THE LANCET

Supplementary appendix

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

Supplement to: Ochomo Eo, Gimnig JE, Awori Q, et al. Effect of a spatial repellent on malaria incidence in an area of western Kenya characterised by high malaria transmission, insecticide resistance, and universal coverage of insecticide treated nets (part of the AEGIS Consortium): a cluster-randomised, controlled trial. *Lancet* 2024; published online Dec 19. https://doi.org/10.1016/S0140-6736(24)02253-0.

S1. CONSORT Checklist

Reporting checklist for randomised trial.

Based on the CONSORT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the CONSORTreporting guidelines, and cite them as:

Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials

		Reporting Item	Page Number
Title and Abstract			
Title	#1a	Identification as a randomized trial in the title.	1-3
Abstract	#1b	Structured summary of trial design, methods, results, and conclusions	Abstract pgs. 2-3
Introduction			
Background and objectives	#2a	Scientific background and explanation of rationale	Introduction pgs. 3-4
Background and objectives	#2b	Specific objectives or hypothesis	Trial Design pg. 5
Methods			

Trial design	#3a	Description of trial design (such as parallel, factorial) including allocation ratio.	Trial Design pg. 5
Trial design	#3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Randomization and Intervention pg.8
Participants	#4a	Eligibility criteria for participants	Participants pg. 9
Participants	#4b	Settings and locations where the data were collected	Trial Design pg. 5
Interventions	#5	The experimental and control interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Randomization/Intervention pg. 8-9
Outcomes	#6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	Procedures pgs. 10-12 Statistical Analysis pgs. 12-16
Outcomes	#6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a – no changes made
Sample size	#7a	How sample size was determined.	Trial Design pgs. 6-7
Sample size	#7b	When applicable, explanation of any interim analyses and stopping guidelines	Trial Design pg. 6 Statistical Analysis pg. 12
Randomization - Sequence generation	#8a	Method used to generate the random allocation sequence.	Randomization/Intervention pg. 8

Randomization - Sequence generation	#8b	Type of randomization; details of any restriction (such as blocking and block size)	Randomization/Intervention pgs. 8-9
Randomization - 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	Randomization/Intervention pgs. 8-9
Randomization - Implementation	#10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to interventions	Randomization/Intervention pgs. 8-9 Participants pg. 9
Blinding	#11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how.	Randomization/Intervention pg. 8
Blinding	#11b	If relevant, description of the similarity of interventions	Randomization/Intervention pg. 8
Statistical methods	#12a	Statistical methods used to compare groups for primary and secondary outcomes	Methods pg. 5 Statistical Analysis pgs. 11-14
Statistical methods	#12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Methods pg. 4 Statistical Analysis pgs. 12-16

Results

Participant flow diagram (strongly recommended)	#13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	S3 – Supplementary Appendix, Figure 1. CONSORT Diagram Trial Design Pg. 7-8
Participant flow	#13b	For each group, losses and exclusions after randomization, together with reason	S3 – Supplementary Appendix, Figure 1. CONSORT Flow Diagram
Recruitment	#14a	Dates defining the periods of recruitment and follow-up	Figure 1. Timeline Trial Design pg. 7
Recruitment	#14b	Why the trial ended or was stopped	Results pg. 17
Baseline data	#15	A table showing baseline demographic and clinical characteristics for each group	Table 1 Results pg. 16
Numbers analysed	#16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	S3 Supplementary Appendix, Figure 1. CONSORT Diagram Table 2 Results pg. 16
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)	Table 2 Results pgs. 16-19 S3. Supplementary Appendix
Outcomes and estimation	#17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Table 2 Results pgs. 16-19 S3. Supplementary Appendix
Ancillary analyses	#18	Results of any other analyses performed, including subgroup analyses and adjusted analyses,	Results pgs. 19-20 S3. Supplementary Appendix

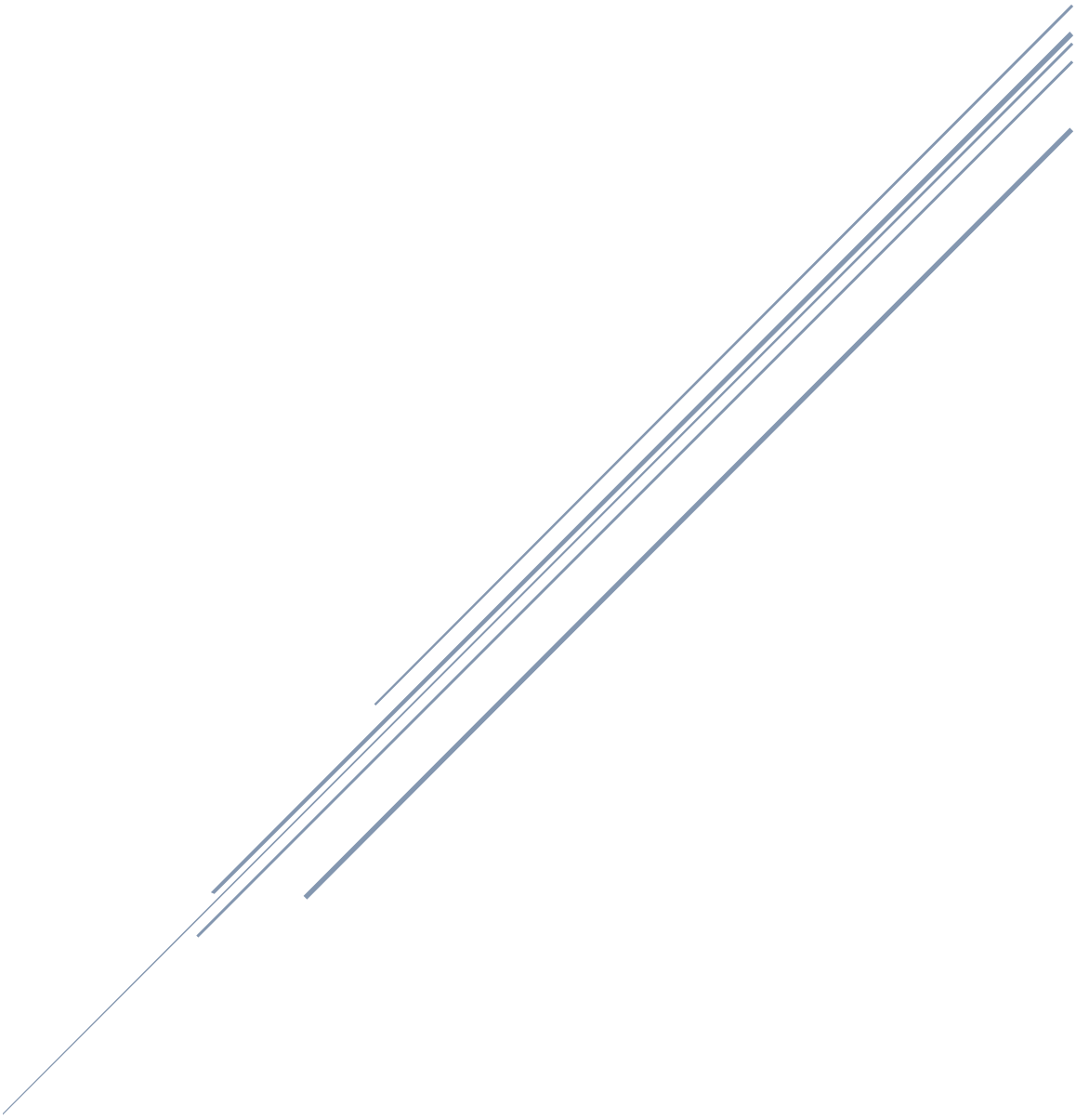
		distinguishing pre-specified from exploratory	
Harms	#19	All important harms or unintended effects in each group (For specific guidance see CONSORT for harms)	Results pgs. 19-20 S5. Supplementary Appendix
Discussion			
Limitations	#20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Discussion pgs.20-22
Generalisability	#21	Generalisability (external validity, applicability) of the trial findings	Discussion pgs. 20-22
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Discussion pgs. 20-22
Registration	#23	Registration number and name of trial registry	Methods pg.5
Other information			
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Discussion pgs. 20-22
Registration	#23	Registration number and name of trial registry	Methods pg.5
Protocol	#24	Where the full trial protocol can be accessed, if available	Methods pg.5 S2. Study Protocol
Funding	#25	Sources of funding and other support (such as supply of drugs), role of funders	Financial Disclosure Statement pgs. 26

None The CONSORT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist can be completed online using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

S2. Study Protocol

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Ochomo EO, Gimnig JE, et al. Effect of a spatial repellent on malaria incidence in an area of western Kenya characterized by high malaria transmission, insecticide resistance and universal coverage of insecticide treated nets: a cluster-randomized, controlled trial



CLINICAL TRIAL PROTOCOL

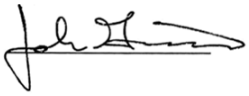
Title: A cluster randomized trial of the efficacy of a spatial repellent on malaria incidence as measured by time to first infection in western Kenya.

Protocol No: 3870

University Notre Dame No.:	**19-08-5506**
Clinical Trials Registration No.:	**NCT04766879**
Brief Title:	Spatial Repellents for the Prevention of Malaria
Protocol Version – Date:	**18 Apr 2022, v9.1**
Sponsor:	University of Notre Dame, Notre Dame, IN 46556
Principal Investigator:	Eric Ochomo, Ph.D.

SIGNATURE PAGE

The clinical trial will be carried out in accordance with the protocol, the NIH Division of Microbiology and Infectious Diseases Good Clinical Practice Resource Guide and in accordance to local legal and regulatory requirements.

Principal Investigator:	**Signature:**	**Date:**
Dr Eric Ochomo		**18 April 2022**
Dr John Grieco		**18 April 2022**

PROTOCOL AMENDMENT(S)

Amendment #	Version	Principal Investigator	Signature	Date
001	3.1	Dr Eric Ochomo		16 Oct 2019
002	5.0	Dr Eric Ochomo		06 Dec 2019
003	6.0	Dr Eric Ochomo		20Jul2020
004	7.0	Dr Eric Ochomo		20Nov2020
005	8.0	Dr Eric Ochomo		01Sep2021
006	9.0	Dr Eric Ochomo		19Oct2021
007	9.1	Dr Eric Ochomo		18Apr2022

Version Control		
Version	**Date**	**Notes**
1.0	**16 April 2019**	**Resubmission to SERU**
2.0	**21 June 2019**	**Resubmission to SERU**
3.0	**19 July 2019**	**Resubmission to SERU**
3.1	**16 October 2019**	**Amendment 1**
4.0	**06 December 2019**	**Amendment 2**
5.0	**05 Feb 2020**	**Resubmission of Amendment 2**
6.0	**20 July 2020**	**Amendment 3**
7.0	**20 November 2020**	**Amendment 4**
8.0	**01 September 2021**	**Amendment 5**
9.0	**19 October 2021**	**Amendment 6**
9.1	**18 April 2022**	**Amendment 7**

Table of Contents

TITLE OF THE PROJECT 11
1. INVESTIGATORS AND INSTITUTIONAL AFFILIATIONS 11
2. LAY SUMMARY 12
3. ABSTRACT 12
4. INTRODUCTION/BACKGROUND 14
5. JUSTIFICATION OF THE STUDY: 14
6. MAIN OBJECTIVE: 14
7. SPECIFIC OBJECTIVES AND HYPOTHESES TO BE TESTED: 15
8. OUTCOME MEASURES 15
9. DESIGN AND METHODOLOGY: 15
(a) Study site and population 15
(b) Cohort Study Inclusion/Exclusion criteria 16
(c) Sample size calculation 17
(d) Data Analysis 19
(e) Procedures 23
10. DATA MANAGEMENT 31
11. TIME FRAME/DURATION OF THE PROJECT 33
12. ETHICAL CONSIDERATIONS 35
13. EXPECTED APPLICATION OF THE RESULTS 40
14. REFERENCES 40
15. BUDGET 41
List of Appendices 46

TITLE OF THE PROJECT

Spatial Repellent Products for Control of Vector Borne Diseases

1. INVESTIGATORS AND INSTITUTIONAL AFFILIATIONS

Principal Investigators (Entomology)

Eric Ochomo[1]
John Gimnig[2]

Principal Investigators (Epidemiology)
Achuyt Bhattarai[2]

Co-investigators:
Aaron Samuels[2]
Simon Kariuki[1]
George Okello[1]
Benard Abong'o[1]
Eunice Ouma[1]
Meghna Desai[2]
Jackline Kosgei[1]
Stephen Munga[1]
William Hawley[2]
Kiambo Njagi[3]
John Grieco[4]
Nicole Achee[4]
Fang Liu[4]
Wycliffe Odongo[2]
Quentin Awori[1]

[1]Kenya Medical Research Institute, Centre for Global Health Research, Kisumu, Kenya
[2]Centers for Disease Control and Prevention, Division of Parasitic Diseases and Malaria, Atlanta, USA
[3]National Malaria Control Program, Ministry of Health, PO Box 19982 Kenyatta National Hospital, Nairobi 00202, Kenya
[4] University of Notre Dame, Notre Dame, IN 46556, USA

2. LAY SUMMARY

Spatial repellents are insecticide treated devices that when placed in a room, make that room non-conducive for mosquitoes. These tools can be used to help in the fight against vector borne diseases such as malaria and dengue. However, their efficacy in reducing mosquito biting and therefore malaria transmission has never been evaluated in Africa. This study will evaluate the efficacy of spatial repellents in reducing mosquito biting of human beings and measure the impact the reduced biting will have on malaria transmission. We will recruit and follow-up 5984 children between 6 months and <10 years of age in Busia County to determine how many times they will be infected with malaria in villages where we will have distributed spatial repellents and compare the rate of infection to villages where we will not

have distributed the repellent devices. Additionally, we will measure whether the distribution of spatial repellents in one village will drive mosquitoes to their neighbouring houses thereby increasing malaria transmission in those areas. The children participating in the study will be divided into 3 groups (cohorts). The first group will be followed up during the first 4 months before any intervention is distributed and the purpose here will be to determine that the villages are comparable. After this, we will recruit the next group of participants and follow them up for 1 year and repeat this again for another year. During the follow-up, the children will be asked to come to the health facility where they will be tested for malaria using RDT or blood slide for microscopy. Every two weeks, a member of the study team will come to their house and ask them if they had any history of fever. If they had fever, they will be tested for malaria. All children who turn out to be positive for malaria by RDT will be treated free of charge. At the same time, we shall also perform mosquito collections to determine the impact of spatial repellents on the density of *Anopheles* mosquitoes.

3. ABSTRACT

Spatial repellents (SRs) have been widely used for the prevention of mosquito bites but their efficacy in reducing mosquito-borne diseases has never been evaluated in Africa. To address this knowledge gap, western Kenya was selected as a site to estimate the impact of the **Mosquito Shield™**, an SR that incorporates transfluthrin on a plastic sheet, on malaria-related outcomes in Busia County, where baseline malaria transmission ranges from 2.5 to 4.1 new infections per person per year. Children between 6 months and <10 years of age will be enrolled into active case detection and active infection detection cohorts for a four-month baseline prior to placement of the SR intervention. After the implementation of the SR, a second cohort of participants will be enrolled and followed for one year. A third cohort of children will be enrolled to provide a total of two years of follow up. A total of 5984 children from 60 clusters (30 intervention and 30 control) will be enrolled in three separate cohorts (baseline, cohort 1 and cohort 2). After baseline, each of cohorts during the intervention will be split into two groups, one to estimate the direct effect of the SR (1624 children in two arms) and a second to estimate the degree of diversion (or mass effect) of mosquitoes and malaria transmission from persons protected by the SR to persons who are unprotected (2320 children in 2 arms). All cohorts will be followed once every two weeks with finger prick blood samples taken once every 4 weeks to test for malaria or whenever a participant reports a recent (within 48 hours) history of fever. The incidence of malaria in the baseline cohort will be used to validate underlying assumptions prior to intervention. The incidence of malaria in each cohort followed with intervention will be estimated and compared to determine the benefit of using an SR in an area with high, year-round transmission of malaria. Monthly collections of mosquitoes using CDC light traps will be conducted to determine if there are entomological correlates of SR efficacy that may be useful for the evaluation of new SR products. Quarterly human landing catches will be done to assess the behavioral effects of the SR.

4. INTRODUCTION/BACKGROUND

Malaria transmission and burden in areas of western Kenya have been reported to be among the highest in the world [1]. Despite intensive scale up of ITNs, effective anti-malarials and IRS in some districts/counties, malaria remains one of the primary causes of morbidity and mortality in the region [1]. After a period of decline, malaria burden has remained stable over

the last few years and may be increasing in some areas.

Spatial repellents (SRs) are a promising new vector control paradigm that could add to the existing armamentarium for malaria prevention [4-7]. SRs are chemicals that reduce human–vector contact by eliciting a range of behaviors in insect vectors, including movement away from a chemical stimulus, interference with host detection, attraction inhibition, and reduced feeding response. Current malaria vector control guidelines recommend the use of repellents for personal protection [8], however, spatial repellents such as mosquito coils have been shown to reduce mosquito biting [9, 10] and, in studies conducted in Indonesia [11] and China [12], reduce malaria transmission in human populations.

Despite their promise as a tool for reducing vector-borne diseases, evidence is required to show the efficacy of SRs across a range of malaria transmission endemicities, a range of mosquito vector species and in the context of high ITN coverage before spatial repellents can be recommended as a tool for malaria prevention by health authorities. In this regard, a first set of phase three efficacy trials have just been concluded in Indonesia (the malaria site) and Peru (the Aedes-borne viruses site) using the Shield® spatial repellent product. The data has been shared with the WHO Vector Control Advisory Group (VCAG) but have not yet been officially released. The current study will evaluate the efficacy of the product, "**Mosquito Shield™®**", which is an improvement of shied and lasts up to 4 weeks as opposed to the Shield® that only lasted 2 weeks (Figure 1).



Figure 1: Picture of a spatial repellent product (shield) hanging on a wall in Indonesia

A non-inferiority study [13] comparing the envelope to the shield was conducted in screen houses at the KEMRI CGHR campus in Kisumu with no significant difference detected in the efficacy of the two products against wild *Anopheles* populations of western Kenya (Unpublished data) Furthermore, given their mode of action, the use of SRs raises concerns over diversion of mosquitoes from persons who are protected by SRs to those who are not. It is therefore essential to demonstrate that deployment of SRs will not result in increased malaria transmission and disease among non-users.

The KEMRI/CDC Research Station is based on collaboration between the Kenya Medical Research Institute (KEMRI) and the US Centers for Disease Control and Prevention (CDC). This collaboration began in 1979, and initially focused on malaria research, but has expanded to include public health research on HIV/AIDS, emerging

infectious diseases, tuberculosis, and program implementation and evaluation for HIV/AIDS prevention and treatment. The KEMRI/CDC Malaria Branch has been involved in large-scale studies evaluating vector control tools including insecticide treated bednets (ITNs) (Phillips-Howard et al. 2003) and indoor residual spraying (IRS) (Hamel et al. 2011b).

In the most recent Malaria Indicator Survey, malaria prevalence among children 6 months to 15 years in the Lake endemic region of western Kenya was 42.4% by rapid diagnostic test (RDT) and 26.7% by microscopy. A recent study conducted in Busia County found the incidence of new infections ranged between 2.5 and 4.1 per person per year. This high malaria burden occurs in the context of high coverage of ITNs with 88.2% of households owning at least one ITN and 68.4% of persons reporting sleeping under a net the previous night (Kenya Malaria Indicator Survey, 2015). Because of the high burden of malaria despite high coverage of ITNs and the history of the KEMRI/CDC in this region, the site was selected to evaluate the efficacy of the **Mosquito Shield™**, a new SR product treated with transfluthrin that is formulated to last up to four weeks for the prevention of malaria. This will be a cluster randomized, placebo-controlled trial, whereby children 6 months to <10 years of age will be enrolled into a cohort and followed to determine time to malaria infection with monthly blood samples for microscopic diagnosis. A cluster randomized design was selected as this was considered the most efficient design for spatial repellents given the potential for contamination at the household level. Furthermore, the study design was aligned with that of a previous trial of spatial repellents to maximize comparability between the different studies. This study will include separate cohorts to measure the direct effect of SRs as well as the potential diversion effect of mosquitoes from users of SRs to non-users of SRs. This evaluation will serve as a proof of principle of SR products for sub-Saharan Africa and will be submitted to the Vector Control Advisory Group of the World Health Organization which will determine whether SRs have "public health value." Entomological outcomes will also be measured as proxies of malaria transmission to help develop guidelines for the evaluation of future SR products.

5. JUSTIFICATION OF THE STUDY:

Despite the scale up of effective tools for the prevention and control of malaria, this disease remains one the primary causes of morbidity and mortality in sub-Saharan Africa. New tools are needed to address the threat of insecticide resistance and outdoor biting vectors and to sustain the drive to elimination. SR products have shown promise as a tool to reduce biting by mosquitoes and the WHO Pesticide Evaluation Scheme (WHOPES) has developed methods to evaluate the efficacy of new SR products. However, proof of principle of SRs as tools to reduce disease burden has only been shown under small-scale study designs in two locations. This study will address the knowledge gap of whether or not SRs can reduce human malaria infections in settings where underlying transmission rates are high at baseline, ITNs are widely deployed and/or where mosquito vectors bite outdoors and will inform the policy makers on whether to recommend SRs as a means to further reduce malaria transmission.

6. MAIN OBJECTIVE:

The primary objective of the study is to demonstrate and quantify the protective efficacy (PE) of the **Mosquito Shield™**, a new SR product treated with transfluthrin, in reducing the incidence of malaria infection in human cohorts.

7. SPECIFIC OBJECTIVES AND HYPOTHESES TO BE TESTED:

Secondary objectives will address key issues related to the optimization and application of SR products for public health and confirm the range of contexts within which SR PE can be achieved. Secondary objectives are:

1. To quantify the total number of infections averted due the spatial repellent intervention by comparing the number of infections per person per year in intervention and control clusters over the 2-year follow-up period.
2. To investigate whether the SR intervention induces diversion of mosquitoes from within the intervention areas to locally unprotected individuals thereby having a differential impact on infection incidence among protected and locally unprotected individuals;
3. To measure the impact of the SR intervention on entomological correlates of transmission (e.g., a reduction in vector densities, mosquito infection, biting and parity rates) to set benchmark thresholds and streamline future intervention trials against other SR products by measuring only those endpoints that are correlated to PE;
4. To assess the impact of SR on mosquito biting behavior by observing the changes in host seeking and biting behavior inside and outside intervention and control households

8. OUTCOME MEASURES

Primary Outcome Measures:

The primary outcome measure of the SR trial will be the time to infection as measured by microscopy in children aged 6 months to <10 years.

Secondary Outcome Measures:

1) Cumulative incidence of infection as measured by microscopy in cohorts of children followed for 12 months.
2) Density of mosquitoes as measured by CDC light traps
3) Sporozoite rate in mosquitoes captured in CDC light traps
4) Biting times and locations of mosquitoes as measured by human landing catches.
5) Parity rates of mosquitoes collected by human landing catches.

9. DESIGN AND METHODOLOGY:

(a) Study site and population

The study will be conducted in Busia County, North West of Kisumu City where the KEMRI Centre for Global Health Research (CGHR) is located. This site has been selected based on the absence of other on-going studies as Kenya has been selected to pilot the RTSS vaccine in 60 clusters across western Kenya.

Busia County has a population of 743,946 which is made up of primarly the Luo, Luhya and Teso ethnic groups. The population of the area identified for this study is predominantly of the Teso ethnic group. The population lives in scattered homesteads and survives primarily as subsistence farmers. There are main transmission seasons which follow rainfall patterns. The long rains occur from late

March to early June and the short rains occur around October/November. However, rainfall may occur in all months of the year and malaria transmission occurs year-round. The primary vectors observed in the area include *An. gambiae* s.s., *An. arabiensis* and *An. funestus* (Ochomo et al 2014, Makokha et al in prep). Incidence of infection was estimated in a study to evaluate the impact of insecticide resistance on malaria transmission, ranged between 2.5 and 4.1 infections per person per year (Ochomo et al 2017).

(b) Cohort Study Inclusion/Exclusion criteria

All children aged 6 months to <10 years who report sleeping in selected study clusters >90% of the nights of each month and do not have any plans to travel outside the study area will be eligible for inclusion in the study. The main reason for including children older than 5 years of age is that LLIN coverage is high among children <5 and generally much lower among children 5-<10. Malaria incidence and prevalence therefore tend to be highest among this age group. This will allow us to assess the impact on different age groups and by inference the added benefit on top of LLINs. Children who have a measured hemoglobin at baseline of <=5 mg/dL and <6 mg/dL who have signs of clinical decompensation will be excluded from the study.

