Analysis

For the primary outcome of incidence of all confirmed cases reported through passive and active surveillance, we will assess evidence that the intervention arm had lower village-level confirmed malaria incidence than the control arm in the year 3 post-MDA period. For this primary analysis, an intention-to-treat (ITT). We will use Poisson regression with random intercepts for each cluster. Model will include an indicator variable for MDA which is equal to 1 in the intervention villages during the intervention year and 0 otherwise. A second indicator variable will be included for the sustained effect of MDA in year 3, this variable is set to 1 in intervention villages in year 3 and 0 otherwise. The model will also include a variable for study year (1,2,3). Randomisation was stratified by whether there was a DSDOM present in the village at study start. In those villages that did not have a DSDOM at study start a DSDOM was recruited later and all villages had at least one DSDOM by March of year 2. Therefore, the model will include a binary indicator variable equal to 1 during the periods when a DSDOM was present in the village and 0 otherwise.

As an exploratory analysis, a comparison of incidence in intervention versus control arm in year 3 will also be conducted without adjusting for the baseline year.

All effect estimates will be presented for both (1) unadjusted analyses and (2) analyses adjusted for village-level covariates included in the constrained/stratified randomization scheme. Comparisons of incidence measures will also be expressed as the protective efficacy ($PE = 1 - IRR \times 100\%$).

6.4 Secondary analyses of incidence

Secondary analyses of incidence will follow the same approach as described above in the primary analysis. Sub-group analyses will be performed by age group (<10 and 10 and above) and by transmission intensity as defined by prevalence data in the baseline year.

To evaluate subgroup analyses, statistical tests for interaction, to directly examine the strength of evidence for the treatment difference varying between subgroups, will be

Statistical Design and Power: Mass drug administration with dihydroartemisinin-piperaquine and primaquine to reduce malaria in a moderate-low transmission setting in Senegal- a cluster randomized controlled trial conducted¹². Sub-group analyses will also serve to triangulate findings from the main analyses (i.e. if similar effects in subgroup analyses are observed compared to the main analysis).

6.5 Secondary analyses of prevalence

Effect of MDA on parasite prevalence will be analyzed on an ITT basis. Parasite prevalence by microscopy, PCR, and antigenemia will be measured during cross-sectional surveys conducted in December, pre- and post-MDA. The analysis will use GEE log binomial or logistic regression models to estimate the absolute and relative risk ratios between MDA and control, accounting for clustered observations at the village-level. Effect estimates will be presented for both (1) unadjusted analyses and (2) analyses adjusted for baseline covariates used for the constrained randomization scheme. The same approach will be used for the outcomes of test positivity rate and seroprevalence. For the continuous outcome of seroconversion rate, a linear regression model will be used.

Skeleton tables for the presentation of effectiveness outcomes are presented in Tables 13 to 15 below.

Table 13. Effectiveness outcomes for interim analysis

Outcome	Control ^a	Intervention			
	Events ^b	Events ^b	IRR (95% CI)	p-value	aIRR (95% CI) p-value
Village-level confirmed malaria incidence during implementation period	xx (x.xx)	xx (x.xx)			
Incidence in age <10 years	xx (x.xx)	xx (x.xx)			
Incidence in age ≥10 years	xx (x.xx)	xx (x.xx)			
Village-level suspected incidence during implementation period	xx (x.xx)	xx (x.xx)			
Incidence in age <10 years	xx (x.xx)	xx (x.xx)			
Incidence in age ≥10 years	xx (x.xx)	xx (x.xx)			

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	n (%)	n (%)	PR (95% CI)	p-value	aPR (95% CI)	p-value
Test positivity rate						

^a Reference group

^b Number of events (incidence per person year at risk)

Table 14. Effectiveness outcomes for final analysis, measures of incidence

Outcome	Control ^a	Intervention				
	Events ^b	Events ^b	IRR (95% CI)	p-value	aIRR (95% CI)	p-value
Village-level confirmed malaria incidence during implementation period	xx (x.xx)	xx (x.xx)				
Incidence in age <10 years	xx (x.xx)	xx (x.xx)				
Incidence in age ≥10 years	xx (x.xx)	xx (x.xx)				
Village-level suspected incidence during implementation period	xx (x.xx)	xx (x.xx)				
Incidence in age <10 years	xx (x.xx)	xx (x.xx)				
Incidence in age ≥10 years	xx (x.xx)	xx (x.xx)				
	n/N (%)	n/N (%)	PR (95% CI)	p-value	aPR (95% CI)	p-value
Test positivity rate	x/x (%)	x/x (%)				

^a Reference group

^b Number of events (incidence per person year at risk)

Table 15. Effectiveness outcomes for final analysis, measures of Prevalence

Outcome	Control ^a	Intervention				
	Prevalence	Prevalence	PR (95% CI)	p-value	aPR (95% CI)	p-value
Prevalence measures						
Prevalence of infection by microscopy	x/x (%)	x/x (%)				
Prevalence of infection by PCR	x/x (%)	x/x (%)				
Prevalence of antigenemia						
Pan-Plasmodium aldolase	x/x (%)	x/x (%)				
LDH	x/x (%)	x/x (%)				
HRP2 antigen	x/x (%)	x/x (%)				
Pan-Plasmodium antigens aldolase/LDH + HRP2 antigen	x/x (%)	x/x (%)				
Markers of drug resistance	x/x (%)	x/x (%)				
Sero-prevalence	x/x (%)	x/x (%)				

	Rate	Rate	RR (95% CI)	p-value	aRR (95% CI)	p-value
Sero-conversion rate	X.XX	X.XX				

^a Reference group

6.6 Safety

Adverse events are defined as any undesirable experience occurring during the study whether or not it is considered related to the study procedures. The drugs to be used in the study, AL, SP-AQ, DHA-PQP and PQ have been shown to be safe and efficacious and are part of the national treatment guidelines. The common AEs reported for intervention drugs are as below:

- DHA-PQP: prolonged QT intervals, influenza, cough, fever, abnormal cardiac conduction, leukocytosis, neutropenia, thrombocytopenia, hepatitis and seizure
- PQ: nausea, stomach pain or upset, vomiting, loss of appetite, heartburn, abdominal cramps and hemolysis in G6PD deficient patients.