Persons who are participating in another clinical trial investigating a drug, vaccine, medical device or procedure will also be excluded from the study. The study site will be finalized pending selection of clusters for other studies such as the RTSS pilot which is planned for western Kenya. The written consent of the parent or legal guardian of each child is required for inclusion in the study.

The inclusion/exclusion criteria are listed in the table below:

Inclusion Criteria	Exclusion Criteria
Children aged 6 months to <10 years	Children < 6 months or ≥10 years
Hb > 5mg/dl	Hb <= 5 mg/dL, or Hb <6mg/dL with signs of clinical decompensation
Sleeps in cluster >90% of nights during any given month	Sleeps in cluster <90% of nights during any given month
No plans for extended travel (>1month) outside of home during study	Plans for extended travel (>1month) outside of home during study
Not participating in another clinical trial investigating a vaccine, drug, medical device, or a medical procedure during the Trial	Participating or planned participation in another clinical trial investigating a vaccine, drug, medical device, or a medical procedure during the trial
Provision of informed consent form signed by the parent(s) or guardian	No provision of informed consent form signed by the parent(s) or guardian
Children not on regular malaria prophylaxis*** such as Proguanil	Children on regular malaria prophylaxis*** such as Proguanil
Willingness to take AL and no history of hypersensitivity to AL	Unwillingness or refusal to take AL and history of AL hypersensitivity

*** ***Other malaria prophylaxis medicines:*** **Mefloquine, Atavaquone/Proguanil (Malarone), Doxycycline, Tafenoquine, Sulfadoxine-Pyrimethamine (Fansidar), Amodiaquine and Co-trimoxazole (Septrin)**

(c) Sample size calculation

The sample sizes below might be adjusted based on the data collected during the 4- month baseline period. Since the adjustment will only utilize the baseline data (baseline incidence and CV) with intervention information, the Type-I error rate will not be inflated. The detailed Statistical Analysis Plan can be found in Appendix 8.

Primary hypothesis on first-time malaria infection

The sample size determination on the required number of households per cluster for testing the primary hypothesis on PE is based on the hazard rate comparison in the proportional hazards regression model [10, 11]. With the following specifications: 1- sided type-I error rate = 5%, true PE = 30%, a between-cluster coefficient of variance (CV) of hazard rate = 48% (based on the historical data collected from Kenya), one interim analysis for efficacy and non-binding futility with the O'Brien-Fleming error spending function when 50% information is collected, then 1056 independent malaria events will need to be observed to reach 80% power in testing the primary hypothesis on PE.

With a baseline first-time malaria infection hazard rate of 3.0 per person-year (ppy), 29 clusters per treatment, 28 households per cluster are expected to yield 1056 independent first-time malaria events within 24 months follow-up period per cohort post randomization to yield 80% power. If, by the end of the 2-year study, 1056 independent malaria events are not reached, the study may extend until 1063 events are collected without inflating the type I error rate in the testing of the primary hypothesis. Factoring in a loss to follow-up (LTFU) rate at 35%, the required sample size is 28 households per cluster, which will be split in half between the two sequential cohorts with 14 households per cohort per cluster.

Secondary hypothesis on overall malaria infection

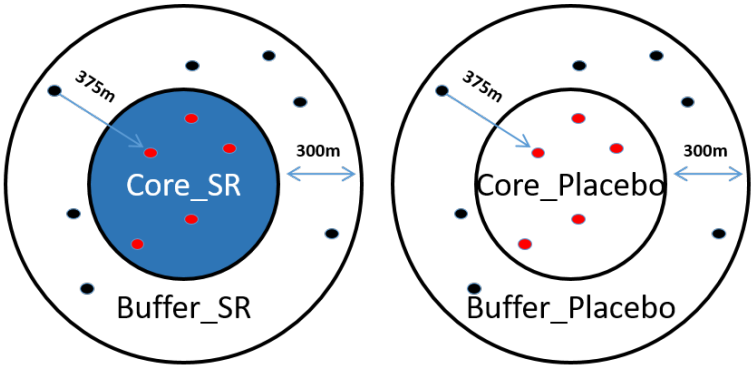
The sample size calculated to yield 80% power for establishing the primary hypothesis on first-time infection PE is expected to leads to 80% power when it comes to the testing of the secondary hypothesis on the overall malaria infection. This is because that the baseline overall malaria incidence rate is likely to be no lower than 3.0 per person-year (the first-time incidence rate) and with a similar CV value; in addition, there is no interim analysis on the second hypothesis.

Quantification of diversion

Since there is no formal hypothesis on the SR-diversion objective, we focus on determining a practical feasible SS that gives a relatively high precision for the estimated PE of SR in the near-zone on the malaria incidence rate. With a 48% between-cluster CV, and a baseline incidence rate of 3.0 per person year, 29 clusters per arm with 30 HHs per cluster lead to a half width of 0.278 for the 95% CI on the log-scale, or the ratio between the upper bound of the 90% CI vs. the point estimate is 1.320 for a hazard ratio estimate between near-SR and near-placebo households. Factoring in a 35% LTFU rate, the required sample size is 40 households in the near zone per cluster. The total households will be split in half between two sequential cohorts, with 20 households per cohort per cluster.

Note: Since the sample sizes for both PE and diversion effect evaluations already factors in the LTFU rate, there is no need for replacement subjects unless the LTFU is larger than assumed. If replacement subjects are to be recruited, they should not have been exposed to the intervention until the time they are considered for replacement.

A summary of the overall study design, including a schematic of the core and buffer zones and the number of households enrolled at each phase are provided in Figure 1.



(1) The protective efficacy of spatial repellents will be estimated by comparing malaria incidence in the core areas of the SR clusters to the core areas of the Placebo clusters.
(2) To estimate the diversion/community effect of SRs, the incidence of malaria will be compared between the buffer areas surrounding the SR clusters and the buffer areas surrounding the Placebo clusters

Baseline Cohort (4-month follow-up + 1-month evaluation)	Intervention Cohorts	
	12 months (Cohort 1)	**12 months (Cohort 2)**
	Core zone (29clusters on SR and 29 clusters on PBO with 28 HHs per cluster	
60 clusters; 20 HHs per cluster	SR (29 clusters; 14 HHs per cluster)	
	PBO (29 clusters; 14 HHs per cluster)	
		SR (29 clusters; 14 HHs per cluster)
		PBO (29 clusters; 14 HHs per cluster)
	Buffer zone (29 clusters on SR and 29 clusters on PBO with 40 HHs per cluster)	
60 clusters; 14 HHs per cluster	SR (29 clusters; 20 HHs per cluster)	
	PBO (29 clusters; 20 HHs per cluster)	
		SR (29 clusters; 20 HHs per cluster)
		PBO (29 clusters; 20 HHs per cluster)

Figure 1. Schematic of cluster organization including core and buffer areas along with a table indicating number of households enrolled during each phase of the study.

In summary, the study will recruit a total of 5,984 participants as follows:

- Baseline: 60 clusters total, followed 4mo
  - from each core zone - 20 subjects (*total, 20 x 60 = 1,200 subjects),
  - from each buffer zone - 14 subjects (*total, 14 x 60 = 840 subjects)
  - giving a total baseline cohort of 2,040 subjects.
- Intervention: 58 clusters total, split into two separate cohorts, each cohort followed 12mo:
  - from each core zone - 14 subjects (*total, 14 x 58 = 812 subjects),

- from each buffer zone - 20 subjects (*total, 20 x 58 = 1160 subjects)
- giving a total of 1,972 subjects per intervention cohort.

(d) Data Analysis

Hypotheses

Primary Hypothesis

H0: SR does not reduce the first-time malaria hazard rate compared to placebo in Kenya. H1: SR reduces the first-time malaria hazard rate compared to placebo (overall malaria hazard ratio between SR and placebo is < 1; the expected hazard ratio is **0.7** or PE is 30%)

Secondary Hypothesis

H0: SR does not reduce the overall malaria hazard rate compared to blank in Kenya. H1: SR reduces the overall malaria hazard rate compared to blank (overall malaria hazard ratio between SR and blank is < 1; the expected hazard ratio is **0.7** or PE is 30%)

Population for analysis

The intention to treat (ITT) analysis is the primary analysis approach for both the primary and secondary objectives. The ITT population includes the first recruited participant from each recruited household that received at least one SR product or placebo according to the cluster randomization schedule. The per-protocol (PP) analysis is included as a supplementary analysis for the primary and secondary objectives. The PP population includes the participants from the ITT population that are treated following the specifications of the study protocol without major protocol deviations.

Statistical Methods

Primary endpoint (ITT Population)

The baseline characteristics of the enrolled subjects, households, and clusters will be summarized by treatment arm. Specifically, we will examine subject age and gender at the individual level; wall type and roof type, the presence of open eaves, # of windows, # of doors at the household levels; and cluster population and baseline overall infection incidence at the cluster level.

The primary hypothesis on PE against the first-time malaria infection will be estimated by comparing the hazard rates of first-time malaria infection between SR and placebo upon the completion of the study in the ITT population. The cloglog regression model $\log(-\log(1-\theta_{kjit})) = \beta_{0t} + \mathbf{x}_{kji}^{t}\boldsymbol{\beta}_1 + z_k + z_{j(k)}$ will be applied [1-4]. θ_{kjit} is the discrete time hazard rate of subject i from household j in cluster k at time t, and $\boldsymbol{x}_{kji}$ contains the individual-level (age, gender), household-level (number of doors, number of windows, open eaves Y or N, wall type, roof type), and cluster-level (baseline incidence rate, cluster population size, intervention group) covariates. If the data are extremely unbalanced in a categorical covariate (e.g., 99% households had the same type of walls) or if a non-ignorable portion of the subjects have missing values on a covariate (due to MAR or MCAR), that covariate maybe may be excluded in the model. $z_k \sim N(0, \sigma_1^2)$ and $z_{j(k)} \sim N(0, \sigma_2^2)$ are the random effects at the cluster and household levels

respectively ($z_{j(k)}$ will be only necessary if some households contribute more than one individuals to the study). The cloglog model is a proportional hazard model and thus HR does not depend on time t. The null hypothesis of PE = 0% is equivalent to $\beta = 0$, which will be tested by the Wald's test $z = \hat{\beta}/s$, where s is the estimated standard error of $\hat{\beta}$. PE is estimated by $(1 - \exp(\hat{\beta})) \times 100\%$, where $\hat{\beta}$ is the estimated regression coefficient associated with the treatment group, and $\exp(\hat{\beta})$ is the estimated hazard ratio (HR) between SR and placebo, with a 90% 2-sided CI based on the Wald test. The lower bound of the 90% CI corresponds to the lower-bound of the 95% 1-sided CI (the hypothesis is one-sided).

Interim analysis: There will be one formal interim analysis to test the primary hypothesis. The interim analysis will decide whether the study will stop for either efficacy or futility using the O'Brien-Fleming error spending function [5-9] in both cases based on the data collected at the time point when 532 events (50% information) are collected. Assuming a baseline incidence rate of 3.0 per person-year and constant average hazard rates for cohort 1 and cohort 2 poster intervention, the interim analysis will occur around the end of the intervention follow-up on Cohort 1 (i.e., the end of Month 12). The decision boundary for futility and efficacy is presented in Figure 2.

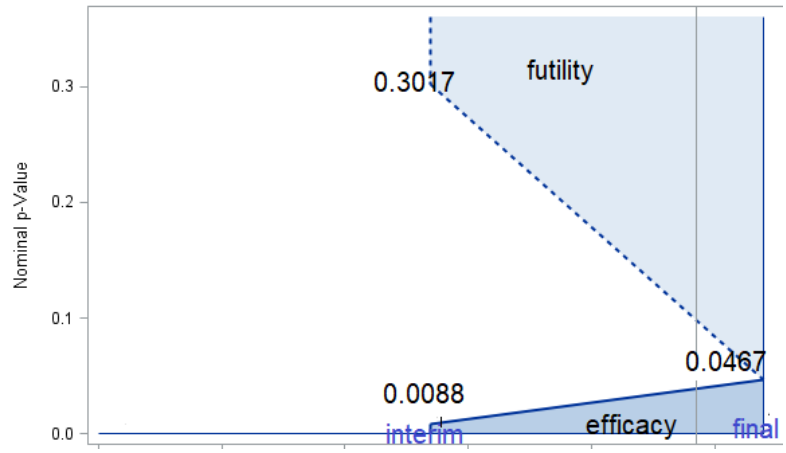


Figure 2: Boundary plot (in p-value) for testing the primary hypothesis on PE (1-sided Type-I error rate α = 0.05, Type-II error rate β = 0.2; between-cluster CV = 47.4%, baseline incidence rate = 3 per person-year; O'Brien-Fleming error spending function)

If the result meets the stopping criterion for futility, that is, the one-sided p-value for the Wald's test on the log(HR) between SR and placebo at the interim is > **0.3017** (see Figure 2), then the study can stop for futility. Since we adopt the non-binding futility boundary, if it is decided the study will continue due to other considerations even if we cross the futility boundary at the interim look, there will be no inflation of type I error. In other words, the trial does not need to stop to accept the null hypothesis when the test statistic falls in the futility region at the interim stage. If the one-sided p-value < 0.00882, then the study can stop for efficacy; otherwise, the study will proceed.

However, if it is decided the study will continue due to other considerations even if we cross the efficacy boundary at the interim look, there will be no inflation of type I error, as efficacy is already established at the interim.

If the one-sided p-value at the interim is > 0.00882 but < **0.3017**, then the study will continue. At the final look, if the one-sided p-value from the Wald's test on the log(HR) between SR

and blank < **0.0467**, we reject the null hypothesis, claiming SR reduces the malaria hazard rate compared to blank in Kenya at the significance level of 5%; otherwise, we fail to reject the null hypothesis, claiming SR does not reduce the malaria hazard rate compared to blank in Kenya.

Secondary endpoints

No interim analysis will be performed on any of the secondary endpoints listed below.

PE and diversion effect of SR protection again the first-time malaria infection

The secondary hypothesis on PE against the overall new malaria infections, as defined in Sec 6, will be tested by comparing the hazard rates of the overall malaria infection between SR and placebo in the ITT population. The complementary log-log (cloglog) regression model $\log(-\log(1-\theta_{kjit})) = \beta_{0t} + \mathbf{x}_{kji}^{t}\boldsymbol{\beta}_1 + z_k + z_{j(k)} + z_{i(jk)}$ will be applied [1-4]. θ_{kjit} is the discrete time hazard rate of subject i from household j in cluster k at time t, and $\boldsymbol{x}_{kji}$ contains the individual-level (age, gender), household-level (number of doors, number of windows, open eaves Y or N, wall type, roof type), and cluster-level (baseline incidence rate, cluster population size, intervention group) covariates. If the data are extremely unbalanced in a categorical covariate (e.g., 99% households had the same type of walls vs 1% that did not) or if an non-ignorable portion of the subjects have missing values on a covariate (due to MAR or MCAR), that covariate maybe may be excluded in the model. $z_k \sim N(0, \sigma_1^2)$, $z_{j(k)} \sim N(0, \sigma_2^2)$, and $z_{i(jk)} \sim N(0, \sigma_3^2)$ are the random effects at the cluster, household, and individual levels respectively ($z_{j(k)}$ will be only necessary if some households contribute more than one individuals to the study). The cloglog model is a proportional hazard model and thus HR does not depend on time t. The null hypothesis of PE = 0% is equivalent to $\beta = 0$, which will be tested by the Wald's test $z = \hat{\beta}/s$, where s is the estimated standard error of $\hat{\beta}$. A one-sided p-value and 90% 2-sided confidence interval (CI) for PE will be provided, the lower bound of which corresponds to the lower-bound of the 95% 1-sided CI (the hypothesis is one-sided). if the one-sided p-value between SR and placebo < 0.05, we reject the null hypothesis, claiming SR reduces the overall malaria hazard rate compared to placebo in Kenya at the significance level of 5%; otherwise, we fail to reject the null hypothesis, claiming SR does not reduce the overall malaria hazard rate compared to placebo in Kenya

Diversion effect

To assess the diversion effect on the first and overall malaria infection a similar model as the model used for analyzing the primary endpoint in Sec 7.1 and 7.2 will be applied. The only difference in the diversion effect assessment is the inclusion of the distance of each household in the buffer zone to the boundary of the core zone, and the interaction term between the distance and treatment arm in addition to the covariates listed in the model in Sec 7.1 and 7.2. How the malaria first-time and overall hazard rates compare in the buffer zones of SR relative to those of the placebo at different distances to the core zone will be quantified.

Subgroup PE analysis by age group

The above analysis of the first time and overall malaria infections in the examination of the PE and diversion effect of SR will be based on all the subjects aged 6 months to **<10** years. The same set of analysis will also be performed by two age subgroups: 6- months to 59-months old, and 60 month- to **<10**-years old to examine if PE and diversion effects of SR will differ by two age groups.

Effects SR on entomological endpoints

Monthly CDC light trap collections will be performed in 10 intervention and 10 control clusters. Collections will consist of 10 light traps (households) in each core area and 15 light traps in the buffer areas. The clusters will be selected at the start of the baseline and will remain fixed throughout the study. However, households within each selected cluster will be randomly selected each month.

In addition, quarterly HLCs will be conducted both indoors and outdoors in 6 intervention and 6 control clusters (the 12 clusters will remain fixed throughout the study). Sampling will be performed for 2 weeks (6 nights per week). Four houses will be randomly selected in each cluster and will be sampled for 2 consecutive nights. With four households sampled in two clusters for two nights across 12 nights of sampling, a total of 48 houses will be sampled across both arms each quarter. The endpoints in the entomological analysis include the HBR (number of anophelines caught during the 12-hr interval overnight), anopheline parity rate, anopheline sporozoite rate, and anopheline EIR averaged over 2 weeks collected by HLC, and the anopheline indoor density collected by light-trap.

We will report the frequencies and proportions of each mosquito genus and species (anopheline and non-anophelines) collected using HLC and light trap methods across clusters and treatment arm. In addition, the following analysis will be performed for each anopheline species and for all anophelines.

The time profile plots of each of aggregated entomological endpoints will be obtained over the baseline and intervention period. An appropriate statistical model for the HBR will be identified after examining the distributional characteristics of the HBR data, which are likely to follow (zero-inflated) Poisson distribution, or (zero-inflated) negative binomial distribution if there is over-dispersion. The covariates in the models will include the fixed effects of intervention, time (biweekly), cluster population size, number of houses in a cluster, location (inside or outside), location and intervention interaction; and a random effect for cluster. The ratio between SR and blank in HBR will be estimated, and the %change in HBR by SR is given by (1-HBR ratio)´100%.

The model for parity rate will be the (zero-inflated) Poisson distribution or a (zero- inflated) negative binomial distribution with the daily porous mosquitos as the outcome and the daily HBR as the offset, and the same set of covariates as those used in the model for analyzing HBR. The model for the sporozoite rate and EIR will be similar to the parity rate with the change of outcome variable to daily mosquitos with positive sporozoite and DIR. Note that if the data on parity, sporozoite positivity, and EIR are highly unbalanced (e.g., 99% nulliparous or 99% negative sporozoite and EIR), then the model might lead to unstable estimates or the model might not even converge. In such cases, only summary statistics will be provided.

The density of mosquitoes in light traps will be obtained over the baseline and intervention periods. An appropriate statistical model will be identified after examining the distributional characteristics of the light trap indoor density which are likely to follow (zero-inflated) Poisson distribution, or (zero-inflated) negative binomial distribution if there is over-dispersion. The covariates in the models will include the fixed effects of intervention, time, cluster population size, and a random effect for cluster. The ratio between SR and blank on

light trap indoor density will be estimated.

Summary statistics will be provided on the insecticide resistance at baseline and each year during the intervention period, aggregated over the clusters on SR.

Relationship between epidemiological and entomological endpoints for anopheline mosquitoes

To explore the relationship between the epidemiological and the entomological endpoints for anopheline mosquitos, a scatter plot between HBR indoor and outdoor vs first-time and overall malaria incidence rates will be provided, a similar model as the cloglog models used to address the primary hypothesis for the first-time malaria infection and the secondary endpoint for the overall malaria infection will be applied to the malaria infection and HBR data in the 6 clusters from which the entomological data are collected. Besides the covariates and random effects specified in each case, the model will also include the average daily HBR taken within 7 to 28 days before each malaria diagnosis over the two-week period and over the 4 households in the same cluster to which the individual under diagnosis belongs to. The regression coefficient associated with the HBR quantifies the change in the hazard rate on the log scale, given one unit increase in HBR. A similar analysis as outlined above for HBR will be provided for the indoor light trap mosquito density, the parity rate, sporozoite rate and EIR, as long as there is enough data collected on these endpoints and they are not highly unbalanced (e.g., 99% mosquitoes caught are nulliparous).

Analysis of baseline

The per-person-year first-time and overall malaria incidence rate from the 60 recruited clusters will be calculated. Since the malaria incidences are collected on a biweekly basis, the mid-point between two visits will be imputed as the time at risk for a malaria event. The average incidence rate will be calculated, together with the coefficients of variation. The baseline analysis will occur at Month 2 and Month 4 during the baseline period internally on blinded data.

Software

Software used will be SAS for Windows, Version 9.4 or higher (SAS Institute, Cary, NC, USA) and Rstudio Version 1.0.143 or higher (RStudio, Inc, Boston, MA, USA).

(e) Procedures

Community sensitization and informed consent

Information will be distributed through community interviewers and community health workers, and other KEMRI/CDC study staff, targeting parent(s)/ guardian(s) of potential participants in the community. Fliers or posters (Appendix 6) will be developed and information will be provided through some of the following means:

- Community meetings will be held at the local Chiefs Barazas and study staff will present the study and have discussions with the community
- Staff will attend church meetings where recruitment scripts will be read and fliers handed to the parent(s)/ guardian(s) of potential participants. Study staff will also be

granted opportunity to explain the study and have discussions with the church members
- Study staff will attend the established local community advisory board (CAB) and opinion leaders' meetings, women groups and men groups

The study will be explained to the compound and household head verbally during which their permission will be sought to list and randomize potentially eligible children in the compound (Appendix 9). Once one child is randomized, a consent form will be read to the parent/guardian of the child recruited to undergo screening for enrolment (Appendices 1a and 1b) or to the head of household or spouse for SR or placebo application in the home (Appendix 3). The study will be explained in local dialect (Teso and Kiswahili), and time allowed for questions to be answered. Once all concerns are addressed, informed consent forms will be signed. An attempt to obtain written, informed consent from both parents of the child will be made, but consent from only one parent will be required for participation. They will not be asked to consent to the long-term storage of residual blood samples (any residual from samples collected after primary laboratory analyses are completed). Thirdly, adult males will be recruited to serve as mosquito collectors. The collectors will be asked to stay up through the night collecting mosquitoes that land on their exposed legs. A consent form will be obtained from the collectors (Appendix 2). Participants from the dispersion zone will also be selected to participate in the follow up cohorts in year 1 and 2 (Appendix 4)

Parent(s)/guardian(s) who cannot sign their names will provide a thumb print on the consent form for documentation of willingness to participate, and a witness not associated with the study will sign the consent form indicating that the informed consent form was read, and that participation and thumb-printing were given willingly without coercion. Time will be granted to those parent(s)/guardian(s) who would wish to make consultations with their family members before signing. It will be stressed to all parents/guardians approached that their children's entry into the study is voluntary and they may withdraw from the study at any time for any reason without any penalty. In households with multiple children that meet the study inclusion criteria, all eligible children will be invited to participate. Consented subjects will be assigned a subject identity (SI) code on enrollment. Consented participants will be screened for inclusion/exclusion criteria.

Informed consent will take place with two study populations. The study will be conducted at the cluster scale (first population) and all households (HHs) within the selected clusters will be eligible to receive the SR product (second population). The Informed Consent Form (ICF) will include informing participants they can come to the study clinic to be assessed and receive essential treatment free of charge whether or not the illness is subsequently determined to be study related. They will not, however, receive free, comprehensive treatment for any illness found to be unrelated to the study product or medicine. They will only receive enough treatment to ensure that they are not disadvantaged, clinically or financially, by going first to the study clinic instead of to the health facility. The ICF will also inform participants that if anyone in their house becomes severely ill, they should go immediately to the nearest health facility.

AEs to be recorded as endpoints (solicited AE) will be pre-defined based on SC Johnson, Inc. toxicology reports of 'probable', 'possible', 'plausible' and 'unlikely' (Appendix 7). Investigator's Brochure):

- Probable: sensory irritation (oral and dermal)

- Possible: nausea/vomiting (oral), skin irritation/rash (dermal), runny nose (inhalation)
- Plausible: salivation
- Unlikely: eye irritation, headache

AEs will be documented in terms of a medical diagnosis. When it is not possible to make a specific medical diagnosis, the adverse event will be documented in terms of signs and/or symptoms observed by the investigator or reported by the participant during scheduled and unscheduled study specific visits. Any hospitalization will be considered a SAE.

During scheduled and unscheduled study-specific visits, Malaria Branch, KEMRI-CGHR will carry out the following lab tests for patient care and/or study procedures free of charge for all study participants: Hemoglobin estimation and malaria diagnosis (RDT and/or malaria smear). The sub-county government hospitals in the study area agree to continue providing any specialized care which is beyond the capacity of the Malaria Branch, KEMRI-CGHR staff (pediatric/surgical consultations etc.)

Microscopy will be the primary endpoint measurement and will be used for treatment where RDT is not done or is negative. RDTs will be used as a point of care diagnostic for participants with a recent history of fever, with microscopy samples taken from febrile subjects used for primary endpoint analyses of incidence. The Malaria Branch of the Kenya Medical Research Institute Centre for Global Health Research (KEMRI-CGHR), will facilitate medical care at the hospital for enrolled participants (incidence cohort and members of enrolled households) during scheduled and unscheduled study-specific visits. The KEMRI-CGHR clinical staff shall conduct the necessary clinical examination and request lab tests as necessary.

In case a study participant is admitted for hospitalization for study procedures, usually not more than a day, the Malaria Branch, KEMRI-CGHR will pay the necessary admission fees. Study participants will access the normal hospital pharmacy for general OPD and IPD formulary needs. The Malaria Branch, KEMRI-CGHR will stock a few selected essential and emergency drugs in the study specific clinics, these drugs will be issued, at the discretion of the study clinician to study populations and non-study participants from the study clusters with AEs of interest and/or severe/emergency cases when alternative medications are not available in the respective sub-county government hospital of the study area.

Cohort children will be provided a transport reimbursement for monthly scheduled clinic visits to offset the cost of coming to the clinic. Transport reimbursement will also be provided to cohort subjects and members of enrolled study households who report to the study clinic with AEs of interest. Transport to hospital, if needed, will be facilitated through transport reimbursement.

Mapping of the study area and baseline measurements

Prior to enrollment, all structures in the study area will be mapped using GPS coordinates and assigned a unique Household Identification Number (HIN). A baseline questionnaire will be administered to measure household and entomological characteristics. Profiles of enrolled houses that could potentially confound effect on mosquitoes will be generated. This includes house construction, socioeconomic status, number of inhabitants and their age, current method(s) used to prevent mosquito bites, including insecticide-treated bednets, domesticated animal type, density and location that are owned by the house. A cluster will be defined as a

village which will serve as the core area where the intervention is implemented plus a buffer area of 300-500m which will be used to estimate diversion of mosquitoes. Since the buffer areas will extend into neighboring villages, it is anticipated that 100-150 villages will be mapped to account for buffer areas. Core areas (villages) plus their buffer areas will be identified using mapping software (ArcGIS or QGIS) based on the feasibility of identifying 60 villages plus their surrounding buffer areas.

Description of study clusters

The unit of randomization for the intervention and placebo will be a cluster. Clusters are defined as a core area where the intervention or placebo will be implemented plus a buffer area measuring 300-500 m beyond the core area where potential divergence of mosquitoes will be measured. The core areas will be discrete villages. In the Health and Demographic Surveillance System maintained by KEMRI and CDC in neighboring Siaya County, the average village has 103 compounds in an area of 1.75km^2. Compounds are defined as family units with 1 or more structures plus surrounding farmland. A typical family compound has 5.5 household members. Therefore, an average population size for a village in this area is estimated to be 567. It is expected that most compounds will have at least one child that meets the inclusion criteria for the study. Therefore, it is anticipated that at least 56 households within each of the core areas will have a child meeting the inclusion criteria.

For the buffer areas, mapping will extend approximately 300-500m from the border of the core areas. Assuming that the core areas are approximately round with an area of 1.75km2, they would have a radius of 0.75km. Extending a buffer area 300 around the core area would result in a radius of 1.05km and extending a buffer area 500 m would result in a radius of 1.25km. Estimating the total area including the buffer areas and then subtracting out the area of the core zone results in areas of 1.7km2 and 3.1km2 for buffer areas of 300m and 500m respectively. Households are randomly distributed in the landscape of western Kenya and it is therefore expected that a 300m buffer area of 1.7km2 should have a similar number of households as the core areas which are estimated to have an area of 1.75km2. Final determination of the buffer areas will be based on mapping and the actual number of households required to meet the sample size of 40 households per cluster for the analysis of mosquito diversion. Because the buffer areas will extend into neighboring villages, we will map approximately 100-150 villages and then select villages as core areas based on feasibility of including a 300-500m buffer around 60 of them.

Clusters will be randomly allocated to intervention and control using standard statistical software (e.g. SAS, STATA or R). Based on the initial baseline estimates of incidence, clusters may be stratified for randomization to reduce the potential for bias due to an imbalance in baseline incidence among the study arms. Since placebos will be provided to the control villages, a public lottery will not be done. All households in each village will be invited to participate in the study by allowing study staff to place SR or placebos in their household. SR or placebo will be placed in each household that consents.

Within each cluster, individual compounds will be enumerated and then randomly selected for inclusion in each cohort. Compounds selected for inclusion in the baseline cohort **will** be eligible for selection for the cohort in year 1 or 2 but not both and similarly, those selected for participation in the baseline cohort or the cohort in year 1 will not be eligible for selection in the cohort in year 2.

Enrollment of the cohort

Cohorts of children aged 6 months to **<10** years will be enrolled within the SR and placebo clusters to assess the effect of the SR product. Cohorts will also be enrolled in the buffer zone surrounding each cluster to determine if there is any evidence for diversion of mosquitoes to unprotected persons due to repellency of mosquitoes from protected to unprotected individuals. Households will be randomly selected from the list of households obtained in the baseline mapping to achieve the desired sample size. Households within each cluster will be identified by simple random sampling using a statistical software package such as SAS, STATA or R. Selected households will be visited and all eligible children in the household invited to participate in the study. The children will be enumerated on a tablet and a randomization program ran to pick one who will be invited to participate in the study. The study will be explained and consent obtained from the child's primary caregiver before enrolling the child in the study. Up to two eligible children may be randomly selected from each selected household and invited to participate in the study.

At enrollment, the age and gender of the child will be recorded and the parent/guardian will be asked about the use of ITNs and anti-malarial drugs. A fingerstick blood sample will be taken for a malaria rapid diagnostic test, a blood smear, and a measurement of hemoglobin.

At this time, cohort participants will be presumptively cleared of parasites with a treatment dose of AL unless they have recently been treated (within the last 2 weeks) in which case, their microscopy results will be fast-tracked to confirm clearance and if not cleared, another dose of AL will be given. Children will be treated according to RDT result throughout the study period unless the microscopy result is positive following a negative RDT or where an RDT was not done.

All children enrolled in the cohort will be provided a long-lasting insecticidal net (LLIN). This will allow us to measure the added benefit of SR product above that provided by currently recommended preventive measures. In addition, at baseline, children enrolled into the cohorts will be provided a treatment dose of artemether-lumefantrine (AL) free of charge according to Kenya national treatment guidelines to clear any prepatent or patent malaria parasites.

Follow up of the cohort

Children enrolled in the baseline cohort will be followed every two weeks during the 4 month period, prior to the distribution of the study product. The cohort participants will be issued with an appointment card where all upcoming appointments will be recorded (Appendix 10). In between the clinic appointments, the community interviewer may refer the participant to the clinic for additional assessment the clinical officer using the participant referral slip (Appendix 14). The distribution of the SR will occur after the completion of the baseline period. Following deployment of the SR intervention, a new cohort will be recruited and followed for 12 months.

To avoid substantial loss to follow up due to study fatigue, the 1st cohort during intervention will end 12 months after the SR is deployed. A second cohort during intervention will be randomly selected and enrolled and cleared of infection with a treatment dose of AL at enrollment as described above. Children enrolled in the baseline will be eligible for inclusion in the 1st or 2nd cohorts during intervention. However, children enrolled in the 1st intervention

cohort will not be eligible for inclusion in the 2nd intervention cohort. The follow up of the 2nd cohort will be the same as the 1st cohort. The second cohort will be followed for a total of 12 months. Therefore, the total period of follow up with be 28 months with 4 months of baseline and 24 months of follow up after deployment of the SR.

In each cohort, all participants will be asked to come to the nearest study health facility for monthly scheduled follow-up and unscheduled sick visits, or they will be visited at their home if they cannot reach the clinic. For intervening scheduled follow-up visits (two weeks after the health facility visit), participants will be visited at home by study staff.

Missed visits will be considered minor protocol deviations and will be collated and reported to KEMRI SERU and study Sponsor along with the annual progress report**.** Three consecutive missed visits will prompt consideration for LTFU and withdrawal from the study.

At each visit, the parent/guardian will be asked about recent use of ITNs and other vector control interventions as well as recent history of child's illness and recent use of anti-malarial drugs. At every other visit (on a monthly basis), a blood smear will be taken for malaria diagnosis. An RDT will be taken if the participant has a recent history of fever. At the intervening visits, a blood sample will only be taken if the child has a recent history of fever **or** other symptoms that may be attributable to malaria infection. Total blood volume for samples at each visit will not exceed 500 microliters.

Cohort children who test positive for malaria by RDT will be treated with artemether-lumefantrine free of charge according to Kenya national treatment guidelines. Blood slides of children who test negative by RDT will be prioritized for examination and treatment will be provided based on a single positive reading. However, the endpoint measurement for formal analysis will be based on examination of all blood slides by at least 2 expert microscopists with any discordant results resolved by a third microscopist**.** Cohort children will be provided a transport reimbursement for monthly scheduled clinic visits to offset the cost of coming to the clinic. Transport to hospital, if needed, will be facilitated through transport reimbursement. Hospital fees will be paid by the study for any illness or injury that is perceived by the participant to be due to study product or procedures and confirmed by clnical staff to be related. If there is illness or injury due to study product or procedures, fees will be paid for care at the government clinic or County or Referral Hospital. Referrals will be done using the general referral form (Appendix 15). If the level of care necessary of the illness/injury is not available at the government hospital, we will pay for care at a private health facility.

Cohorts will also be enrolled to estimate the diversion effect of the SR (Appendix 4). Children in this cohort will be recruited from an area up to 500m from the boundary of each cluster. Households in this area will not receive the SR or the placebo but the enrollment and follow- up procedures will be the same.

<u>Enrollment to receive the SR product</u>

All households within the core areas will be asked to have the SR or placebo placed inside their homes at the recommended rate (2 **Mosquito Shield™** per 9 m^2 floor area), including households that are not enrolled in the cohorts. The study product will be explained to the head of household, as described in the main protocol, and consent for participation will be

obtained prior to participation. The head of household may be asked questions about their perceptions and acceptability of the product after the product has been deployed. No routine blood samples will be sought unless the household is randomly selected and agrees to participate in one of the cohorts.

Application of the spatial repellent during the main trial

The spatial repellent will be a new formulation of transfluthrin. The investigator's brochure is attached in Appendix 5. This active ingredient is widely used in mosquito coils and other household pest control products. The new formulation is a passive emanator that will release the active ingredient (AI) over a period of one month. The emanator will consist of a pre-treated piece of cardstock, cellulose acetate or other medium, which will be positioned within consenting households according to manufacturer specifications. More than one emanator may be placed in houses depending on the size of the house. The product will have a standard amount of AI that will be present throughout the treated space continuously based on a standardized replacement schedule throughout the study. Study teams will be employed to ensure the timely replacement of the SR products and to perform periodic, unannounced spot checks to confirm that the SR product is properly installed. Each SR product and placebo will have a unique code, which will be recorded at the time of installation and the time of replacement. Both participants and study staff will be blinded as to whether the product has the SR or is a placebo.

Entomological measures

Twenty clusters (10 SR, 10 placebo) will be randomly selected to estimate the impact of the SR on entomological measures of malaria transmission. Within each cluster, light trap collections will be conducted in 10 randomly selected households within the core area of each sentinel clusters every month to assess the impact of SRs on the density of *Anopheles* mosquitoes indoors. On the same night, light trap collections will be collected in 15 randomly selected households in the buffer area of the same cluster to estimate the diversion effect of the spatial repellent. The light traps will be deployed next to a person sleeping under a net and will run from approximately 5pm to 7am. The 10 SR and 10 placebo clusters will be randomly selected at the beginning of the study and will remain fixed throughout the study. However, households selected for light trap collections within the core and buffer areas will be randomly selected each month. Households will be sampled with replacement and therefore will be eligible for repeated sampling throughout the study. Households enrolled in the cohort study will not be eligible for mosquito sampling.

Human landing catches will be done indoors and outdoors in 6 intervention and 6 control clusters. The 12 clusters will remain fixed throughout the study. Sampling will be done in four houses (randomly selected) in each cluster for 2 nights (total of 48 houses across both arms) once every quarter (3 months) to determine the effect of SR on the host seeking behavior of mosquitoes. The same clusters and the houses will be sampled each quarter. SR and placebo clusters will be selected in pairs to reduce the degree of heterogeneity between two arms.

Sentinel houses will be chosen such that they are balanced as to house design and inhabitants to reduce bias due to mosquito density heterogeneity (i.e., some houses may be more attractive to mosquitoes than others). Households with children enrolled in the cohort are not eligible for the human landing catches. One pair of clusters will be sampled on any given night. Collections will start at 5pm each night with one person inside and one person outside.

The teams will collect for 45 minutes each hour and then take a 15-minute break before starting the next hour of collection. At the end of each hour, the teams will record the location (outdoors, indoors/awake, indoors/asleep) of the residents of the house that is being sampled. At midnight, a new team will begin collecting and will continue until 7am. Mosquitoes will be sorted by site, date and time of collection. All mosquitoes will be identified to species and all female anopheline mosquitoes will be tested for the presence of sporozoites by ELISA and/or PCR. A subset will be dissected for parity. A team of 16 collectors will be hired to conduct the indoor/outdoor landing catches in 4 houses in each of 12 clusters (6 intervention and 6 control) every quarter. Mosquito collectors will be tested for malaria if they develop symptoms and treated if the result is positive.

Monitoring for insecticide resistance will be done annually in 4 intervention and 4 control clusters spread across the study area to inform on the general status of insecticide resistance in the area. These data will not be used to assess the impact insecticide resistance would have on the intervention. In each site, larvae or adults will be collected and reared in the insectary at a KEMRI facility. Unfed adult females that are 2-5 days old will be tested in CDC bottle bioassays against deltamethrin and transfluthrin. The diagnostic dose for deltamethrin will be 12.5µg per bottle while the diagnostic dose for transfluthrin will be 0.2µg per bottle (Ochomo, unpublished data). Additional bioasssays will be conducted using the WHO tube bioassay technique where resistance will be assessed to 1X, 2X, 5X and 10X dose of deltamethrin, permethrin, pirimiphos methyl, and bendiocarb.

Monitoring for adverse events and severe adverse events.

Adverse events and SAEs of interest listed in the Investigators Brochure for "SAE and AE of interest") (see Appendix 7), will be collected through passive surveillance by community health volunteers on children enrolled in the cohort and on other household members who receive the study product. Additionally, AE and SAEs of interest will be solicited from study participants during followup visits (every 2weeks) either in the house or clinic. Product distributors will also ask of AE and SAEs occurring in the households during product placement and replacement. Anyone experiencing the SAEs or AEs of interest will be encouraged to seek care for at the study clinic where our clinical staff will attend to them at no cost.

Unexpected SAEs affecting the cohort participants determined to be at least "possibly related" will be reported to the KEMRI Scientific and ethical review unit, study sponsor at University of Notre Dame, and Independent Data Safety Monitoring Board (IDSMB) within 24 hours of the PI becoming aware of the SAE. The initial report will be a short description by email, which will be followed within 7 days by a more detailed description of the SAE. AEs of interest considered at least "possibly related" will be reported to the same groups on at least an annual basis.

Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

An AE or suspected adverse event is considered "serious" if it meets the following conditions:

- Results in death
- Is immediately life-threatening

- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

All SAEs starting from enrolment until the last contact with the participant, whether or not they are related to the study product, must be reported..

The DAIDS AE Grading Tables will be used for AE grading in the study

DAIDS AE Grading Table	Online link, last accessed 25 Aug 2017
Grading the Severity of Adult and Pediatric Adverse Events, Corrected V 2.1, July 2017	http://rsc.tech-res.com/docs/default-source/safety/division-of-aids-(daids)-table-for-grading-the-severity-of-adult-and-pediatric-adverse-events-corrected-v-2-1.pdf?sfvrsn=2
Addendum 1 – Female Genital Grading Table for Use in Microbicide Trials	http://rsc.tech-res.com/docs/default-source/safety/addendum_1_female_genital_grading_table_v1_nov_2007.pdf?sfvrsn=8

Medical staff

At KEMRI/CDC, study participants will be followed up at home by field workers. Care will be provided at the study clinics by clinical officers, rather than physicians as outlined in the main protocol. Few physicians practice in western Kenya, and patients routinely receive care from clinical officers at health facilities and hospitals.

Laboratory procedures

Microscope slides will be stained and stored with desiccant until transported to the KEMRI central laboratory where they will be stored according to routine laboratory procedures until destruction.

10. DATA MANAGEMENT

A combination of standardized paper-based or digital forms (under Android tablets) will be used. KEMRI and UND/Centre for Research Computing (CRC) will work together to develop the quantitative forms to be uploaded on Android phones. All data issuing from the electronic data collection system will follow the same data collection processes outlined in the paragraph below. Any changes to quantitative data forms will need to be agreed by the KEMRI PI (in consultation with CDC technical advisors) and UND's co- PI. In the event that all three individuals (or five individuals, when it pertains to the social sciences forms) cannot find a consensus on proposed changes, UND's PI will make the final decision.

A Privacy Impact Assessment will be developed for the project, and a set of protocols and

contingency plans for emergency paper based and digital data destruction will be developed in order to guarantee privacy of research subjects in case of unforeseen risks.

a. Data Sharing Policy

Any data collected on paper forms (including consent/assent forms) will be scanned and transferred to binders for storage in a secure and locked restricted access area, while all electronic captured data will be archived with a documented history of changes or corrections at the local study site. Using CommCare, KEMRI will collect data which will be securely stored on Android devices and then synchronized to CommCare cloud. Data will then undergo an initial cleaning and de-identification by KEMRI, before being synced to UND's central database. Data from KEMRI to University of Notre Dame will be transferred through a dedicated secure FTP server with password protect access from KEMRI.

This project will generate considerable data and biological samples over the course of the 2-year proposed study period. The data management plan will follow the guidelines and suggestions put forward by the NIH in its online guidance document https://humansubjects.nih.gov/data_safety and by the respective institutions involved in the research (Kenya Medical Research Institute, University of Notre Dame, and Centers for Disease Control and Prevention), as well as by the community of interest (comprised of colleagues, scientists working in the same field, the biomedical community researching tropical parasitic diseases, and public health officials). The goal is transparent sharing of key findings and data so that the broad impacts of the research are meaningful and useful to key stakeholders and will therefore be shared with stakeholders as may be required.

Every consideration will be given to the nature of beneficence and justice expressed in the guiding documents for research on human subjects. Biological samples from mosquitoes and parasites will be maintained appropriately to avoid deterioration. These materials will be made available to researchers upon reasonable request and with the caveat that any forthcoming publications from research on the samples should give consideration to the original researchers and their inclusion in the publications should the situation warrant it.

b. Data storage

Standardized data forms using paper, or android tablets will be used across sites such that variable codes can be cross-referenced during interim and final analyses. Any data collected on paper forms will be scanned and transferred to binders for storage, while all electronic captured data will be archived with a documented history of changes or corrections at the local study site.

A password protected central study database warehousing data will be developed and managed by the University of Notre Dame and serve as a data repository and utilized for safe data storage, extraction, integration and analysis. The data warehouse and file repository will be backed up weekly at the local server level to ease recovery as needed. In addition, data will be backed up on servers at the US Centers for Disease Control as a secondary back up. Data will be transferred through a dedicated FTP server with password protect access from both KEMRI and CDC.

In addition, data will be stored and backed-up on CommCare cloud. Access to study data is controlled through centralized administration and access will be granted only through the PI's permission. Research records for all study subjects including history and physical findings, and results of consultations are to be maintained by the local site PI in a secure storage facility and by the University of Notre Dame and KEMRI, for a minimum of 3 years after the end of the projects or until notified by grantee. Research records for all study subjects including history and physical findings, laboratory data, and results of consultations are to be maintained by the local site PI in a secure storage facility for 3 years or until notified by grantee.

Research records for all study subjects including history and physical findings, laboratory data, and results of consultations are to be maintained by the local site PI in a secure storage facility for 3 years or until notified by grantee.

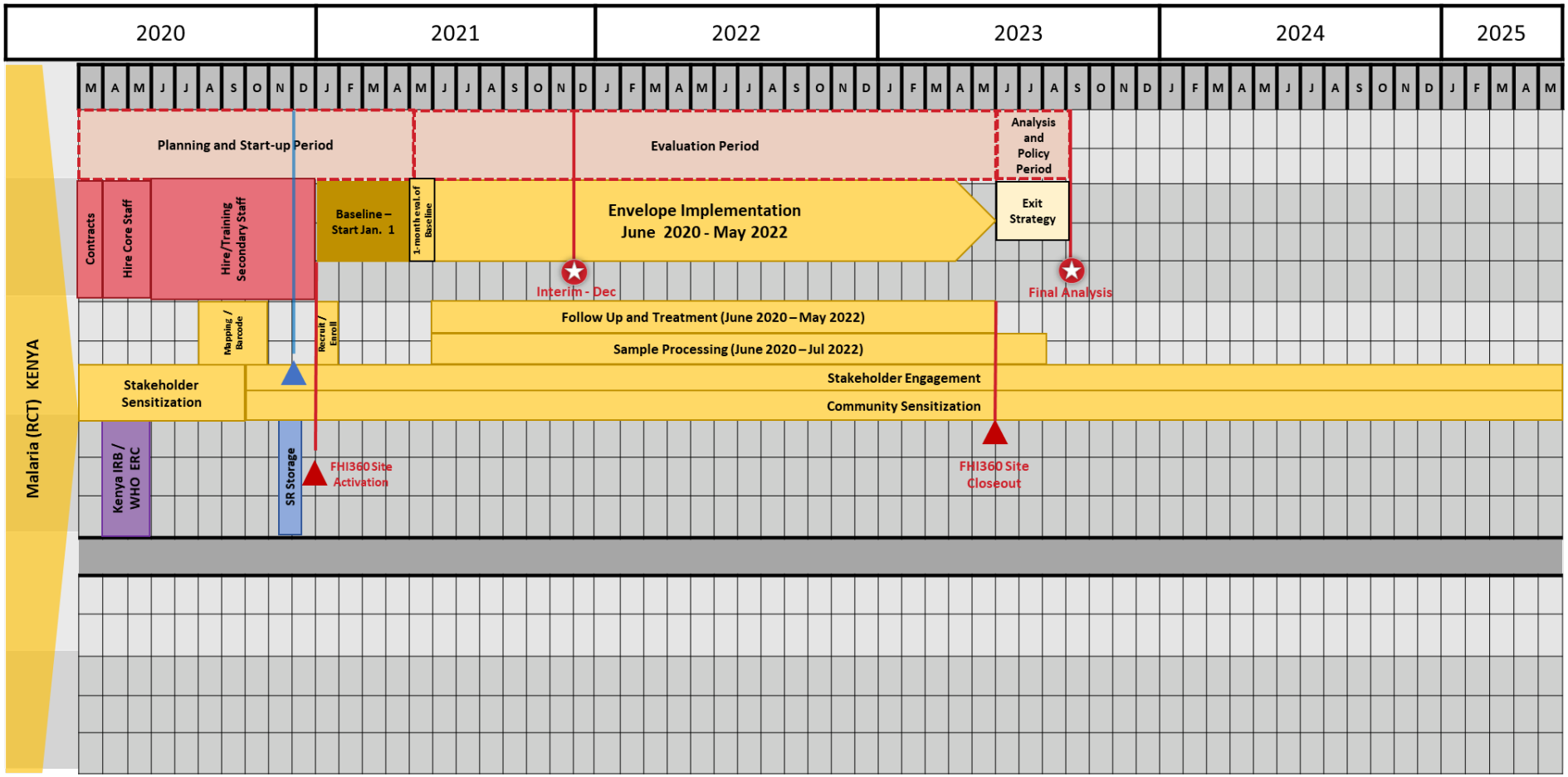
c. Data analysis

Details are described in the Statistical Analyses Plan (Appendix 8). For estimates of protective efficacy, poisson regression will be used to estimate differences in the time to first infection based on microscopy. Similarly, poisson regression will be used to estimate differences in the incidence density of repeated malaria infections over the course of 1.5 years. Models will control for age, gender, ITN use, and recent use of anti-malarials. Models will be adjusted for within cluster correlation and repeated measures within the same household for households with more than one child enrolled in the study. Initial analyses will compare the core SR areas with the core placebo areas to estimate the direct effect of the SR. Additional analyses will 1) compare the incidence of malaria in the dispersion zone around SR clusters with that in the dispersion zone around the placebo clusters and 2) compare the incidence of malaria in the dispersion zone around SR clusters adjusted by distance to nearest household receiving SR product in order to determine whether there is evidence for diversion of mosquitoes from the SR clusters and if this effect can be predicted by distance.