The number of adverse events, assessed through passive and active surveillance, will be compared between MDA and SMC using a GEE negative binomial model, accounting for clustering at the village level. Significance testing will be conducted using a two-tailed alpha test. If GEE models result in estimation problems (e.g. does not converge), a mixed effects model with random intercepts for each village will be used. A skeleton table for the presentation of adverse event outcomes is presented in Table 15 below.

Table 16. Measures of adverse event

Outcome	Control ^b	Intervention		
Prevalence measures	Prevalence	Prevalence	PR (95% CI)	p-value
Adverse event following administration of study drugs ^a				
Observed after administration of 1 st dose	n/N (%)	n/N (%)		
Observed after administration of any 2 nd dose	n/N (%)	n/N (%)		
Observed after administration of any 3 rd dose	n/N (%)	n/N (%)		

Incidence measures	Events ^c	Events ^c	IRR (95% CI)	p-value
Individual adverse events of any severity ^a				
XXXX	xx (x.xx)	xx (x.xx)		
XXXX	xx (x.xx)	xx (x.xx)		
XXXX	xx (x.xx)	xx (x.xx)		
XXXX	xx (x.xx)	xx (x.xx)		
XXXX	xx (x.xx)	xx (x.xx)		
All serious adverse events	xx (x.xx)	xx (x.xx)		
All serious adverse events				
XXXX	xx (x.xx)	xx (x.xx)		
XXXX	xx (x.xx)	xx (x.xx)		

^a Includes any undesirable experience occurring during the study

^b Reference group

^c Number of events (incidence per person year at risk)

6.7 Acceptability

We will gather qualitative data regarding community and community health worker's perception of the desirability, benefits, and challenges around MDA. During the intervention period, the team will use a range of research methods, including structured observations, in-depth interviews, and focus group discussions with 12 community members and health workers (at health facilities and among CHWs) to explore how the interventions are implemented in practice, the factors enabling and constraining implementation, and perceptions of the interventions and their impact. The following questions will be discussed:

- How do people perceive this dispensation of medication?
- What are the perceptions about children's health and their ability to protect them from malaria?
- How are side effects perceived and how does the project team address these issues with the families?

In this process, a team of investigators will monitor the side effects over time from the point of view of intra-structure, community management by asking those around them about the perception of side effects and the way of which she represents the administration campaign. Health care providers will also be interviewed to see their perceptions of the intervention, as well as the way in which they face the communities' perceptions of these side effects. Individual and group interviews will be recorded whenever possible with the consent of participants. They will then be transcribed in

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French and entered in Word format. The transcripts will be imported into N'Vivo software and analyzed for interpretation.

Descriptions will be conducted during the cross-sectional surveys using a mixed-methods approach. Questionnaires and/or focus group discussions will be conducted among a random small subset of participants, CHWs, and/or health facility staff. Analyses for these outcomes will mainly be descriptive, but will use simple statistics (χ^2 -tests, Student t-tests, or Mann-Whitney tests) to evaluate differences between arms, when appropriate. For the qualitative study, transcripts and interview notes will be analyzed by thematic content analysis and coding used to identify key themes. N'Vivo software program or similar will be used to aggregate the data by codes and to assist with the findings.

6.8 Economic Evaluation

Using cost data and outcomes, we will calculate the cost per case averted for intervention and control arms. We will test the hypothesis that MDA is more cost-effective than control. We also test the adherence, adverse events, cost per case averted, and describe community and health worker perceptions of the desirability, benefits, and challenges around MDA.

A cost-effectiveness analysis will be conducted from the program perspective. An economic evaluation will be used to assess the costs, affordability, and cost-effectiveness of the interventions. Incremental financial and economic costs to the health system and to households of each of the intervention components (e.g. enhanced surveillance and control activities, MDA, optimized control with SMC, PBO nets, PECADOM+ and treatment at health facilities and by DSDOM) relative to standard malaria surveillance and control measures in the local area will be assessed through a combination of bottom-up and top-down costing.

Costs of MDA and optimized control will be collected throughout the study period. The primary outcome will be the calculation of the incremental cost-effectiveness ratio (ICER) comparing the cost-effectiveness of MDA to optimized control.

In accordance with the latest guidelines and building on previous economic work in Senegal, we will examine cost variation and cost functions, and use these to model the likely costs of the interventions outside a trial context and in other relevant geographies and to explore the affordability of these interventions in Senegal. The incremental cost-effectiveness of each intervention strategy will be assessed using a decision-tree model. Both cost per case averted and cost per disability-adjusted life-year (DALY)

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averted will be assessed. DALY estimates will include and compare both the health benefits from reduced malaria transmission and the harms associated with side effects of drug administration. We will use both deterministic and probabilistic sensitivity analyses to explore the robustness of our findings to assumptions, uncertainty, and heterogeneity in costs and outcomes.

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