Similarly, poisson regression will be used to compare mosquito numbers between SR and placebo clusters. For the estimates of mosquito diversion, mosquito numbers in the dispersion zone around the SR clusters will be compared to those in the dispersion zone around the placebo clusters. For the human landing catches, total mosquito numbers will be compared in intervention versus placebo clusters using poisson regression. In addition, poisson regression will be used to compare the time of biting between intervention and placebo clusters. All analyses will be adjusted for correlation within the same households**.**

11. TIME FRAME/DURATION OF THE PROJECT

The trial is expected to begin in Q3/Q4 2020 and continue for 2.4 years, including 4 months of baseline data collection and 2 years of follow-up after the deployment of the SRs. A timeline of events by month is outlined below:


2020
2021
2022
2023
2024
2025
Planning and Start-up Period
Evaluation Period
Analysis and Policy Period
Contracts
Hire Core Staff
Hire/Training Secondary Staff
Baseline – Start Jan. 1
1-month eval of Baseline
Envelope Implementation June 2020 - May 2022
Exit Strategy
Interim - Dec
Final Analysis
Malaria (RCT) KENYA
Mapping / Barcode
Recruit / Enroll
Follow Up and Treatment (June 2020 – May 2022)
Sample Processing (June 2020 – Jul 2022)
Stakeholder Sensitization
Stakeholder Engagement
Community Sensitization
Kenya IRB / WHO ERC
SR Storage
FHI360 Site Activation
FHI360 Site Closeout

12. ETHICAL CONSIDERATIONS

a. Consent

Community sensitization will occur before consent is obtained. The study will be presented at Chiefs barazas, church meetings, and community advisory board (CAB) meetings. Once each community has agreed to participate in the study, informed consent of household heads and parents or guardians of cohort participants and individual mosquito collectors will be obtained. Consent will be obtained from 3 populations. First, consent will be sought from the parents/guardians of children selected to participate in the cohort studies either in the core or dispersion zones of the study clusters (Appendix 1a, 1b, 4). Separate consents will be obtained for each cohort (baseline or post-intervention and core vs. buffer areas). Secondly, consent will be sought from the heads of all households to receive the SR product (or placebo) in their house, for study staff to replace the SR product every 4 weeks and for study staff to perform periodic spot checks on the placement of the SR product (Appendix 3). Thirdly, consent will be sought from those who agree to participate as mosquito collectors (Appendix 2). In all cases, the study will be explained in the local language (Teso and Kiswahili) and study staff will ensure that all questions have been addressed before the consent from is signed. All the study consent forms will be used along with a coversheet (Appendix 11). Additionally, all data collection instruments have been translated to Kiswahili and Teso languages (Appendix 5). For a household to receive the SR product, the head of house or his/her spouse will sign the form. A parent or guardian will be required to sign for the participation of children. The mosquito collectors will be required to give consent for themselves. In all cases, written consent will be obtained. If the participant or guardian is not able to write, a witness not associated with the study will be asked to sign to confirm that the person has consented to participate. Study participants will be reimbursed for the cost of transport at the rate of 400 shillings each time they come to the health facility for the scheduled monthly follow-up visits and 300 shillings each time they come to the health facility on a sick visit. Human landing catches volunteers will be compensated at the rate of 1000 shillings for every night of collections.

Informed consent will take place with two study populations. The study will be conducted at the cluster scale (first population) and all households (HHs) within the selected clusters will be eligible to receive the SR product (second population). The Informed Consent Form (ICF) will include informing participants they can come to the study clinic to be assessed and receive essential treatment free of charge whether or not the illness is subsequently determined to be study related. They will not, however, receive free, comprehensive treatment for any illness found to be unrelated to the study product or medicine. They will only receive enough treatment to ensure that they are not disadvantaged, clinically or financially, by going first to the study clinic instead of to the health facility. The ICF will also inform participants that if anyone in their house becomes severely ill, they should go immediately to the nearest health facility.

AEs to be recorded as endpoints (solicited AE) will be pre-defined based on SC Johnson, Inc. toxicology reports of ‘probable’, ‘possible’, ‘plausible’ and ‘unlikely’ (Appendix 7). Investigator’s Brochure):

- Probable: sensory irritation (oral and dermal)
- Possible: nausea/vomiting (oral), skin irritation/rash (dermal), runny nose (inhalation)
- Plausible: salivation

• Unlikely: eye irritation, headache

AEs will be documented in terms of a medical diagnosis. When it is not possible to make a specific medical diagnosis, the adverse event will be documented in terms of signs and/or symptoms observed by the investigator or reported by the participant during scheduled and unscheduled study specific visits. Any hospitalization will be considered a SAE.

During scheduled and unscheduled study-specific visits, Malaria Branch, KEMRI-CGHR will carry out the following lab tests for patient care and/or study procedures free of charge for all study participants: Hemoglobin estimation and malaria diagnosis (RDT and/or malaria smear). The sub-county government hospitals in the study area agree to continue providing any specialized care which is beyond the capacity of the Malaria Branch, KEMRI-CGHR staff (pediatric/surgical consultations etc.)

Cohort children who test positive for malaria by RDT will be treated with artemether-lumefantrine free of charge according to Kenya national treatment guidelines. Microscopy will be for endpoint measurement only, will not be done in real time, and will not be used for treatment except in cases where the RDT result is negative but microscopy result is positive. The Malaria Branch of the Kenya Medical Research Institute Centre for Global Health Research (KEMRI-CGHR), will facilitate medical care at the hospital for enrolled participants (incidence cohort and members of enrolled households) during scheduled and unscheduled study-specific visits. The KEMRI-CGHR clinical staff shall conduct the necessary clinical examination and request lab tests as necessary.

In case a study participant is admitted for hospitalization for study procedures, usually not more than a day, the Malaria Branch, KEMRI-CGHR will pay the necessary admission fees. Study participants will access the normal hospital pharmacy for general OPD and IPD formulary needs. The Malaria Branch, KEMRI-CGHR will stock a few selected essential and emergency drugs in the study specific clinics, these drugs will be issued, at the discretion of the study clinician to study populations and non-study participants from the study clusters with AEs of interest and/or severe/emergency cases when alternative medications are not available in the respective sub-county government hospital of the study area.

Cohort children will be provided a transport reimbursement for monthly scheduled clinic visits to offset the cost of coming to the clinic. Transport reimbursement will also be provided to cohort subjects and members of enrolled study households who report to the study clinic with AEs of interest. Transport to hospital, if needed, will be facilitated through transport reimbursement.

All parents/guardians whose child may die at home in the course of study will be visited at home as soon as possible for a detailed verbal autopsy interview using the standardized World Health Organization's questionnaires that will be used to categorize the potential cause of death.

b. Risks to study participants

The Spatial Repellent product contains transfluthrin which has undergone human safety testing and is currently registered in many countries throughout the world and used in currently available household products for mosquito control in the form of mosquito coils or other household pesticide products. It may cause mild eye and skin irritation, so household owners will be advised to avoid contact with eye, skin and clothing. These effects are usually

transient and disappear after time. Inhalation of transfluthrin/metofluthrin may cause central nervous system effects, so household owners will also be advised to avoid breathing vapors directly. However, CNS effects are unlikely at the low doses at which the product will be deployed in houses. The product may be harmful if chewed on or swallowed, so recipients will be advised to keep it away from children. The SR product will be fixed at a position that is out of the reach of children and it will be monitored at replacement to ensure that it has not been moved. If a product is found to have been removed from its position in the household, study staff will discuss with the household owner to determine why it was removed and if there was any problem that led to its removal. Study staff will also reiterate safety precautions that should be taken in regard to the SR product.

Children enrolled in the cohort will be asked to provide blood at every scheduled monthly visit, every interim visit where there is a history of fever, and every sick visit for an RDT and blood smear. Participants may experience mild pain at the site of the finger stick and there is a risk of infection although our staff will use procedures to minimize this risk.

Persons assisting in the collection of mosquitoes will potentially be exposed to the bites of infectious mosquitoes at times when they would normally be expected to be under bednets. Mefloquine prophylaxis will be provided to mitigate the risk of malaria infection. We will also monitor the collectors at regular intervals to ensure that they are not infected with malaria. Mefloquine has some minor side effects including nausea, vomiting, abdominal pain and diarrhea. Less common side effects include headache, dizziness, sleep disturbance, nightmares, convulsions, depression, and anxiety. Severe psychiatric problems occur rarely.

c. Benefits to study participants

All participants in the cohort will be provided with a LLIN recommended by the WHO Pesticide Evaluation Scheme and currently listed as WHO pre-qualified. These have been shown to reduce morbidity and mortality due to malaria in sub-Saharan Africa. Cohort participants will also be provided regular testing for malaria and will be treated immediately when they test positive. The testing and treatment will be provided without cost. Lastly, those clusters that will receive spatial repellents which have been shown to reduce mosquito biting in many settings, may experience reduce malaria transmission and malaria illness.

d. Safety precautions to protect study participants and study staff from Covid-19 illness.

The circulation of sars-cov-2 virus in-country will affect the manner in which we conduct research with the aim to contain and/or mitigate the spread of COVID-19 disease. KEMRI SERU issued guidelines for conduct of research during the Covid-19 pandemic in the document, “KEMRI SERU GUIDELINES FOR CONDUCT OF RESEARCH DURING THE COVID-19 PANDEMIC IN KENYA approved on 22 June 2020” (Appendix 13). During the conduct of this study, we will follow these guidelines and practices to ensure the safety of study participants and study staff in line with section 3.2.5 of the said guidelines

Measures to protect study participants:

Measures will be put in place to mitigate risk of sars-cov-2 transmission from potentially infected study staff to study participants. These will include:

- All study investigators, coordinators, clinical officers, community interviewers and other staff in will wear masks. Staff may use additional protective equipment during their interactions with participants, for example, clinical officers and medical doctors

will have face shields in addition to masks and standard protective clothing (lab coat, surgical masks and gloves).

- We will provide each participant and a parent/guardian a single, reusable, cloth mask. Participants and guardians will be required to wear these masks when we visit their house or when they come to the clinic.
- All study team members will be screened daily for COVID-19 symptoms before they come into the workstation. If any study staff has symptoms, they will be tested for COVID-19 and quarantine as recommended by the Ministry of Health. Any member of staff who have come into close contact with staff who turn out to have COVID-19 will be required to quarantine for 14 days.
- We will also screen you for symptoms on the day of your visit. If you or your child has a fever in addition to other symptoms characteristic of COVID-19 (cough or shortness of breath, sore throat, fever, muscle aches, headache, loss of taste or smell, repeated or shaking chills with or without history of exposure to a confirmed COVID-19 case), we will refer you for COVID-19 testing in addition/after completing questions and procedures for the study. If the child participant, or parent/guardian responsible for taking the child to the scheduled clinic visits, become positive for COVID-19 during the study and is placed under quarantine, we may send clinical staff to conduct follow-up visits at your home or quarantine centre. Additionally, study staff will still be available to attend to the child should he/she fall sick.
- We will be careful about who we ask to come for in-person study visits, and when possible, we will use telephone communication to schedule visits to reduce the number of research participants coming to our research areas at the same time.
- We will practice social distancing by maintaining 2m distance between staff and participants where feasible (e.g. except during clinical examination). We will request that the participant be accompanied by a maximum of two people for their study visits. We will rearrange the furniture in our waiting areas to enforce strict social distancing practices.
- We will practice strict infection control practices, including disinfection, wearing gloves, wearing masks, and hand washing during all our procedures. We will ensure access to hand sanitizer at study clinics health facilities and request that study participants and their parent/guardian that may accompany them to sanitize their hands before and after interaction with our study staff.

Measures to protect study staff:

- All staff will be trained on COVID-19 prevention measures, provided with PPE (including masks and hand sanitizers;
- Staff will be required to take their temperature measurement on a daily basis. Any staff with fever will not be allowed back to work until they seek medical assessment and the fever is completely resolved. All staff will be regularly reminded to stay at home if they are sick or experiencing symptoms of illness (regardless of minor severity). These members of staff will be required to visit a health facility for assessment of symptoms and testing for Covid-19 if they fit the assessment criteria.

- Meetings of the Core study team (PI, Component leads, study coordinator, administrator, QA manager and data manager) shall happen virtually/online via Zoom. Where physical meetings are necessary, members shall adorn personal protective equipment (PPE) such as face masks and observe physical distancing (sit 2m from one another);
- Each member of the Core study team shall train and appoint a junior member of their team to be able to act in their stead in at full capacity therefore ensuring continuity of their research duties if indisposed due to Covid-19 infection.
- In addition to face masks, all study clinicians will be provided face shields for use during clinical examinations of study subjects.
- If half of the core team and/or one quarter of the entire study team is indisposed due to COVID-19 at the same time, the trial shall be suspended, except for care to study participants.

Measures to prevent disruption of study activities:

- Online training to enforce social distancing is the most effective way of mitigating infection. We will ensure all study staff have access to smart phones, airtime and adequate internet coverage in their homes. Zoom calls have been already adopted for virtual/online training and routine meetings of study staff;
- Face to face training may be required. If conducted, all staff attendees will be required to use PPE. Any such trainings will be coordinated to ensure smaller groups of $\leq$15 persons to reduce risk of infection and take place in open spaces, when possible, to encourage circulation of fresh air;
- All staff shall receive additional training on sars-cov-2 infection prevention strategies to put in practice during subject recruitment and consenting visits. This will include observing social distance, hand hygiene and use of face masks by both community participants and staff during consenting.
- If any of the collaborating clinics is converted to a COVID-19 isolation centre, the study staff will be moved to temporary facilities at the KEMRI Alupe Campus or neighbouring health facilities. If such a clinic is more than 10km away from the KEMRI Alupe Centre, transport reimbursement will be doubled for study participants.

Potential effect of Covid-19 on scientific and logistical aspects of the study:

- Symptomatic cases of Covid-19 in study participants will necessitate isolation/quarantine which may result in:
    1. missed visits – protocol deviations. Participants who fall ill due to sars-cov-2 infection will undergo the MOH requirement/observation and will be discharged only after 2 negative results. During this time, we may be unable to continue follow-up procedures.
    2. greater loss to follow-up than assumed in power calculations if more than 3 consectuve missed visits occur or death due to illness
    3. increase in AEs –more use of concomitant medications (double quantities of current projection may be required)

- Some of the SR side effects (respiratory effects) may mimic the Covid-19 symptoms. This may cause anxiety to the community and may potentially lead to refusals and/or withdrawal from the study. Thorough sensitization shall be conducted prior to and following distribution of SRs to address these issues;
- Staff that have had contact with a Covid-19 case will lead to quarantine/isolation of that staff member, hence the need for back-up of trained junior staff with adequate capacity to ensure continuity in study activities;
- We will ensure adequate supply of PPEs for all study participants, clinic and field staff during reported periods of sars-cov-2 transmission with assurances of stock covering at least 1 year;
- In case there's a lockdown we may not be able to conduct follow-up visits which require face to face interactions. Lockdowns may limit movement of both the study staff and study participants. In this scenario, study procedures will be suspended, and only medical staff allowed to attend to participants as may be required.
- Study procedures such as Human Landing Collection will involve face-to-face interactions with enrolled households. The HLC collectors and staff performing supervision will be spending up to 14 hours in the collection houses. This would lead to possible exposure of both staff and households. For this reason, we will restrict HLC collectors to be conducted only by members of that specific household.

We shall continually assess and update the above measures to ensure study participants and study staff are protected from possible risk of sars-cov-2 transmission due to study activities.

13. EXPECTED APPLICATION OF THE RESULTS

Data from the western Kenya study site will be submitted to the WHO Vector Control Advisory Group which will use the data to determine whether the WHO Global Malaria Programme should recommend spatial repellents as a new product category for vector control. If the SR product is effective, it may be deployed in malarious areas to complement other vector control interventions such as ITNs to help mitigate the problem of insecticide resistance, outdoor vector biting where ITNs may be ineffective and to further drive malaria towards elimination.

14. REFERENCES

1. WHO: World Malaria Report. Geneva, Switzerland: World Health Organization; 2018.
2. Hamel MJ, Adazu K, Obor D, Sewe M, Vulule J, Williamson JM, Slutsker L, Feikin DR, Laserson KF: A Reversal in Reductions of Child Mortality in Western Kenya, 2003–2009. *American Journal of Tropical Medicine and Hygiene* 2011, 85:597–605.
3. Zhou G, Afrane YA, Vardo-Zalik AM, Atieli H, Zhong D, Wamae P, Himeidan YE, Minakawa N, Githeko AK, Yan G: Changing patterns of malaria epidemiology between 2002 and 2010 in Western Kenya: the fall and rise of malaria. *PLoS ONE* 2011, 6:e20318.
4. Ogoma SB, Moore SJ, Maia MF: A systematic review of mosquito coils and passive emanators: defining recommendations for spatial repellency testing methodologies. *Parasites and Vectors* 2012, 5:287.
5. Ogoma SB, Ngonyani H, Simfukwe ET, Mseka A, Moore J, Killeen GF: Spatial

repellency of transfluthrin-treated hessian strips against laboratory-reared *Anopheles arabiensis* mosquitoes in a semi-field tunnel cage. *Parasit Vectors* 2012, 5:54.
6. Ogoma SB, Ngonyani H, Simfukwe ET, Mseka A, Moore J, Maia MF, Moore SJ, Lorenz LM: The mode of action of spatial repellents and their impact on vectorial capacity of *Anopheles gambiae* sensu stricto. *PLoS One* 2014, 9:e110433.
7. Achee NL, Bangs MJ, Farlow R, Killeen GF, Lindsay S, Logan JG, Moore SJ, Rowland M, Sweeney K, Torr SJ: Spatial repellents: from discovery and development to evidence-based validation. *Malaria Journal* 2012, 11:164.
8. WHO: Guidelines for Malaria Vector Control. Geneva, Switzerland: World Health Organization; 2019.
9. Lucas JR, Shono Y, Iwasaki T, Ishiwatari T, Spero N, Benzon G: U.S. laboratory and field trials of metofluthrin (SUMIONE®) emanators for reducing mosquito biting outdoors. *Journal of the American Mosquito Control Association* 2007, 23:47-54.
10. Kawada H, Temu EA, Minjas JN, Matsumoto O, Iwasaki T, Takagi M: Field evaluation of spatial repellency of metofluthrin-impregnated plastic strips against Anopheles gambiae complex in Bagamoyo, coastal Tanzania. *Journal of the American Mosquito Control Association* 2008, 24:404-409.
11. Syafruddin D, Bangs MJ, Sidik D, Elyazar I, Asih PB, Chan K, Nurleila S, Nixon C, Hendarto J, Wahid I, et al: Impact of a spatial repellent on malaria incidence in two villages in Sumba, Indonesia. *Am J Trop Med Hyg* 2014, 91:1079-1087.
12. Hill N, Zhou HN, Wang P, Guo X, Carneiro I, Moore SJ: A household randomized, controlled trial of the efficacy of 0.03% transfluthrin coils alone and in combination with long-lasting insecticidal nets on the incidence of Plasmodium falciparum and Plasmodium vivax malaria in Western Yunnan Province, China. *Malaria Journal* 2014, 13:208.
13. WHO-GMP: Data requirements and protocol for determining non-inferiority of insecticide-treated net and indoor residual spraying products within an established WHO intervention class. Geneva, Switzerland: Global Malaria Program, World Health Organization; 2019.

15. BUDGET

Budget Item	Title	Number	Cost Per Person	Total Cost(USD)	Total Cost (KShs)
Personell	Project coordinator	1	243,859.92	243,859.92	19,508,793.69
	Admin officer	1	101,381.52	101,381.52	8,110,521.55
	Data manager	1	173,228.54	173,228.54	13,858,283.18
	Data specialist	1	101,381.52	101,381.52	8,110,521.55

	Human resources	1	50,690.76	50,690.76	4,055,260.77
	Procurement	1	50,690.76	50,690.76	4,055,260.77
	Accounts	1	50,690.76	50,690.76	4,055,260.77
	Community liaison	1	50,690.76	50,690.76	4,055,260.77
	Clinical officers	9	34,424.63	309,821.63	24,785,730.00
	Community interviewers	30	15,375.00	461,250.00	36,900,000.00
	Entomology technicians	4	63,772.69	255,090.77	20,407,261.33
	Intervention manager		92,789.16	-	-
	Intervention specialist	4	23,659.56	94,638.25	7,571,060.00
	Microscopist	2	173,228.54	346,457.08	27,716,566.35
	Lab Technician	2	101,381.52	202,763.04	16,221,043.10
Travels	Kisumu to Nairobi	10		5,000.00	400,000.00
	Kisumu to field	650		68,628.16	5,490,252.50
Supplies	RDTs	1		43,545.60	3,483,648.00
	Netbooks	500		12,500.00	1,000,000.00
	Enrollment survey	25,000		25,000.00	2,000,000.00

	Mapping	10,000		10,000.00	800,000.00
	Microscope slides	1		36,288.00	2,903,040.00
	Vehicle	60,000		60,000.00	4,800,000.00
	"Service Fee"	-		101,885.00	8,150,800.00
	Building costs/rental	30,000		60,000.00	4,800,000.00
	Coartem treatment			9,072.00	725,760.00
	Other drugs at health facilities			6,000.00	480,000.00
	Filter papers			1,000.00	80,000.00
	Training of staff			2,000.00	160,000.00
	ID cards for participants			2,000.00	160,000.00
	Cabinets at health facilities			300.00	24,000.00
	Refurbishment of facilities			3,500.00	280,000.00
	Shipping costs			3,000.00	240,000.00
	Community meetings			1,200.00	96,000.00
	Computers			9,000.00	720,000.00
	Bicycles			2,800.00	224,000.00

Total				2,955,354	236,428,324
Overheads			15%	443,303	35,464,249
Grand Total				3,398,657	271,892,573

Budget Justification Project Staff

1. Site PI (Entomologist): The site PI will provide day to day oversight on on study design, implementation and management of entomological and epidemiological aspects of the study
2. Project coordinator will work alongside the Entomologist to oversee the day to day management of all entomological aspects of the project.
3. Epidemiologist: Will provide day to day oversight on study design, implementation and management of epidemiological aspects of the study
4. Field Supervisor: Will provide day to day oversight on study design, implementation and management of epidemiological aspects of the study
5. Administrative Officer: This person will be responsible for logistical and administrative activities related to the project at KEMRI
6. Project accountant: Working closely with the study administrative officer, this person will be responsible for all financial aspects of the project. He/she will be based in Nairobi at KEMRI headquarters to ensure funds are received by KEMRI and made available to CGHR, in Kisumu and accounted back to Nairobi.
7. Human Resources Officer: This person will be responsible for all personell issues of the project, from hiring, to coordination of training and other HR support activities for the project
8. A full time driver is needed to transport entomology staff to and from the field as well as to transport specimens from the field to the lab for processing
9. Data Manager: This person will be responsible for designing data entry screens, cleaning data and providing interim data summaries
10. Data Specialist: The data specialist will assist the data manager in data entry and cleaning
11. Procurement officer: This person will be responsible for ordering, stocking and maintaining supplies for the project
12. Community Liason: This person will be responsible for meeting with community leaders and conducting community outreach to ensure community acceptance of the project. This role will be particularly important at the start of the study, during the epidemiological and social science components of the study and at the dissemination of the study to the communities.
13. Clinical Officers: One clinical officer will be recruited per facility (one facility per 4 clusters -15) including 1 backup CO. The 16 Clinical officers will participate in enrollment of subjects and will be the primary interviewers at routine follow ups. They will also be available to study participants for clinical consultation during the cohort study
14. Community Interviewers: Sixteen community interviewers will be recruited to work with the 16 Cos. The CIswill interview participants during the follow up and will take blood samples from health participants. They will refer to the clinical officers if participants report any signs of illness
15. Entomology technicians: Six entomology technicians will be responsible for the

collection and processing of mosquitoes

16. Intervention manager: Three intervention managers will be responsible for maintain stocks of the spatial repellent, distributing them to the intervention technicians and ensuring that the repellents are in place each night by performing routine and random checks in the field.
17. Microscopist: The six microscopists will be responsible for reading blood smears collected as part of the study
18. Lab Technician: The two lab technicians will be responsible for receiving, cataloging and maintaining samples from the field.

Additional personnel:

KEMRI will collaborate with John Hopkins University on the Social Science Component of the Study and will need the following additional staff:

Social Scientist: This person will be responsible for community entry, sensitization and outreach.

Data collectors will work with the social scientist to collect data for the IDIs and TIPs activities (month 1 to 18 months after intervention different time points see timeline)

External Professional Services

Mosquito collectors will be hired for all night landing catches; 32 needed per night for 12 nights four times per year-12 villages per sampling effort)

Travel Related

Travels from Kisumu to the field will cater for vehicle transportation from the research station in Kisian to the field sites. This will only cater for the administrative and lead staff such as the PI, Social Scientist, and administrative officer who will be based at KEMRI CGHR. All other staff will be based in the KEMRI Alupe Campus located within the study site. Per-diems will be paid to staff who work overnight during the supervision of human landing catch collections. Travels from Kisumu to Nairobi will cover airfare and per-diems for staff who will be spending their nights in Nairobi to take care of the project management and dissemination meetings to be held in Nairobi with the Malaria Control unit and other partners.

Supplies

These are the items/ services that will be needed in the day to day running the project over the project period. They include consumables such as RDTs, and slides for testing and diagnosis of malaria. Equipment for data collection such as tablets, motor vehicle, light traps and their chargers, among others.

Clinical Trial Insurance

This insurance will provide protection to the study staff, in respect of claims that may be made against them by the study participants or other people regarding issues related to conduct of the study. It indemnifies the study staff and funders of any liability arising from legal redress sought against the study.

List of Appendices

Consent 1a(i)-Informed Consent for Cohort Participation - Baseline

Consent 1a(ii)-Informed Consent for Cohort Participation - Baseline English-Ateso translation

Consent 1a(ii)-Informed Consent for Cohort Participation - Baseline Ateso-English backtranslation

Consent 1a(iv)-Informed Consent for Cohort Participation - Baseline English-Kiswahili translation

Consent 1a(v)-Informed Consent for Cohort Participation - Baseline Kiswahili-English backtranslation

Consent 1b(i)-Informed Consent for Cohort Participation - 12-month followup

Consent 1b(ii)-Informed Consent for Cohort Participation - 12-month followup

Consent 1b(iii)-Informed Consent for Cohort Participation - 12-month followup: Ateso to English Backtranslation

Consent 1b(iv)- Kidhinisho la Ushauri wa Ushiriki wa Cohort – kufuatilia miezi 12

Consent 1b(v)- Cohort Participation Consultation - tracking 12 months Spatial Repellent Products for Control of Vector Borne Diseases Kiswahili English Backtranslation

Consent 2(i): Informed consent for human landing catches

Consent 2(ii): Informed consent for human landing catches English to Teso Translation

Consent 2(iii): Informed consent for human landing catches Teso to English Backtranslation

Consent 2(iv): Informed consent for human landing catches English to Kiswahili Translation

Consent 2(v): Informed consent for human landing catches Kiswahili to English Backtranslation

Consent 3(i): Informed Consent to Receive SR Intervention

Consent 3(ii): Informed Consent to Receive SR Intervention

Consent 3(iii): Informed Consent to Get SR Involvement Teso to English Backtranslation

Consent 3(iv): Informed Consent to receive SR Intervention English to Kiswahili

Consent 3(v): Informed Consent to receive SR Intervention Kiswahili to English Backtranslation

Consent 4a(i)-Informed Consent for Cohort Participation: Dispersion Evaluation

Consent 4a(ii)-Informed Consent for Cohort Participation: Dispersion Evaluation

Consent4a(iii)-Informed Consent for group engagement: Dispersion Assessment Teso to English Backtranslation

Consent 4a(iv)-Informed Consent for Cohort Participation: Dispersion Evaluation. English to kiswahili Translation

Consent 4a(v)-Informed Consent for Cohort Participation: Dispersion Evaluation Swahili to English Backtranslation

Appendix 5 a(i) Baseline enrolment questionnaire English

Appendix 5 a(ii) Baseline enrolment questionnaire English to Ateso Translation

Appendix 5 a(iii) Baseline enrolment questionnaire Ateso to English translation

Appendix 5 a(iv) Baseline enrolment questionnaire English to Kiswahili translation

Appendix 5 a(v) Baseline enrolment questionnaire Kiswahili to English Back translation

Appendix 5 b(i) Subject follow up

Appendix 5 b(ii) Subject follow up English to Teso translation.

Appendix 5 b(iii) Subject follow up Teso to English Backtranslation

Appendix 5 b(iv) Subject follow up English to Kiswahili Translation

Appendix 5 b(v) Subject follow up Kiswahili to English Backtranslation

Appendix 5 c(i) Look up Tables

Appendix 5 c(ii) Look up Tables English to Ateso

Appendix 5 c(iii) Look up Tables Teso to English Backtranslation

Appendix 5 c(iv) Look up Tables English to Kiswahili Translation

Appendix 5 c(v) Look Up tables Kiswahili to English backtranslation

Appendix 5 d(i) Final status

Appendix 5 d(ii) Final status

Appendix 5 d(iii) Final status Ateso to English Back translation

Appendix 5 d(iv) Final status English to Kiswahili

Appendix 5 d(v) Final status Kiswahili to English backtranslation

APPENDIX 6 (i)– Information sheet for study posters and fliers

APPENDIX 6 (ii) – Information sheet for study posters and fliers Teso translation

Appendix 6 (iii): Information sheet with announcements and posters about the research-Teso- English back translation.

Appendix 6 (iv): Information sheet with announcements and posters about the research-Kiswahili translation.

Appendix 6 (v): Information sheet with announcements and posters about the research-Kiswahili- English back translation.

APPENDIX 7 – Mosquito Shield™ Investigator Brochure

APPENDIX 8– KENYA Statistical Analysis Plan (SAP)

Appendix 9 (i)Verbal Consent to Line list and Randomize potential cohort participants-English

Appendix 9 (ii)Verbal Consent to Line list and Randomize potential cohort participants-English to Teso translation

Appendix 9 (iii)Verbal Consent to Line list and Randomize potential cohort participants-Teso to English Backtranslation

Appendix 9 (iv)Verbal Consent to Line list and Randomize potential cohort participants-English to Kiswahili Translation

Appendix 9 (v)Verbal Consent to Line list and Randomize potential cohort participants-English to Kiswahili Backtranslation

Appendix 10: Cohort Participants Appointment Card

Appendix 11: Consent form cover sheet

Appendix 12 (i): Script for CDC light traps collection - English

Appendix 12 (ii): Script for CDC light traps collection – English to Teso Translation

Appendix 12 (iii): Script for CDC light traps collection – Teso to English Backtranslation

Appendix 12 (iv): Script for CDC light traps collection –English to Kiswahili Translation

Appendix 12 (v): Script for CDC light traps collection – Kiswahili to English Back translation

Appendix 13: KEMRI SERU GUIDELINES FOR CONDUCT OF RESEARCH DURING THE COVID-19 PANDEMIC IN KENYA approved on 22 June 2020

Appendix 14: Participant Referral Slip

Appendix 15: General Referral Forms

Appendix 16: Pictorial brochure

S3. Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Ochomo EO, Gimnig JE, et al. Effect of a spatial repellent on malaria incidence in an area of western Kenya characterized by high malaria transmission, insecticide resistance and universal coverage of insecticide treated nets: a cluster-randomized, controlled trial

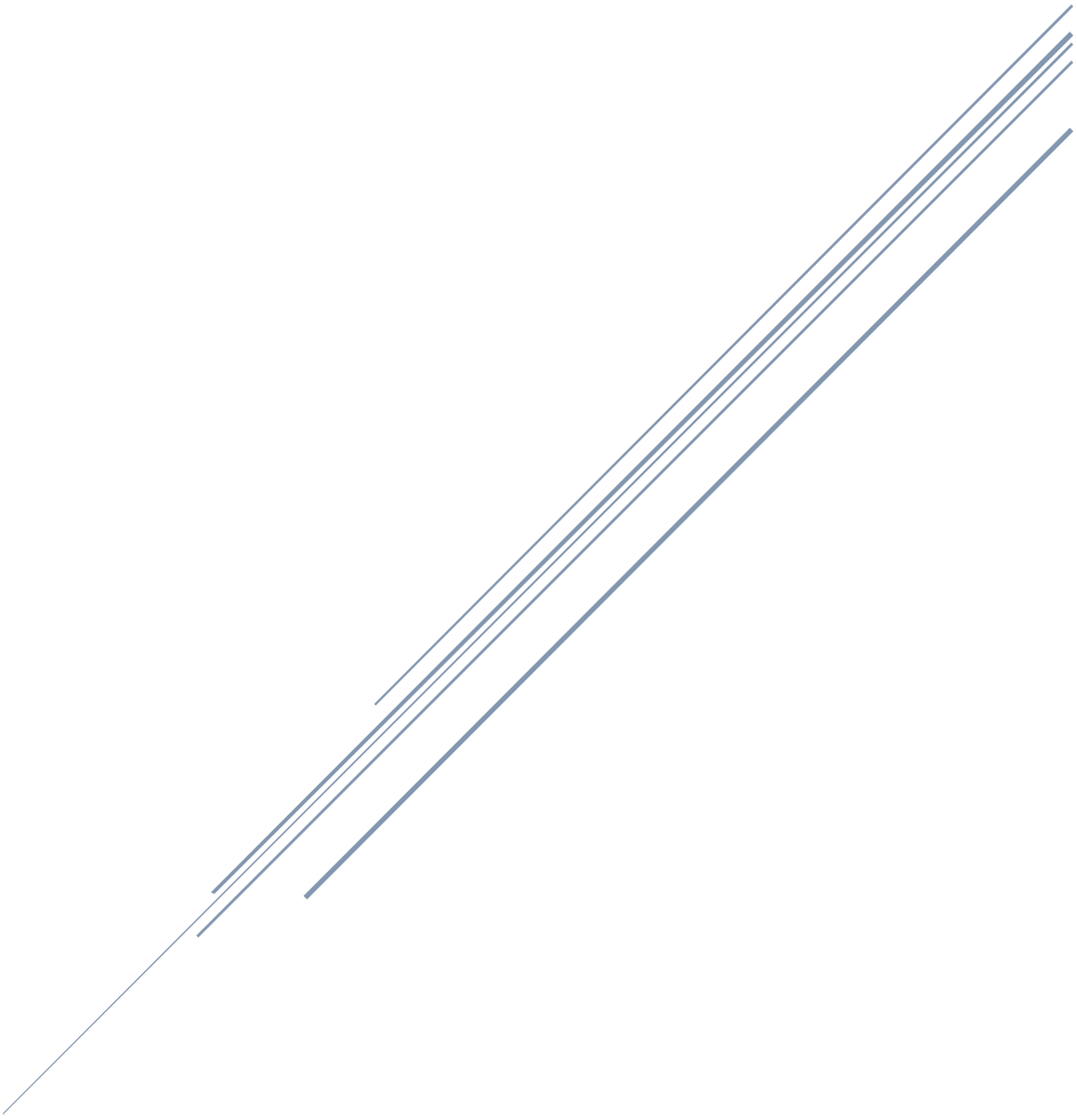


Table of Contents

Figure 1: Location of (A) 60 study clusters (core, buffer) from which baseline and (B) 58 study clusters that received intervention were monitored for malaria incidence in Teso North and Teso South Districts, Busia County, Kenya. 53

Entomology Methodology 54

Table 1: PE of SR against overall new infections 55

Table 2: Diversion effect of SR on 1st-time infection 55

Table 3: Diversion effect of SR on overall new infections 55

Table 4: Summary of baseline covariates of the clusters in the core zones in interim dataset 56

Table 5: Summary of baseline covariates of the clusters in the buffer zone in interim dataset 57

Table 6: Summary of baseline covariates of the clusters in the core zones in final dataset 58

Table 7: Summary on baseline covariates of the clusters in the buffer zones in final dataset 59

Figure 2: Time profile of mean (SD) household product application rate (0 to 100%) by treatment group 60

Figure 3: Malaria incidence rates. 60

Table 8: Number of subjects at risk for first-time infection during intervention period in interim dataset 61

Table 9: Number of subjects at risk for the first-time infection during the intervention period in final dataset 61

Table 10: PE of SR estimated by model without baseline covariates 61

Table 11: PE of SR against first-time infection by age group in interim data 61

Table 12: PE of SR against first-time infection by age group in final data 62

Table 13: PE of SR against overall new infections by age group in interim data 62

Table 14: PE of SR against overall new infections by age group in final data 62

Figure 4: Time profile of mean (SD) HLR by treatment in the HLC collection in the core zones in the interim dataset (averaged over 6 cluster per treatment with roughly 4 households per cluster) 63

Figure 5: Time profile of mean (SD) HLR by treatment in the HLC collection in the core zones in the final dataset (averaged over 6 cluster per treatment with roughly 4 households per cluster) 64

Table 15: Summary statistics of HLR in core zone HLC collection in interim dataset 65

Table 16: Summary statistics of HLR in core zone HLC collection in final dataset 65

Table 17: Effects of SR and covariates on HLR in HLC collection in core zones in interim dataset 65

Table 18: Effects of SR and covariates on HLR in HLC collection in core zones in final dataset 65

Table 19: Frequency and percentage of different *anopheles* species in HLC collection in core zones in final dataset 66

Table 20: Summary statistics and parity rate in HLC collection in core zones in interim dataset 66

Table 21: Summary statistics and parity rate in HLC collection in core zones in final dataset 66

Table 22: Frequency and percentage of parous status in female anopheline in HLC collection in interim dataset (n=6 clusters per treatment arm) 67

Table 23: Frequency and percentage of parous status in female anopheline in HLC collection in final dataset (n=6 clusters per treatment arm) 67

Table 24: Effects of SR and covariates on parity rate in HLC collection in core zones in interim dataset 67

Table 25: Effects of SR and covariates on parity rate in HLC collection in core zones in final dataset 67

Figure 6: Time profile of mean (SD) anopheline density by treatment in LT collection in core zones in interim dataset (averaged over 10 clusters per treatment with roughly 10 households per cluster) 68

Figure 7: Time profile of mean (SD) anopheline density by treatment in LT collection in core zones in final dataset (averaged over 10 cluster per treatment with roughly 10 households per cluster) 68

Table 28: Effects of SR and other covariates on anopheline density in LT collection in core zones in interim dataset 69

Table 29: Effects of SR and other covariates on anopheline density in LT collection in core zones in final dataset 69

Table 30: Frequency and percentage of abdominal status in female anopheline in LT collection in core zones in interim dataset 69

Table 31: Frequency and percentage of abdominal status in female anopheline in LT collection in core zones in final dataset 70

Table 34: Effects of covariates on blood fed rate in LT collection in core zones in interim dataset 70

Table 35: Effects of covariates on blood fed rate in LT collection in core zones in final dataset 70

Table 36: Summary statistics on sporozoite positivity in HLC collection (core zone) in interim dataset 71

Table 37: Summary statistics on sporozoite positivity in HLC collection (core zone) in final dataset 71

Table 38: Summary statistics of EIR in HLC collection (core zone) in interim dataset 71

Table 39: Summary statistics of EIR in HLC collection (core zone) in final dataset 71

Table 40: Summary statistics on sporozoite positivity in LT collection (core zone) in interim dataset 72

Table 41: Summary statistics on sporozoite positivity in LT collection (core zone) in final dataset 72

Figure 8: Time profile of mean (SD) anopheline density by treatment in the LT collection in the buffer zones in the interim dataset (averaged over 10 clusters per treatment with roughly 15 houses per cluster) 73

Figure 9: Time profile of mean (SD) anopheline density by treatment in the LT collection in the buffer zones in the final dataset (averaged over 10 clusters per treatment with roughly 15 houses per cluster) 73

Table 42: Summary statistics on LT anopheline density in LT collection in buffer zones in interim dataset 74

Table 45: Effects of SR and other covariates on anopheline density per household-day in LT collection in buffer zones in final dataset 74

Table 46: Frequency and percentage for female anopheline abdominal status in LT collection in buffer zones in interim dataset 74

Table 47: Frequency and percentage for female anopheline abdominal status in LT collection in buffer zones in final dataset 75

Table 50: Effects of covariates on blood fed rate (fed + gravid + half gravid) in LT collection in buffer zones in interim data 75

Table 51: Effects of covariates on blood fed rate (fed + gravid + half gravid) in LT collection in buffer zones in final data 75

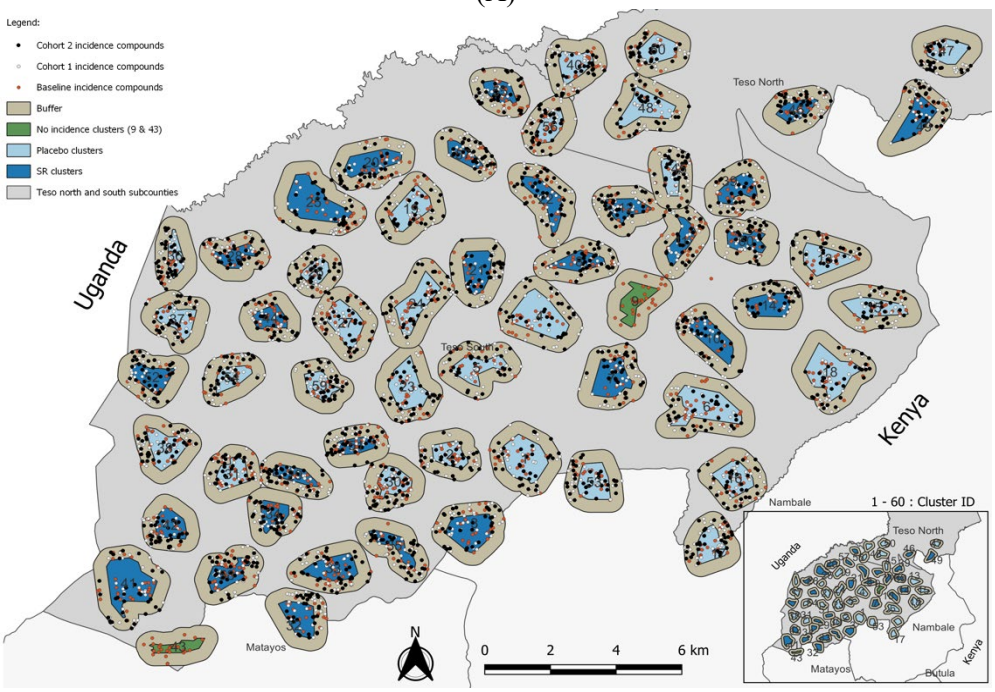
Table 52: Summary statistics on sporozoite positivity in LT collection in buffer zones in interim data 76

Table 53: Summary statistics on sporozoite positivity in LT collection in buffer zones in final data 76

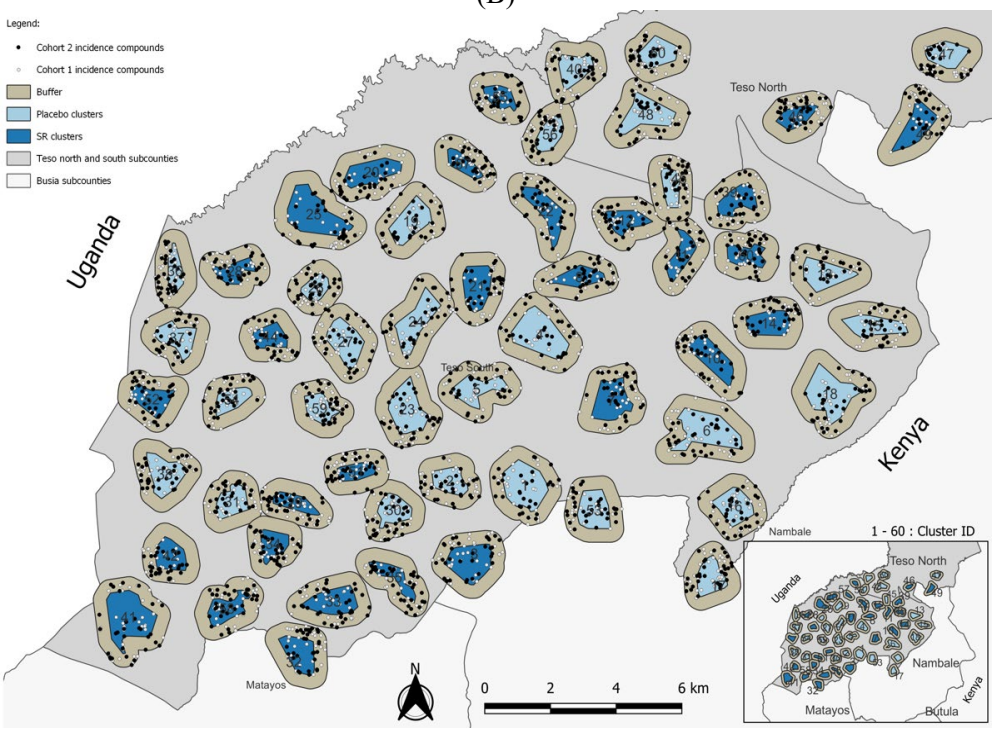
Figure 1: Location of (A) 60 study clusters (core, buffer) from which baseline and (B) 58 study clusters that received intervention were monitored for malaria incidence in Teso North and Teso South Districts, Busia County, Kenya.

Green clusters: Clusters 9 and 43 were removed from randomization and treatment allocation prior to intervention (see Methods).

(A)



(B)



Entomology Methodology

CDC-LT sampling was conducted monthly in 20 clusters (10 SR, 10 placebo). Clusters allocated to CDC-LT were randomly selected prior to baseline, then fixed throughout study. Ten houses in each core and 15 houses in each buffer area were randomly selected monthly for sampling (1-night collection; 5pm to 7am), allowing for repeated measures.

HLC sampling was conducted quarterly in core areas of 12 clusters (6 SR, 6 placebo). Clusters allocated to HLC were a random subset of the 20 clusters selected for CDC-LT, selected prior to baseline, and then fixed throughout the study. Ten houses in each core area were randomly selected at the beginning of baseline and remained fixed for sampling (3-night collections; 5pm to 7am) throughout baseline and C1 study periods. A new set of 10 houses (from the same 12 HLC clusters) were randomly selected prior to C2 and remained fixed for sampling throughout the remainder of the intervention period.

Mosquitoes collected by CDC-LT and HLC were identified to species using morphological keys[1] and species confirmed by PCR.[2] Blood-fed status of anophelines collected by CDC-LT was measured by direct observation using a stereoscope. Samples were grouped per household, per collection night, and tested for sporozoite infectivity.[3] Standard insecticide susceptibility assays[4] were conducted with wild-type anopheline vectors from the study area once at baseline and at the end of intervention period against permethrin (0.75), permethrin+PBO (synergist) and transfluthrin (2ug/ml).

Table 1: PE of SR against overall new infections

	number of subjects	number of overall new infections	person-years	incidence rate per person-year (SE)	hazard ratio[↑] (95% one-sided CI); (95% two-sided CI)	PE[#] (%) (95% one-sided CI); (95% two-sided CI)	one-sided p-value; two-sided p-value
interim data							
SR	764	434	337	1.36 (0.121)	0.68 (0, 0.81); (0.55, 0.84)	32.1 (18.8, 100); (15.9, 45.2)	0.0002; 0.0004
Placebo	762	618	338	1.97 (0.185)			
final data							
SR	769	793	644	1.29 (0.106)	0.70 (0, 0.85); (0.57, 0.88)	29.5 (15.1, 100); (12.0, 43.5)	0.0010; 0.0020
Placebo	777	1105	645	1.84 (0.155)			

[↑] obtained from the cloglog (grouped proportional hazard) model
[#] PE = (1-harzard ratio) ×100%
* the secondary hypothesis on the PE of SR against new infection is one-sided per the study protocol and the pre-specified statistical analysis plan (the rationale for using the one-sided is provide in SI5). The reviewers suggested presenting two-sided 95% CI and two-sided p-value as the primary results in the main text. Whether one-side or two-sided, there is confirmatory evidence on the PE of SR against new malaria infection.

Table 2: Diversion effect of SR on 1st-time infection

	number of subjects	number of overall new infections	person-years	incidence rate per person-year (SE)	hazard ratio[↑] (95% CI)	% reduction[#] (95% CI)
interim data						
SR	1097	342	331	1.03 (0.096)	0.72 (0.58, 0.90)	27.7 (9.9, 41.9)
Placebo	1042	390	303	1.29 (0.127)		
final data						
SR	1106	584	630	0.93 (0.085)	0.73 (0.59, 0.90)	26.8 (9.9, 40.6)
Placebo	1089	642	586	1.10 (0.094)		

[↑] obtained from the cloglog (grouped proportional hazard) model
[#] PE = (1-hazard ratio) ×100%

Table 3: Diversion effect of SR on overall new infections

	number of subjects	number of overall new infections	person-years	incidence rate per person-year (SE)	hazard ratio[↑] (95% CI)	% reduction[#] (95% CI)
interim data						
SR	1097	734	482.3	1.62 (0.149)	0.77 (0.62, 0.95)	23.0 (4.8, 37.6)
Placebo	1042	864	472.7	1.97 (0.185)		
final data						
SR	1106	1325	925.5	1.52 (0.133)	0.84 (0.69, 1.01)	16.5 (-1.5, 31.4)
Placebo	1089	1530	904.8	1.81 (0.148)		

[↑] obtained from the cloglog (grouped proportional hazard) model
[#] (1-harzard ratio) ×100%

Table 4: Summary of baseline covariates of the clusters in the core zones in interim dataset

Subject level		
	SR (n = 764)	**Placebo (n = 762)**
Age at enrollment (years, mean ± SD) (min, max))	5.5 ± 2.6 (1.1, 10.9)	5.8 ± 2.6 (1.2, 10.9)
Sex (% of male)	47.1%	47.6%
Household level		
	SR (n = 764)	**Placebo (n = 762)**
House wall type (Mud %)	78.9%	82.4%
House wall type (Bricks/cement %)	20.4%	16.4%
House roof type (Corrugated iron %)	81.9%	84.0%
House roof type (Grass thatch %)	17.8%	15.6%
Open eaves (Yes %)	69.5%	68.8%
# of doors (mean ± SD) (min, max)	1.07 ± 0.27 (1, 4)	1.06 ± 0.24 (1, 3)
# of windows (mean ± SD) (min, max))	2.32 ± 1.72 (0, 14)	2.32 ± 1.63 (0, 20)
# of glass windows (mean ± SD) (min, max)	1.02 ± 1.84 (0, 13)	0.81 ± 1.63 (0, 9)
# of screen windows (mean ± SD) (min, max)	0.42 ± 1.36 (0, 13)	0.38 ± 1.13 (0, 8)
# of wooden windows (mean ± SD) (min, max)	1.84 ± 1.88 (0, 14)	1.64 ± 1.66 (0, 9)
Cluster level		
	SR (n = 29)	**Placebo (n = 29)**
Cluster population (mean ± SD (min, max))	777.3 ± 55.9 (694, 918)	770.1 ± 60.3 (657, 865)
Baseline incidence rate per person-year (mean ± SD), (min, max))	3.266 ± 1.846 (0.9, 7.7)	3.138 ± 1.381 (1.1, 6.9)
One subject per household was recruited, so the number of subjects and the number of households are the same.		

Table 5: Summary of baseline covariates of the clusters in the buffer zone in interim dataset

Subject level		
	SR (n = 1097)	**Placebo (n = 1042)**
Age at enrollment (years, mean ± SD) (min, max))	5.5 ± 2.6 (0.6, 10.9)	5.8 ± 2.7 (1.0, 10.9)
Sex (% of male)	50.9%	53.1%
Household level		
	SR (n = 1097)	**Placebo (n = 1042)**
House wall type (Mud %)	76.8%	77.7%
House wall type (Bricks/cement %)	22.1%	21.7%
House roof type (Corrugated iron %)	83.0%	82.0%
House roof type (Grass thatch %)	16.4%	17.8%
Open eaves (Yes %)	68.3%	66.5%
# of doors (mean ± SD) (min, max)	1.10 ± 0.43 (1, 11)	1.08 ± 0.30 (1, 5)
# of windows (mean ± SD) (min, max))	2.37 ± 1.86 (0, 17)	2.45 ± 1.76 (0, 16)
# of glass windows (mean ± SD) (min, max)	1.16 ± 2.02 (0, 17)	1.05 ± 1.96 (0, 16)
	SR (n = 29)	**Placebo (n = 29)**
Cluster population (mean ± SD (min, max))	777.3 ± 55.9 (694, 918)	770.1 ± 60.3 (657, 865)
Baseline incidence rate per person-year (mean ± SD), (min, max))	3.266 ± 1.846 (0.9, 7.7)	3.138 ± 1.381 (1.1, 6.9)
One subject per household was recruited, so the number of subjects and the number of households are the same.		

Table 6: Summary of baseline covariates of the clusters in the core zones in final dataset

Subject level		
	SR (n = 769)	**Placebo (n = 777)**
Age at enrollment (years, mean ± SD) (min, max))	5.5 ± 2.6 (1.1, 10.9)	5.8 ± 2.6 (1.2, 10.9)
Sex (% of male)	47.1%	47.1%
Household level		
	SR (n = 769)	**Placebo (n = 777)**
House wall type (Mud %)	78.9%	82.4%
House wall type (Bricks/cement %)	20.4%	16.5%
House roof type (Corrugated iron %)	81.5%	83.9%
House roof type (Grass thatch %)	18.2%	15.7%
Open eaves (Yes %)	69.6%	69.0%
# of doors (mean ± SD) (min, max)	1.07 ± 0.27 (1, 4)	1.06 ± 0.24 (1, 3)
# of windows (mean ± SD) (min, max))	2.32 ± 1.72 (0, 14)	2.33 ± 1.64 (0, 20)
# of glass windows (mean ± SD) (min, max)	1.03 ± 1.85 (0, 13)	0.82 ± 1.65 (0, 9)
# of screen windows (mean ± SD) (min, max)	0.42 ± 1.36 (0, 13)	0.39 ± 1.17 (0, 9)
# of wooden windows (mean ± SD) (min, max)	1.85 ± 1.89 (0, 14)	1.65 ± 1.68 (0, 9)
Cluster level		
	SR (n = 29)	**Placebo (n = 29)**
Cluster population (mean ± SD (min, max))	777.3 ± 55.9 (694, 918)	770.1 ± 60.3 (657, 865)
Baseline incidence rate per person-year (mean ± SD), (min, max))	3.266 ± 1.846 (0.9, 7.7)	3.138 ± 1.381 (1.1, 6.9)
One subject per household was recruited, so the number of subjects and the number of households are the same.		

Table 7: Summary on baseline covariates of the clusters in the buffer zones in final dataset

Subject level		
	SR (n = 1106)	**Placebo (n = 1089)**
Age at enrollment (years, mean ± SD) (min, max))	5.5 ± 2.6 (0.6, 10.9)	5.8 ± 2.7 (1.0, 11.0)
Sex (% of male)	50.7%	53.6%
Household level		
	SR (n = 1106)	**Placebo (n = 1089)**
House wall type (Mud %)	76.7%	77.3%
House wall type (Bricks/cement %)	22.2%	22.1%
House roof type (Corrugated iron %)	83.0%	82.3%
House roof type (Grass thatch %)	16.4%	17.4%
Open eaves (Yes %)	68.3%	66.1%
# of doors (mean ± SD) (min, max)	1.10 ± 0.43 (1, 11)	1.08 ± 0.30 (1, 5)
# of windows (mean ± SD) (min, max))	2.37 ± 1.86 (0, 17)	2.47 ± 1.75 (0, 16)
# of glass windows (mean ± SD) (min, max)	1.16 ± 2.02 (0, 17)	1.05 ± 1.95 (0, 16)
# of screen windows (mean ± SD) (min, max)	0.52 ± 1.53 (0, 11)	0.53 ± 1.50 (0, 16)
# of wooden windows (mean ± SD) (min, max)	1.90 ± 1.98 (0, 17)	1.80 ± 1.96 (0, 16)
Cluster level		
	SR (n = 29)	**Placebo (n = 29)**
Cluster population (mean ± SD (min, max))	777.3 ± 55.9 (694, 918)	770.1 ± 60.3 (657, 865)
Baseline incidence rate per person-year (mean ± SD), (min, max))	3.266 ± 1.846 (0.9, 7.7)	3.138 ± 1.381 (1.1, 6.9)
One subject per household was recruited, so the number of subjects and the number of households are the same.		

Figure 2: Time profile of mean (SD) household product application rate (0 to 100%) by treatment group

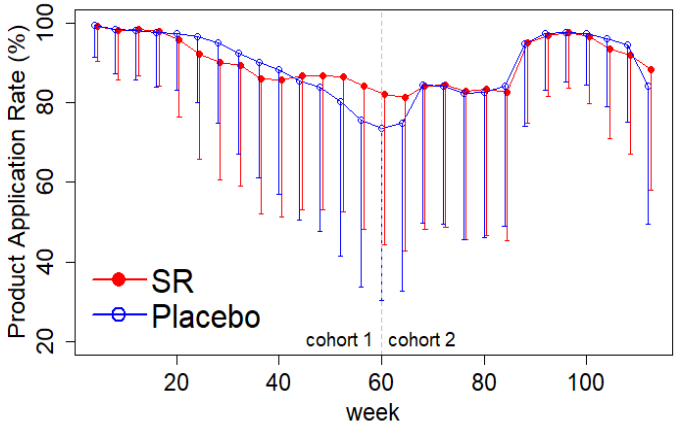


Figure 3: Malaria incidence rates. Mean (+/-SE) incidence rate of the first-time malaria infection (primary endpoint) along with cluster-level incidence rates for 29 spatial repellent (SR) and 29 placebo clusters in participants from cluster core areas at interim and through end of intervention period (2 cohorts, each cohort was followed up for about a year).

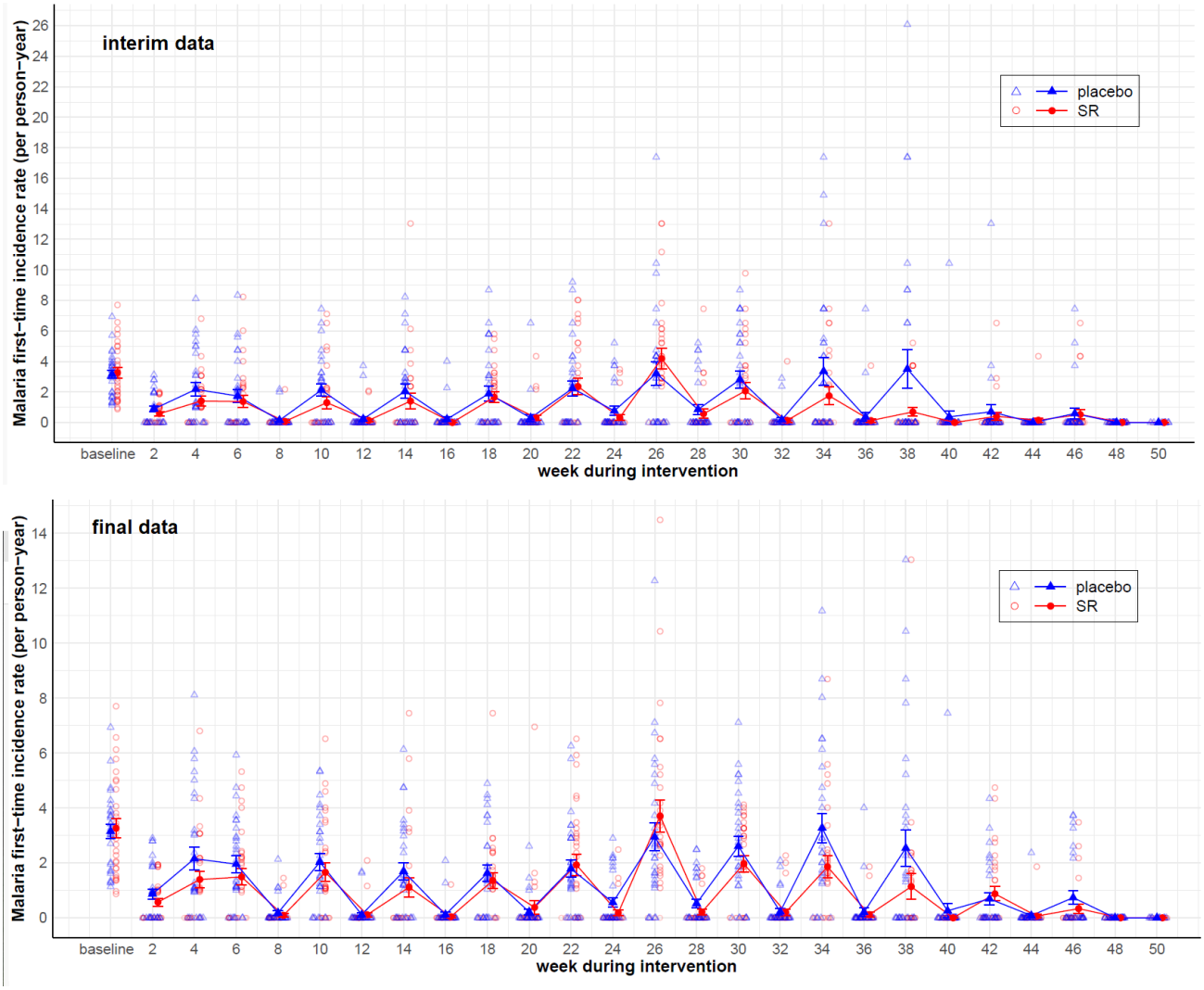


Table 8 and 9 list number of subjects at risk for first-time infection during intervention period on which Figure 3 in SI3 and Figure 3 in main manuscript are based, along with number of clusters with at least one subjects at risk for first-time infection.

Table 8: Number of subjects at risk for first-time infection during intervention period in interim dataset

Treatment	**Week during intervention**												
Number of subjects at risk for the first-time infection													
	4	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Placebo	762	362	321	291	263	242	217	186	162	142	130	125	13
SR	764	362	332	312	292	268	242	201	183	172	166	159	10
Number of clusters with at least one subjects at risk for the first-time infection													
	4	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Placebo	29	29	29	29	29	29	29	29	29	29	29	29	10
SR	29	29	29	29	29	29	29	29	29	29	29	29	9
There were 465 censored subjects in the Placebo arm, and 531 censored subjects under the SR at various time points before the end of their follow-up.													

Table 9: Number of subjects at risk for the first-time infection during the intervention period in final dataset

Treatment	**Week during intervention**												
Number of subjects at risk for the first-time infection													
	4	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Placebo	777	689	631	576	534	498	455	399	353	313	287	275	16
SR	769	711	667	622	589	552	510	442	405	379	365	348	14
Number of clusters with at least subjects at risk for the first-time infection													
	4	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Placebo	29	29	29	29	29	29	29	29	29	29	29	29	10
SR	29	29	29	29	29	29	29	29	29	29	29	29	11
There were 295 censored subjects in the Placebo arm, and 377 censored subjects under the SR at various time points before the end of their follow-up.													

Table 10: PE of SR estimated by model without baseline covariates

Interim data		Final data	
1st-time infection			
Hazard ratio (95% CI)	PE (%) (95% CI)	Hazard ratio (95% CI)	PE (%) (95% CI)
0.63(0.45, 0.90)	36.6 (9.6, 55.5)	0.67 (0.48, 0.93)	33.2 (7.3, 51.9)
Overall new infections			
0.64(0.48, 0.85)	36.3 (14.8, 52.4)	0.651(0.48, 0.87)	34.9 (12.6, 51.6)

Table 11: PE of SR against first-time infection by age group in interim data

Treatment	# of subjects	# of 1st-time infections	Hazard ratio (95% CI)	PE (%) (95% CI)
	Age group [13 months, 59 months)			
SR	370	92	0.66 (0.42, 1.05)	34.0 (-4.8, 58.4)
Placebo	317	97		
	Age group [59 months, 10 years)			
SR	394	141	0.64 (0.47, 0.88)	35.7 (12.2, 52.9)
Placebo	445	200		

Table 12: PE of SR against first-time infection by age group in final data

Treatment	# of subjects	# of 1st-time infections	Hazard ratio (95% CI)	PE (%) (95% CI)
	Age group [13 months, 59 months)			
SR	373	158	0.75 (0.52, 1.09)	24.8 (-8.5, 47.9)
Placebo	326	164		
	Age group [59 months, 11 years)			
SR	396	234	0.61(0.47, 0.81)	38.7 (19.4, 53.3)
Placebo	451	318		

Table 13: PE of SR against overall new infections by age group in interim data

Treatment	# of subjects	# of new infections	Hazard ratio (95% CI)	PE (%) (95% CI)
	Age group [13 months, 59 months)			
SR	370	148	0.73 (0.51, 1.05)	26.9 (-4.8, 49.0)
Placebo	317	174		
	Age group [59 months, 11 years)			
SR	394	286	0.64 (0.51, 0.79)	36.3 (21.1, 48.6)
Placebo	445	444		

Table 14: PE of SR against overall new infections by age group in final data

Treatment	# of subjects	# of new infections	Hazard ratio (95% CI)	PE (%) (95% CI)
	Age group [13 months, 59 months)			
SR	373	283	0.77 (0.56, 1.07)	22.9 (-6.6, 44.3)
Placebo	326	336		
	Age group [59 months, 11 years)			
SR	396	510	0.67 (0.54, 0.82)	33.3 (18.3, 45.6)
Placebo	451	769		

Figure 4: Time profile of mean (SD) HLR by treatment in the HLC collection in the core zones in the interim dataset (averaged over 6 cluster per treatment with roughly 4 households per cluster)

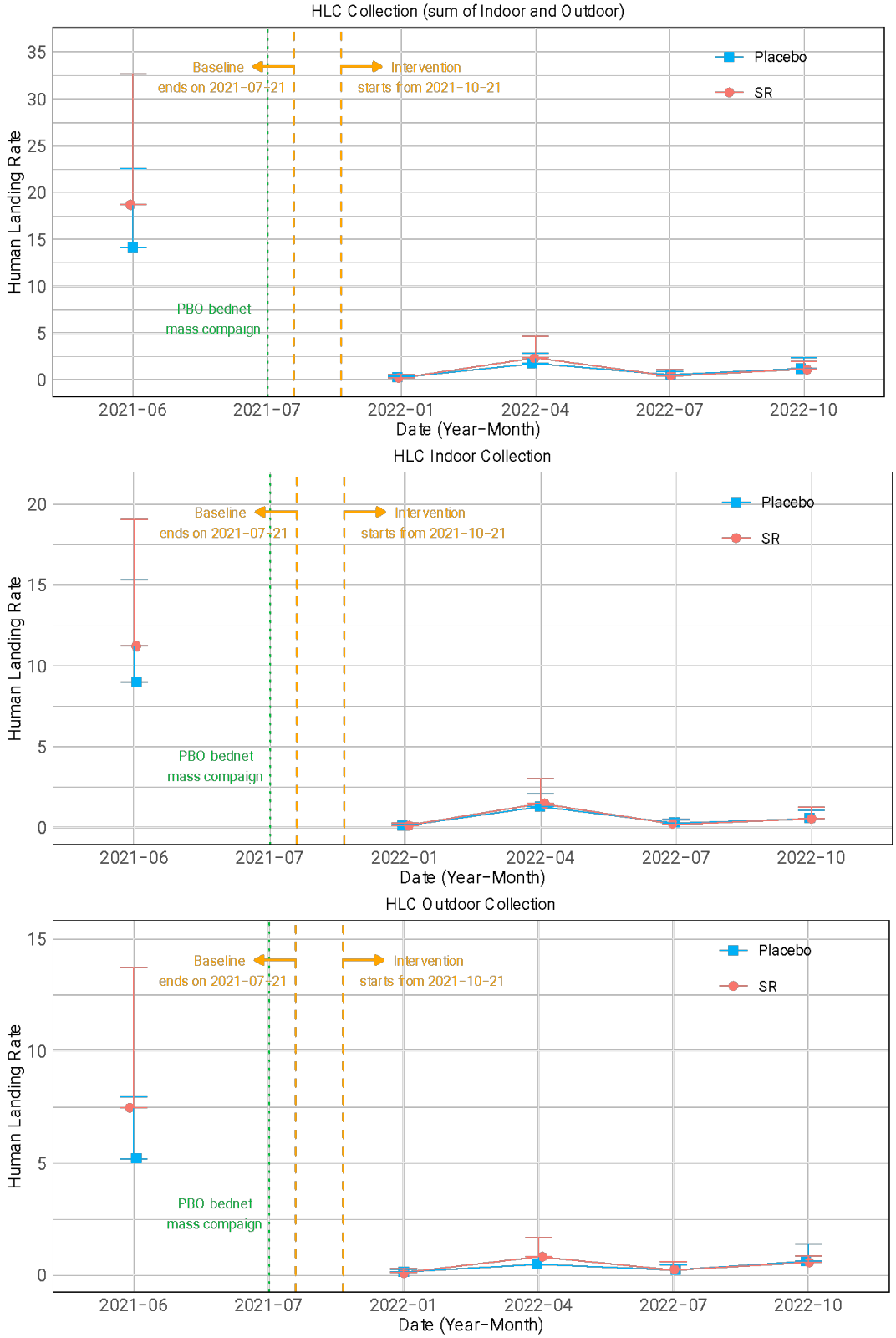


Figure 5: Time profile of mean (SD) HLR by treatment in the HLC collection in the core zones in the final dataset (averaged over 6 cluster per treatment with roughly 4 households per cluster)

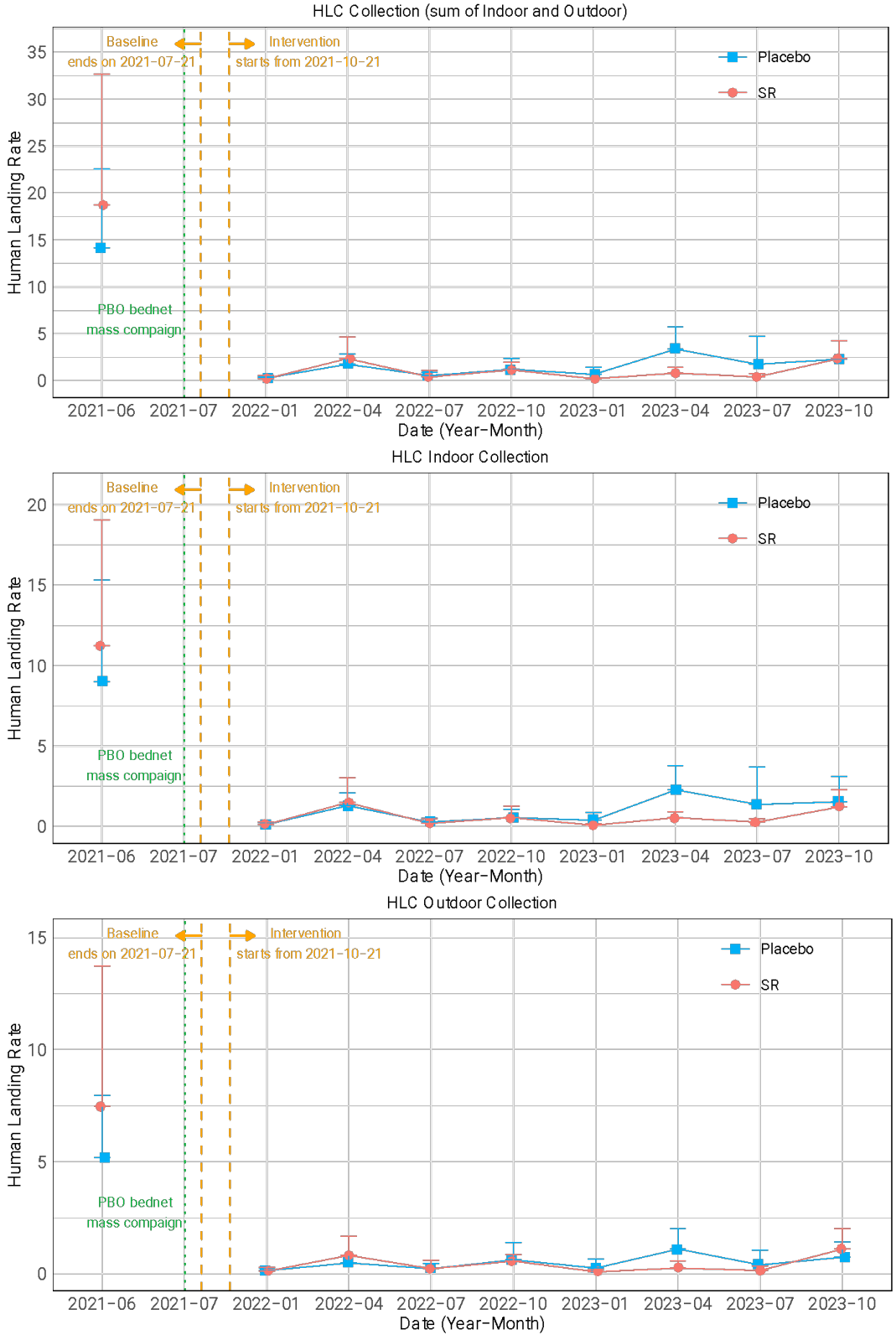


Table 15: Summary statistics of HLR in core zone HLC collection in interim dataset
(n is number of clusters)

		mean (± SD) HLR per household-day (min, max)	
study phase	**location**	**SR (n = 6)**	**placebo (n = 6)**
baseline	Indoor	11.22 ± 7.81 (2.25, 21.33)	8.99 ± 6.34 (4.00, 18.25)
	outdoor	7.47 ± 6.24 (0.83, 15.75)	5.18 ± 2.78 (1.75, 8.50)
intervention	Indoor	0.60 ± 0.59 (0.10, 1.56)	0.58 ± 0.29 (0.31, 1.04)
	outdoor	0.44 ± 0.35 (0, 0.94)	0.37 ± 0.26 (0.13, 0.81)

Table 16: Summary statistics of HLR in core zone HLC collection in final dataset
(n is number of clusters)

		mean (± SD) HLR per household-day (min, max)	
study phase	**location**	**SR (n = 6)**	**placebo (n = 6)**
baseline	Indoor	11.22 ± 7.81 (2.25, 21.33)	8.99 ± 6.34 (4.00, 18.25)
	outdoor	7.47 ± 6.24 (0.83, 15.75)	5.18 ± 2.78 (1.75, 8.50)
intervention	Indoor	0.57 ± 0.41 (0.07, 1.21)	0.99 ± 0.58 (0.24, 1.77)
	outdoor	0.42 ± 0.28 (0.04, 0.76)	0.50 ± 0.27 (0.10, 0.82)

Table 17: Effects of SR and covariates on HLR in HLC collection in core zones in interim dataset

Comparison	**% Change (95% CI)**
Indoor: SR vs placebo	-15.0 (-66.4, 115.2)
Outdoor: SR vs placebo	15.2 (-55.6, 198.6)
Cluster population (increased by 100)	7.82 (-45.2, 111.9)
Baseline HLR (increase by 1 unit)	2.9 (-2.1, 8.1)

Table 18: Effects of SR and covariates on HLR in HLC collection in core zones in final dataset

Comparison	**% Change (95% CI)**
Indoor: SR vs placebo	-29.2 (-69.8, 66.2)
Outdoor: SR vs placebo	10.4 (-53.6, 162.7)
Cluster population (increased by 100)	11.5 (-41.6, 112.9)
Baseline HLR (increased by 1unit)	2.2 (-1.5, 6.2)

Table 19: Frequency and percentage of different *anopheles* species in HLC collection in core zones in final dataset

Anopheles Species	baseline				intervention				Total
	indoor		outdoor		indoor		outdoor		
	SR	placebo	SR	placebo	SR	placebo	SR	placebo	
Anopheles coustani	10 (1.2%)	1 (0.15%)	15 (2.8%)	17 (4.6%)	4 (1.2%)	6 (1.1%)	14 (5.8%)	32 (11.1%)	99
Anopheles funestus s.l.	243 (30.1%)	135 (20.9%)	106 (19.7%)	45 (12.1%)	88 (27.0%)	169 (29.6%)	27 (11.2%)	32 (11.1%)	845
Anopheles gambiae s.l.	554 (68.6%)	509 (78.7%)	417 (77.5%)	311 (83.4%)	234 (71.8%)	395 (69.3%)	200 (83.0%)	215 (74.7%)	2835
Anopheles rufipes	0 (0%)	2 (0.31%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.35%)	3
Anopheles maculipalpis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.35%)	1
Anopheles unknown	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (2.4%)	8
Total	808 (100%)	647 (100%)	538 (100%)	373 (100%)	326 (100%)	570 (100%)	241 (100%)	288 (100%)	3791

Table 20: Summary statistics and parity rate in HLC collection in core zones in interim dataset (n is number of clusters)

		mean (± SD) parity rate per household-day (min, max)	
study phase	**location**	**SR (n = 6)**	**placebo (n = 6)**
baseline	Indoor	84% ± 7% (73%, 91%)	61% ± 19% (29%, 84%)
	outdoor	70%± 14% (50%, 84%)	67% ± 18% (50%, 98%)
intervention	Indoor	77% ± 18% (52%, 100%)[↑]	73% ± 25% (39%, 100%)[↑]
	outdoor	67% ± 17% (46%, 83%)	79% ± 22% (40%, 100%)[↑]

[↑] Some clusters at some collection time point had data from only one household that had a large portion of missing values on parity due to either "NA" or "not performed" or no mosquito was caught. Among the available data points collected from a single household in that cluster, 100% of the mosquitos were parous, leading to a 100% parity rate.

Table 21: Summary statistics and parity rate in HLC collection in core zones in final dataset (n is number of clusters)

		mean (± SD) parity rate per household-day (min, max)	
study phase	**location**	**SR (n = 6)**	**placebo (n = 6)**
baseline	Indoor	84% ± 7% (73%, 91%)	61% ± 19% (29%, 84%)
	outdoor	70%± 14% (50%, 84%)	67% ± 18% (50%, 98%)
intervention	Indoor	61% ± 25% (29%, 100%)[↑]	65% ± 14% (47%, 80%)
	outdoor	65% ± 11% (50%, 78%)	67% ± 14% (46%, 83%)

[↑] Some clusters at some collection time point had data from only one household that had a large portion of missing values on parity due to either "NA" or "not performed" or no mosquito was caught. Among the available data points collected from a single household in that cluster, 100% of the mosquitos were parous, leading to a 100% parity rate.

Table 22: Frequency and percentage of parous status in female anopheline in HLC collection in interim dataset (n=6 clusters per treatment arm)

Parous status	baseline				intervention				Total
	indoor		outdoor		indoor		outdoor		
	SR	placebo	SR	placebo	SR	placebo	SR	placebo	
Parous	319 (82.9%)	228 (71.9%)	209 (78.6%)	154 (72.6%)	47 (61.8%)	40 (65.6%)	39 (67.2%)	26 (53.1%)	1062
Nulliparous	66 (17.1%)	89 (28.1)	57 (21.4%)	58 (27.4%)	29 (38.2%)	21 (34.4%)	19 (32.8%)	23 (46.9%)	362
Total dissected	385 (100%)	317 (100%)	266 (100%)	212 (100%)	76 (100%)	61 (100%)	58 (100%)	49 (100%)	1424

Table 23: Frequency and percentage of parous status in female anopheline in HLC collection in final dataset (n=6 clusters per treatment arm)

Parous status	baseline				intervention				Total
	indoor		outdoor		indoor		outdoor		
	SR	placebo	SR	placebo	SR	placebo	SR	placebo	
Parous	319 (82.9%)	228 (71.9%)	209 (78.6%)	154 (72.6%)	110 (53.9%)	193 (50.4%)	88 (59.5%)	99 (49.5%)	1400
Nulliparous	66 (17.1%)	89 (28.1)	57 (21.4%)	58 (27.4%)	94 (46.1%)	190 (49.6%)	60 (40.5%)	101 (50.5%)	715
Total dissected	385 (100%)	317 (100%)	266 (100%)	212 (100%)	204 (100%)	383 (100%)	148 (100%)	200 (100%)	2115

Table 24: Effects of SR and covariates on parity rate in HLC collection in core zones in interim dataset

Comparison	**Odds ratio (95% CI)**
Indoor: SR vs placebo	0.59 (0.11, 3.12)
Outdoor: SR vs placebo	1.37 (0.29, 6.44)
Cluster population (increased by 100)	1.90 (0.71, 5.03)
Baseline parity rate (increased by 1%)	1.02 (0.99, 1.05)
Examples on the result interpretation: the odds of being parous decreased by 41% in the SR clusters compared to the placebo clusters in the HLC indoor collection; the odds of being parous increased by 37% in the SR clusters compared to the placebo clusters in the HLC outdoor collection.	

Table 25: Effects of SR and covariates on parity rate in HLC collection in core zones in final dataset

Comparison	**Odds ratio (95% CI)**
Indoor: SR vs placebo	0.78 (0.35, 1.73)
Outdoor: SR vs placebo	1.08 (0.49, 2.35)
Cluster population (increased by 100)	1.47 (0.93, 2.35)
Baseline parity rate (increased by 1%)	1.00 (0.99, 1.02)
Examples on the result interpretation: the odds of being parous decreased by 22% in the SR clusters compared to the placebo clusters in the HLC indoor collection; the odds of being parous increased by 8% in the SR clusters compared to the placebo clusters in the HLC outdoor collection.	

Figure 6: Time profile of mean (SD) anopheline density by treatment in LT collection in core zones in interim dataset (averaged over 10 clusters per treatment with roughly 10 households per cluster)

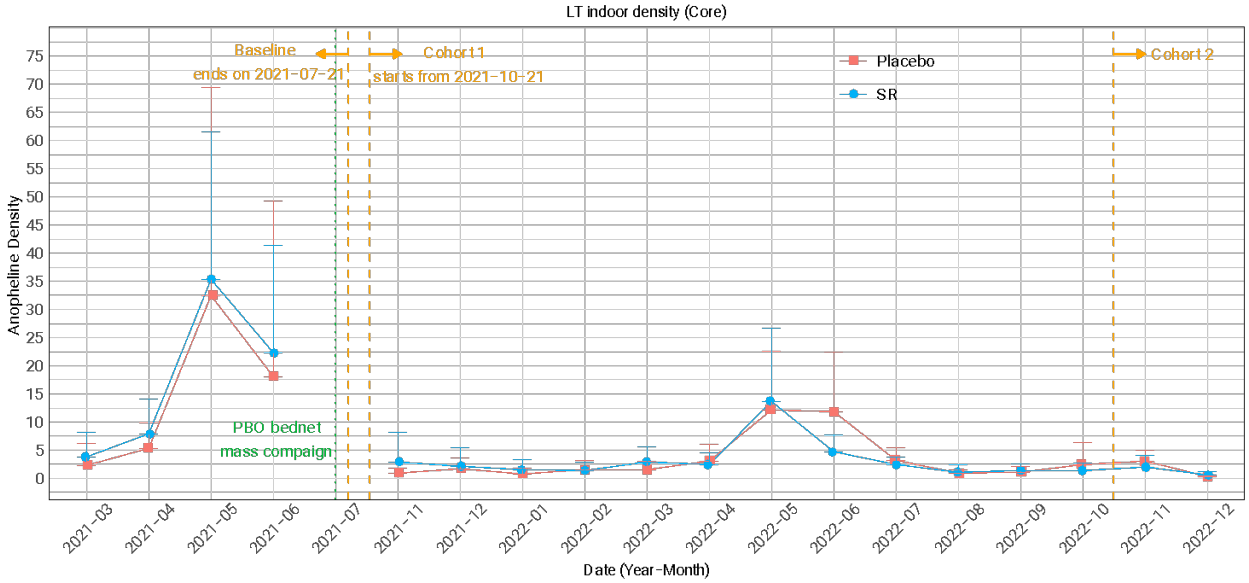


Figure 7: Time profile of mean (SD) anopheline density by treatment in LT collection in core zones in final dataset (averaged over 10 cluster per treatment with roughly 10 households per cluster)

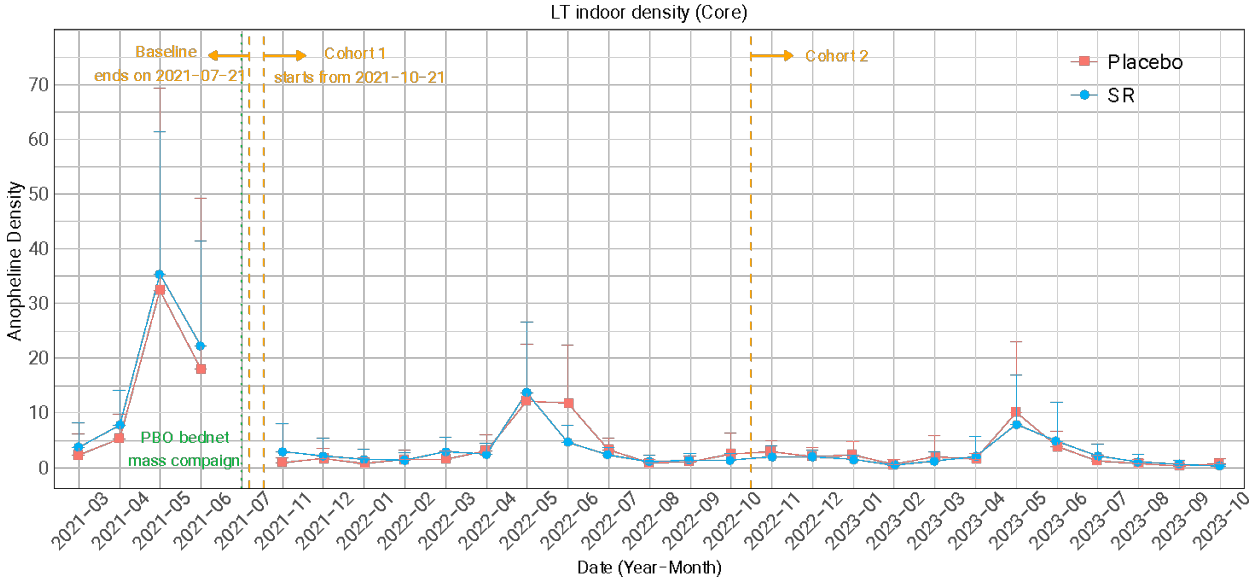


Table 26: Summary statistics on anopheline density in LT collection in core zones in interim dataset (n is number of clusters)

	SR (n = 10)	**placebo (n = 10)**
Baseline anopheline count per household-day (mean ± SD, (min, max))	17.25 ± 11.27 (2.40, 35.25)	13.85 ± 11.05 (2.35, 31.86)
Intervention anopheline count per household-day (mean ± SD, (min, max))	3.00 ± 2.40 (0.72, 7.92)	3.34 ± 2.13 (0.46, 6.29)

Table 27: Summary statistics on anopheline density in LT collection in core zones in final dataset (n is number of clusters)

	SR (n = 10)	**placebo (n = 10)**
Baseline anopheline count per household-day (mean ± SD, (min, max))	17.25 ± 11.27 (2.40, 35.25)	13.85 ± 11.05 (2.35, 31.86)
Intervention anopheline count per household-day (mean ± SD, (min, max))	2.61 ± 2.22 (0.64, 7.77)	2.86 ± 1.88 (0.46, 6.39)

Table 28: Effects of SR and other covariates on anopheline density in LT collection in core zones in interim dataset

Comparison	**% Change (95% CI)**
SR vs placebo	-5.9 (-42.0, 52.6)
Cluster population (every 100 increase)	0.4 (-35.1, 55.5)
Baseline density (every 1 unit increase)	4.3 (2.0, 6.7)

Table 29: Effects of SR and other covariates on anopheline density in LT collection in core zones in final dataset

Comparison	**% Change (95% CI)**
SR vs placebo	-6.6 (-41.0, 47.8)
Cluster population (every 100 increase)	-2.3 (-35.5, 47.9)
Baseline density (every 1 unit increase)	4.0 (1.9, 6.3)

Table 30: Frequency and percentage of abdominal status in female anopheline in LT collection in core zones in interim dataset

abdominal status	**baseline**		**intervention**		**Total**
	SR	**placebo**	**SR**	**placebo**	
Fed	775 (9.62%)	347 (5.42%)	407 (6.5%)	333 (5.19%)	1862
Gravid	259 (3.21%)	113 (1.77%)	143 (2.28%)	185 (2.88%)	700
Half Gravid	36 (0.45%)	30 (0.47%)	51 (0.81%)	53 (0.83%)	170
Unfed	6990 (86.72%)	5908 (92.34%)	5661 (90.4%)	5850 (91.11%)	24409
Total	8060 (100%)	6398 (100%)	6262(100%)	6421 (100%)	27141

Table 31: Frequency and percentage of abdominal status in female anopheline in LT collection in core zones in final dataset

abdominal status	baseline		intervention		Total
	SR	placebo	SR	placebo	
Fed	775 (9.62%)	347 (5.42%)	631 (6.53%)	577 (5.7%)	2330
Gravid	259 (3.21%)	113 (1.77%)	333 (3.45%)	445 (4.39%)	1150
Half Gravid	36 (0.45%)	30 (0.47%)	82 (0.85%)	65 (0.64%)	213
Unfed	6990 (86.72%)	5908 (92.34%)	861 (89.18%)	9039 (89.27%)	30555
Total	8060 (100%)	6398 (100%)	9664 (100%)	10126 (100%)	34248

Table 32: Summary statistics on blood fed rate in LT collection in core zones in interim dataset (n is number of clusters)

Study phase	SR (n = 10)	placebo (n = 10)
Baseline (mean ± SD, (min, max))	0.143 ± 0.053 (0.079, 0.248)	0.134 ± 0.086 (0.044, 0.347)
Intervention (mean ± SD, (min, max))	0.104 ± 0.029 (0.064, 0.146)	0.118 ± 0.016 (0.094, 0.142)

Table 33: Summary statistics on blood fed rate in LT collection in core zones in final dataset (n is number of clusters)

Study phase	SR (n = 10)	placebo (n = 10)
Baseline (mean ± SD, (min, max))	0.143 ± 0.053 (0.079, 0.248)	0.134 ± 0.086 (0.044, 0.347)
Intervention (mean ± SD, (min, max))	0.138 ± 0.040 (0.082, 0.183)	0.143 ± 0.026 (0.096, 0.177)

Table 34: Effects of covariates on blood fed rate in LT collection in core zones in interim dataset

Comparison	Odds ratio (95% CI)
SR vs placebo	1.00 (0.78, 1.29)
Cluster population (every 100 increase)	1.20 (0.93, 1.54)
Baseline blood fed rate (increased by 1%)	1.02 (1.00, 1.04)

Table 35: Effects of covariates on blood fed rate in LT collection in core zones in final dataset

Comparison	Odds ratio (95% CI)
SR vs placebo	0.95 (0.78, 1.15)
Cluster population (every 100 increase)	1.19 (0.97, 1.45)
Baseline blood fed rate (increased by 1%)	1.02 (1.01, 1.04)

Table 36: Summary statistics on sporozoite positivity in HLC collection (core zone) in interim dataset

Treatment	Positive	Negative	Sporozoite Positivity Rate
baseline			
SR	1	464	0.0022
placebo	0	447	0.0000
Intervention			
SR	4	270	0.0148
placebo	3	209	0.0144

Table 37: Summary statistics on sporozoite positivity in HLC collection (core zone) in final dataset

Treatment	Positive	Negative	Sporozoite Positivity Rate
baseline			
SR	1	464	0.0022
placebo	0	447	0.0000
intervention			
SR	6	528	0.0114
placebo	8	781	0.0102

Table 38: Summary statistics of EIR in HLC collection (core zone) in interim dataset

Location	Treatment	Baseline	Intervention
Indoor	SR	0.0114	0.0347
	placebo	0	0.0271
Outdoor	SR	0	0.0161
	placebo	0	0
The baseline HLC collection started on May 31, 2021 and ended on June 18, 2021. The intervention HLC collection in Cohort 1 started on Jan 17, 2022 and ended on Oct 14, 2022.			

Table 39: Summary statistics of EIR in HLC collection (core zone) in final dataset

Location	Treatment	Baseline	Cohort 1	Cohort 2
Indoor	SR	0.0114	0.0347	0.0071
	placebo	0	0.0271	0.0165
Outdoor	SR	0	0.0161	0.0083
	placebo	0	0	0.0093
The baseline HLC collection started on May 31, 2021 and ended on June 18, 2021. The intervention HLC collection in Cohort 1 started on Jan 17, 2022 and ended on Oct 14, 2022. The intervention HLC collection in Cohort 2 started on Jan 16, 2023 and ended on Oct 27, 2023				

Table 40: Summary statistics on sporozoite positivity in LT collection (core zone) in interim dataset

Treatment	Positive	Negative	Sporozoite Positivity Rate
Baseline			
SR	32	1269	0.0252
placebo	12	1049	0.0114
Cohort 1			
SR	19	2147	0.0088
placebo	28	1989	0.0141
Cohort 2			
SR	1	164	0.0061
placebo	1	161	0.0062

Table 41: Summary statistics on sporozoite positivity in LT collection (core zone) in final dataset

Treatment	Positive	Negative	Sporozoite Positivity Rate
Baseline			
SR	32	1269	0.0252
placebo	12	1049	0.0114
Cohort 1			
SR	19	2147	0.0088
placebo	28	1989	0.0141
Cohort 2			
SR	35	1792	0.0195
placebo	41	1610	0.0255

Figure 8: Time profile of mean (SD) anopheline density by treatment in the LT collection in the buffer zones in the interim dataset (averaged over 10 clusters per treatment with roughly 15 houses per cluster)

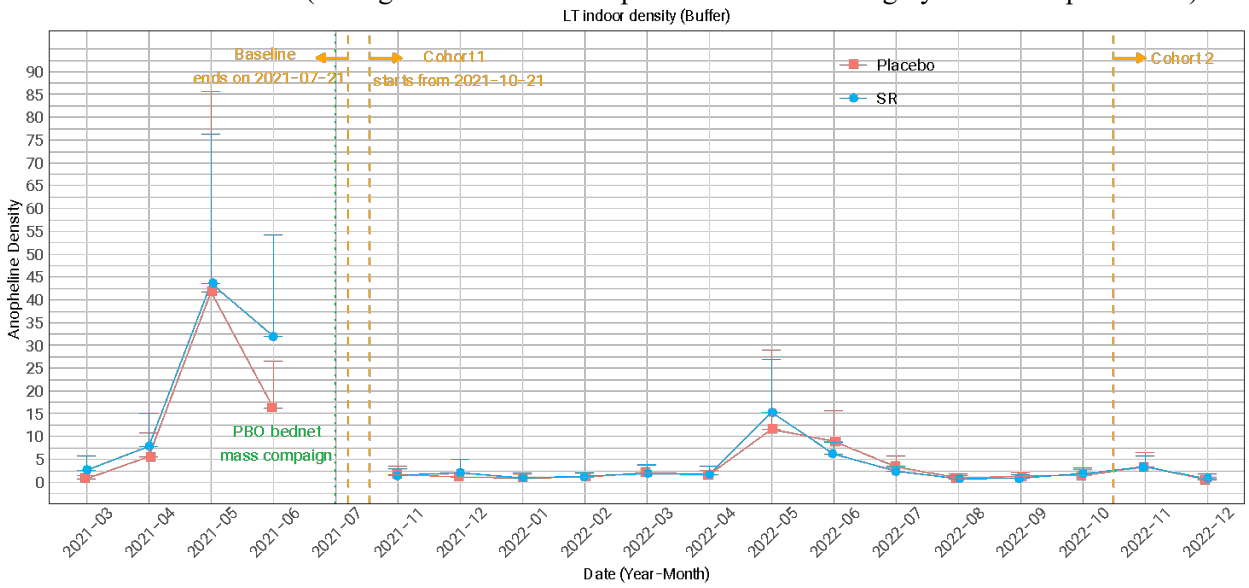


Figure 9: Time profile of mean (SD) anopheline density by treatment in the LT collection in the buffer zones in the final dataset (averaged over 10 clusters per treatment with roughly 15 houses per cluster)

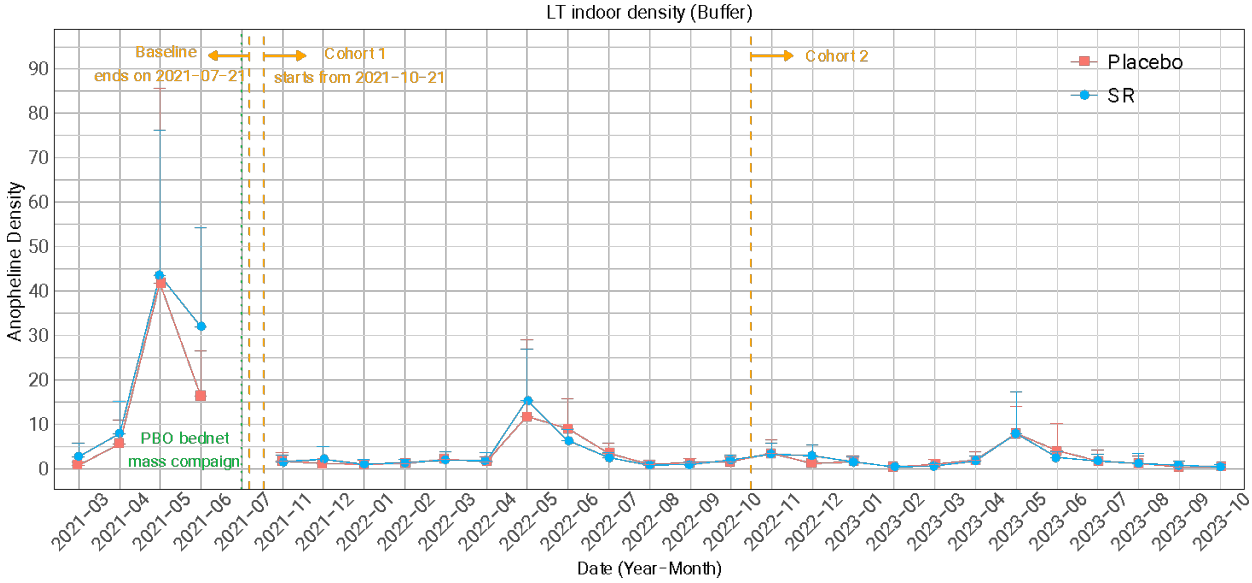


Table 42: Summary statistics on LT anopheline density in LT collection in buffer zones in interim dataset (n is number of clusters)

Study phase	SR (n = 10)	placebo (n = 10)
Baseline (mean ± SD, (min, max))	22.36 ± 13.76 (0.33, 42.87)	15.03 ± 13.29 (0.95, 44.96)
Intervention (mean ± SD, (min, max))	3.05 ± 1.77 (0.73, 5.71)	2.98 ± 2.27 (0.67, 8.17)

Table 43: Summary statistics on LT anopheline density per house-day in LT collection in buffer zones in final dataset (n is number of clusters)

Study phase	SR (n = 10)	placebo (n = 10)
Baseline (mean ± SD, (min, max))	22.36 ± 13.76 (0.33, 42.87)	15.03 ± 13.29 (0.95, 44.96)
Intervention (mean ± SD, (min, max))	2.51 ± 1.49 (0.60, 5.76)	2.47 ± 1.88 (0.44, 6.98)

Table 44: Effects of SR and other covariates on anopheline density per household-day in LT collection in buffer zones in interim dataset

Comparison	% Change (95% CI)
SR vs placebo	-20.6 (-45.1, 15.1)
Cluster population (every 100 increase)	54.8 (11.8, 114.5)
Baseline density (every 1 unit increase)	3.7 (2.3, 5.2)

Ochomo et al. Spatial Repellent Efficacy in Kenya

Table 45: Effects of SR and other covariates on anopheline density per household-day in LT collection in buffer zones in final dataset

Comparison	% Change (95% CI)
SR vs placebo	-19.2 (-46.0, 20.9)
Cluster population (every 100 increase)	53.6 (7.7, 119.0)
Baseline density (every 1 unit increase)	3.7 (2.1, 5.2)

Table 46: Frequency and percentage for female anopheline abdominal status in LT collection in buffer zones in interim dataset

Abdominal Status	baseline		intervention		Total
	SR	placebo	SR	placebo	
Fed	881 (7.46%)	639 (7.24%)	702 (8.03%)	489 (5.63%)	2711
Gravid	394 (3.34%)	262 (2.97%)	251 (2.87%)	363 (4.18%)	1270
Half Gravid	55 (0.47%)	28 (0.32%)	63 (0.72%)	85 (0.98%)	231
Unfed	10475 (88.73%)	7895 (89.47%)	7724 (88.38%)	7744 (89.21%)	33838
Total	11805 (100%)	8824 (100%)	8740 (100%)	8681 (100%)	38050

Table 47: Frequency and percentage for female anopheline abdominal status in LT collection in buffer zones in final dataset

Abdominal Status	baseline		intervention		Total
	SR	placebo	SR	placebo	
Fed	881 (7.46%)	639 (7.24%)	924 (6.88%)	774 (6.01%)	3218
Gravid	394 (3.34%)	262 (2.97%)	487 (3.63%)	669 (5.19%)	1812
Half Gravid	55 (0.47%)	28 (0.32%)	91 (0.68%)	119 (0.92%)	293
Unfed	10475 (88.73%)	7895 (89.47%)	11930 (88.82%)	11325 (87.88%)	41625
Total	11805 (100%)	8824 (100%)	13432 (100%)	12887 (100%)	46948

Table 48: Summary statistics on blood fed rate (fed + gravid + half gravid) in LT collection in buffer zones in interim data (n is number of clusters)

Study phase	SR (n = 10)	placebo (n = 10)
Baseline (mean ± SD, (min, max))	0.167 ± 0.089 (0.048, 0.330)	0.128 ± 0.074 (0.041, 0.280)
Intervention (mean ± SD, (min, max))	0.121 ± 0.034 (0.085, 0.204)	0.11.8 ± 0.035 (0.068, 0.170)

Table 49: Summary statistics on blood fed rate (fed + gravid + half gravid) in LT collection in buffer zones in final data (n is number of clusters)

Study phase	SR (n = 10)	placebo (n = 10)
Baseline (mean ± SD, (min, max))	0.167 ± 0.089 (0.048, 0.330)	0.128 ± 0.074 (0.041, 0.280)
Intervention (mean ± SD, (min, max))	0.14.3 ± 0.043 (0.104, 0.237)	0.15.6 ± 0.027 (0.107, 0.187)

Table 50: Effects of covariates on blood fed rate (fed + gravid + half gravid) in LT collection in buffer zones in interim data

Comparison	Odds ratio (95% CI)
SR vs placebo	1.05 (0.83, 1.33)
Cluster population (every 100 increase)	1.03 (0.83, 1.28)
Baseline blood fed rate (increased by 1%)	1.00 (0.98, 1.01)

Table 51: Effects of covariates on blood fed rate (fed + gravid + half gravid) in LT collection in buffer zones in final data

Comparison	Odds ratio (95% CI)
SR vs placebo	0.93 (0.78, 1.12)
Cluster population (every 100 increase)	1.01 (0.86, 1.20)
Baseline blood fed rate (increased by 1%)	1.00 (0.99, 1.01)

Table 52: Summary statistics on sporozoite positivity in LT collection in buffer zones in interim data

Treatment	Positive	Negative	Sporozoite Positivity Rate
Baseline			
SR	69	1821	0.0379
placebo	36	1397	0.0258
Cohort 1			
SR	36	2316	0.0155
placebo	24	2333	0.0103
Cohort 2			
SR	1	302	0.0033
placebo	1	313	0.0032

Table 53: Summary statistics on sporozoite positivity in LT collection in buffer zones in final data

Treatment	Positive	Negative	Sporozoite Positivity Rate
Baseline			
SR	69	1821	0.0379
placebo	36	1397	0.0258
Cohort 1			
SR	36	2316	0.0155
placebo	24	2333	0.0103
Cohort 2			
SR	35	1804	0.0194
placebo	47	2132	0.0220

References

1. Coetzee M. Key to the females of afrotropical anopheles mosquitoes (Diptera: Culicidae). Malar J. 2020;19:1-20.

2. Scott JA, Brogdon WG, Collins FH. Identification of single specimens of the Anopheles gambiae complex by the polymerase chain reaction. Am J Trop Med Hyg. 1993;49(4):520-9.

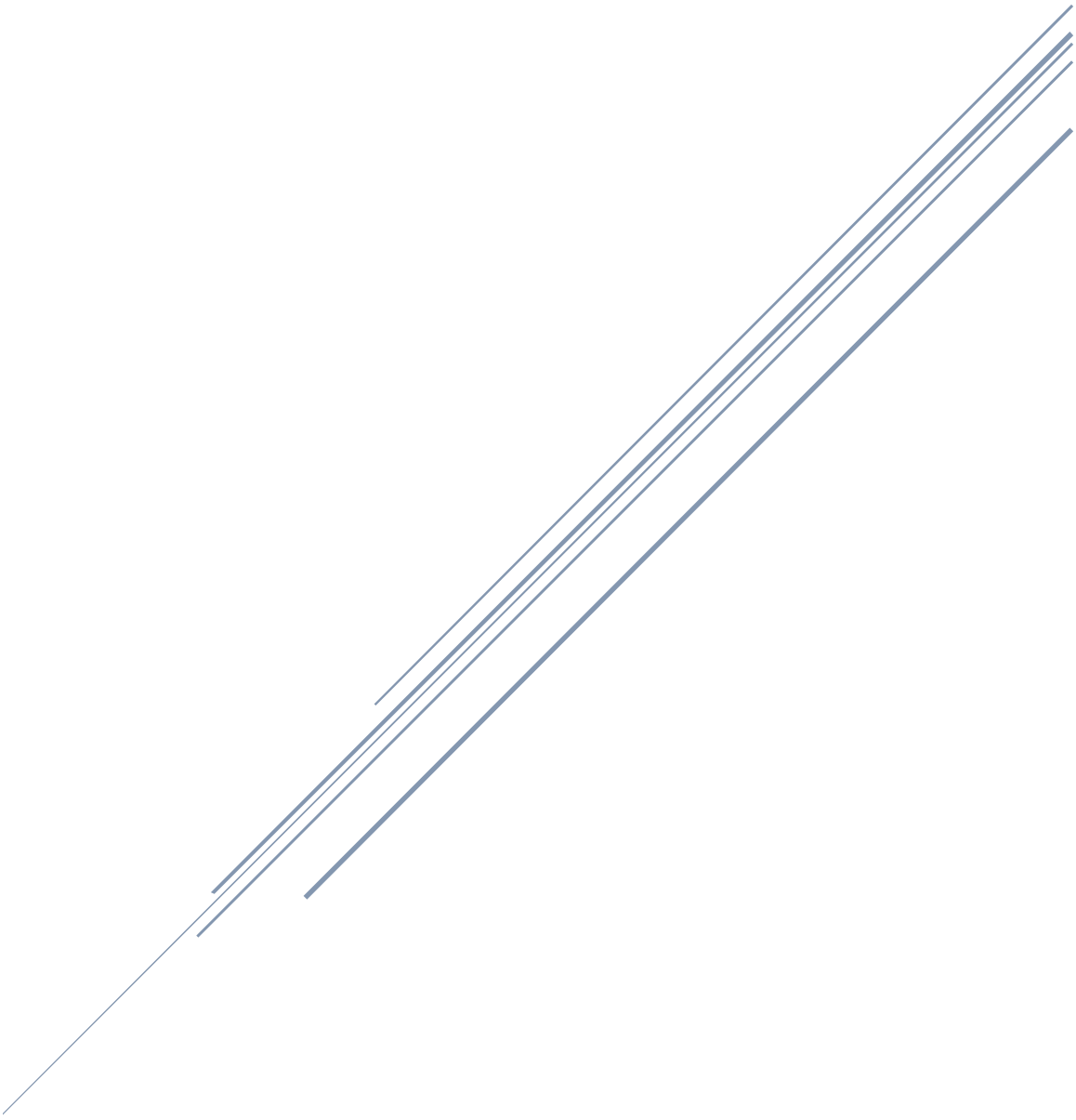
3. Wirtz RA, Zavala F, Chareonvit Y, et al. Comparative testing of monoclonal antibodies against plasmodium falciparum sporozoites for ELISA development. Bull World Health Organ. 1987;65(1):39-45.

4. CDC. Global manual for evaluating insecticide resistance using the CDC Bottle Bioassay. 2011.

S4. Statistical Analysis Plan

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Ochomo EO, Gimnig JE, et al. Effect of a spatial repellent on malaria incidence in an area of western Kenya characterized by high malaria transmission, insecticide resistance and universal coverage of insecticide treated nets: a cluster-randomized, controlled trial



Spatial Repellent Products for Control of Vector Borne Diseases

Kenya

Statistical Analysis Plan

Version 6.3

April 3, 2024

Prepared by Fang Liu

fang.liu.131@nd.edu

Summary of Changes of the Kenya Study SAP

Version	Date	Summary of Major Changes
V1.0	May, 2018	A very early draft
V2.0	June 18, 2018	Revised based on the feedback from UNITAID consortium meeting on May 30 and 31, 2018
V3.0	Aug 14, 2018	Added more details to the secondary and tertiary objectives and the associated endpoints.
V4.0	Sep 11, 2018	Corrected the terminology in the description of the entomological endpoints
V4.1	Oct 19, 2018	study design changed from one cohort with 12-month follow-up to one cohort with 18-month follow-up
V4.2	Dec 19, 2018	study design changed from one cohort with 18-month follow-up to two cohort with 12-month follow-up each
V4.3	Apr 14, 2019	Proofreading before sending to VCAG for review
V4.4	July 21, 2019	Addressed VCAG off-cycle comments
V4.4.1 V4.4.2	Aug 27, 2019	Added the adjusted (human landing rate) HB=LR analysis based on the feedback from the JHU (Johns Hopkins University)
V4.4.3	Nov 7, 2019	Replotted Figure 1 to clarify the study design schematic
V5.0	Feb 13, 2020	Revised according to the Nov 12, 2019 VCAG comments
V5.1	Nov 18, 2020	Reduced the upper age limit at time of enrollment from 15 years to 9 years and 11 months, per the request of WHO ethical panel to remove pregnancy testing from the study procedures.
V5.2	Jan 19, 2021	Corrected a typo (“overall new Pf malaria infection” was misplaced under “primary endpoint” in Sec 3 and should be under “secondary endpoints” in Sec 3)
V5.3	March 4, 2021	Modified the subsection (7.4) on how missing data will be handled; adjusted the definition of new infection and protection period after malaria clearance treatment in Sec 6.
V6	Aug 26, 2021	Adjustment of sample size based on the results from the baseline data analysis. Specifically, one cluster (#43) had 0 malaria infections during the 4-month baseline period. If included in the intervention phase, the data from the cluster could bias the PE estimation. This version of the SAP is based on the scenario of dropping cluster #43 and one additional cluster to maintain the balance between treatment arms (29 clusters per arm instead of the originally planned 30). We reduce the study power from the original 85% to 80% to mitigate the impact on the change in the # of households per cluster from dropping two clusters. There are no other changes in the SAP.
V6.1	Sep 2, 2021	Added the justification for removing clusters #43 and #9 in Section 4 (Study Design) and corrected a few typos.
V6.2	Nov 1, 2021	1) Revised the safety and AE analysis plan per the request of the UNITAID DSMB; 2) added the formula for calculating EIR
V6.2.1	April 15, 2022	Provided clear and precise definition on the endpoints in the primary and secondary hypotheses.

V6.3	April 3, 2024	**1)** Added the analysis on LT data to examine the effect of SR on blood fed rate using abdominal status and on sporozoite positivity rate. The results were part of the package submitted to VCAG in Feb, 2024. **2)** Updated the term "human biting rate" (HBR) to "human landing rate" (HLR). No change in the analysis plan for the endpoint **3)** Removed the summary statistics analysis on AE/SAE by "Probable", "Possible", "Plausible", "Unlikely" due to SR as no such data were collected. **4)** Removed the PE analysis by malaria parasites species given tha Pf accounted for about 95% of malaria infections. **5)** Removed the entomology analysis by anopheline species for the following reasons. First, among all the anopheline species, Anopheles gambiae s.l. and Anopheles funestus s.l. accounted for >95% mosquitos caught by HLC and ~99% caught by LT. Second, there was no statistically significant differences between SR and placebo across all anopheline species combined, no difference is expected for the by-species analysis. **6)** Changed the models for sporozoite positivity and parity status to logistic regression models based on how the data was collected and for consistency reasons. **7)** Removed the human-behavior-adjusted HLR analysis as data were not properly collected to support such an analysis. Specifically, in order to run the analysis, the human behavior data (e.g. how many people slept indoors or outdoors) are paired with the entomology data by time and household. However, the data in the database suggest that the two types of data were collected days and weeks apart, deviating from what the team had planned to do. The social science expert suggested human behaviors can vary greatly day to day and it would not be meaningful to pair the human behavior data and entomology data collected in different time periods. **8)** Removed the PE analysis by year given that the two cohorts were followed up sequentially and each cohort was only followed-up for one year. In other words, cohort is a complete confounder for year, and the two cohorts are just two random samples from the population and no differences are expected in the two cohorts on PE and there is no interest or scientific justification for detecting cohort differences. The effect on seasonality on PE will be run as planned with some flexibility around the wording for this analysis, depending on what types of data are collected on seasonality from the study. **9)** For the human-behavior-adjusted PE, added wording to allow for flexibility around this analysis, depending on what data is collected, and added a note to state the reasons why the analysis adjusting for bednet usage and travelling will not be run. Added the sensitivity

		analyses on PE to account for possible subjects' non-respondence and non-compliance to the anti-malaria treatment. **10)** Moved the analysis on PE-adjusted for the product application rate from the human-behavior-adjusted PE to the per-protocol analysis section and added more details on the statistical methods for this PP analysis. Added a note to state the reasons why the PP analysis considering treatment switching and absence of product protection due to travelling and hospitalization cannot be conducted in this study. **11)** Added the following post-hoc analysis per a VCAG request from the 2024-March meeting: include an interaction term between treatment and age group (<59-month old vs. >= 59-month old) and examine if the interaction is significant or not. **12)** Corrected a few typos.

Contents

Summary of changes of the Kenya Study SAP 84
1 Objectives 84
2 Hypotheses 84
3 Endpoints 85
4 Study Design 85
5 Population for analysis 86
6 Definition of new malaria infection 87
7 Statistical Methods 88
7.1 Primary endpoint (ITT Population) 88
7.2 Secondary endpoints (ITT Population) 89
7.3 Supplementary analysis 93
7.4 Handling of missing data 95
7.5 Analysis of baseline 95
7.6 Interim analysis 95
8 Software 86
9 Sample Size Determination 96
Reference 97
Appendix 98
I. Sample size under different assumptions of baseline incidence rate and between-cluster CV 98
II. Mock Tables and Figures 100
III. Some sample SAS and R procedures used in the analysis 103

Remark 1: Unless otherwise stated, the term "first-time infection" in the primary hypothesis refers to the first-time malaria infection in the core zone per a positive diagnosis either independently for Pf, Pv, Po, Pm, or any combinations of the four; and the term "overall infection" in the secondary hypothesis refers to the overall malaria infections in the core zone per a positive diagnosis independently either for Pf, Pv, Po, Pm, or any combinations of the four.

1 Objectives

Primary Objective

1. To evaluate the protective efficacy (PE) of spatial repellent (SR) against the first-time malaria infection in the core zones in Kenya.

Secondary Objectives

1. To evaluate the PE of SR against overall malaria infections (both first-time and recurrent new infections) in the core zones.
2. To evaluate the PE of SR against first-time and overall malaria infections by two age subgroups (≤ 59 months old; 5 years old to 9 years and 11 months old) in the core zones and examine if the PE is different for the two age groups
3. To assess the diversion effect (dispersion effect) of SR on malaria infections (both first-time and overall) in Kenya.
4. To evaluate the effect of SR on anopheline-human contact using human landing rate (HLR) as an indicator indoor and outdoor for all anopheline
5. To evaluate the effect of SR on anopheline survival and population age structure using parity rate as an indicator for all anopheline.
6. To evaluate the effect of SR on anopheline infectivity using sporozoite positivity rate as an indicator for all anopheline.
7. To evaluate the effect of SR on anopheline infectivity using entomological inoculation rate (EIR) as an indicator for all anopheline.
8. To evaluate the effect of SR on light trap indoor density, blood fed rate via abdominal status, and sporozoite positivity rate for all anopheline in both the core zone and the buffer zone
9. To investigate the relationships between the reduction in first-time and overall malaria infection and the HLC HLR, mosquito density by light trap indoor density, the parity rate, the sporozoite rate, and the EIR for all anopheline.
10. To evaluate SR insecticide resistance at baseline and each year during the intervention period and to explore its relationship with PE
11. To assess the safety of SR.

2 Hypotheses

Primary Hypothesis

H_0: SR does not reduce the first-time malaria hazard rate compared to placebo in Kenya.

H_1: SR reduces the first-time malaria hazard rate compared to placebo (overall malaria hazard ratio between SR and placebo is < 1; the expected PE is 30%)

Secondary Hypothesis

H_0: SR does not reduce the overall malaria hazard rate compared to placebo in Kenya.

H_1: SR reduces the overall malaria hazard rate compared to placebo (overall malaria hazard ratio between SR and placebo is < 1; the expected PE is 30%)

3 Endpoints

The primary endpoint is the first-time malaria infection in the core zones from the intervention follow-up period.

The second endpoints include:

1. Overall new malaria infection during the intervention follow-up period in the core zones.
2. The first-time and overall malaria infections during the follow-up period in the buffer zones.
3. The first-time and overall malaria infections by two age groups (≤ 59 months old; 5 years old to 9 years and 11 months old)).
4. Anopheline-human contact using HLR as an indicator indoor and outdoor for all anopheline species.
5. Anopheline survival and population age structure using parity rate as an indicator for all anopheline species.
6. Anopheline infectivity using sporozoite rate as an indicator for all anopheline
7. Anopheline infectivity using EIR as an indicator for all anopheline.
8. Light trap indoor density, abdominal status, and sporozoite positivity rate for all anopheline in both the core zone and the buffer zone.
9. Baseline and annual insecticide resistance.
10. Adverse events and serious adverse events.

4 Study Design

The original study design had 30 clusters per treatment arm during both the baseline and intervention periods. The analysis results of the baseline data (read 1 of microscopy) on Aug 9 suggested that **Cluster 43** has zero malaria infections during a 4-month baseline period. For this reason, we have proposed to VCAG, and received endorsement, to remove Cluster 43 (the zero-incidence cluster) and one additional study cluster (two clusters total) in order to maintain balance between treatment arms. The resulting ratio of SR to placebo is 29:29 (58 total clusters) vs. 30:30 originally proposed.

Cluster 09 is the second cluster selected to be removed from the intervention phase. This cluster was selected by consensus from the UND, KEMRI and CDC teams based on the following criteria: 1) Cluster 09 was excluded from the entomology sampling frame during baseline due to the rapid urbanization of the village, therefore baseline entomology endpoints will not be affected; 2) Cluster 09 is experiencing rapid urbanization trends similar to Cluster 43 which will lead to challenges in SR product application inside homes due to housing construction (cemented painted walls as opposed to mud walls), as more people are refusing installation of the wall hanging devices(hooks, screws and tapes) as well as potential bias in exposure to malaria risk. Cluster 09 also happened to have the third-lowest baseline incidence rate based on the preliminary baseline data analysis.

The study design is a cluster randomized trial with 29 clusters per intervention arm (SR and Placebo), with a 4-month baseline follow-up (60 clusters in total), one month of baseline data evaluation before randomization, and a total of post-randomization follow-up period of 24 months.

The clusters post randomization will be split into two temporally and spatially non-overlapping cohorts, and each cohort will be followed up for 12 months after they receive intervention.

For the evaluation of the primary objective, 28 households are recruited from each cluster or equivalently 14 households per cohort per cluster (factoring in a 35% loss-to-follow-up rate). For the evaluation of the secondary objective on the diversion effect, 40 households or equivalently 20 households per cohort are recruited from each cluster (factoring in a 35% loss-to-follow-up rate). One kid aged from 6 months old to 9 years and 11 months old from each household is recruited for the biweekly (every 2 weeks) malaria check-up during the intervention follow-up period. The design schematic is illustrated in Figure 1 below.

Twenty clusters (10 SR, 10 placebo) will be randomly selected to estimate the impact of the SR on entomological measures of malaria transmission. Within each cluster, light trap collections will be conducted in 10 randomly selected households within the core area of each sentinel clusters every month to assess the impact of SRs on the density of Anopheles mosquitoes indoors. On the same night, light trap collections will be collected in 15 randomly selected households in the buffer area of the same cluster to estimate the diversion effect of the spatial repellent. The indoor/outdoor human landing catches (HLC) will be conducted in 4 houses in each of 12 clusters (6 intervention and 6 control) every quarter.

<table>
<tr><td rowspan="2">Baseline Cohort
(4-month follow-up + 1-month evaluation)</td><td colspan="2">Intervention Cohorts</td></tr>
<tr><td>12 months (Cohort 1)</td><td>12 months (Cohort 2)</td></tr>
<tr><td></td><td colspan="2">Core zone (29clusters on SR and 29 clusters on PBO with 28 HHs per cluster)</td></tr>
<tr><td rowspan="4">60 clusters;
20 HHs per cluster</td><td>SR (29 clusters; 14 HHs per cluster)</td><td rowspan="2"></td></tr>
<tr><td>PBO (29 clusters; 14 HHs per cluster)</td></tr>
<tr><td rowspan="2"></td><td>SR (29 clusters; 14 HHs per cluster)</td></tr>
<tr><td>PBO (29 clusters; 14 HHs per cluster)</td></tr>
<tr><td></td><td colspan="2">Buffer zone (29 clusters on SR and 29 clusters on PBO with 40 HHs per cluster)</td></tr>
<tr><td rowspan="4">60 clusters;
14 HHs per cluster</td><td>SR (29 clusters; 20 HHs per cluster)</td><td rowspan="2"></td></tr>
<tr><td>PBO (29 clusters; 20 HHs per cluster)</td></tr>
<tr><td rowspan="2"></td><td>SR (29 clusters; 20 HHs per cluster)</td></tr>
<tr><td>PBO (29 clusters; 20 HHs per cluster)</td></tr>
</table>

Figure 1: Study Design Schematic for PE evaluation

5 Population for analysis

The intention to treat (ITT) analysis is the primary analysis approach for both the primary and secondary objectives. The ITT population includes the first recruited kid from each recruited household that receives at least one SR product or placebo per the cluster randomization schedule. If a recruited subject comes from a household used for entomological data collection, that subject will be not used in the ITT analysis. The per-protocol (PP) analysis is included as a supplementary analysis for the primary and secondary objectives. The PP population includes the subjects from the ITT population that are treated following the specifications of the study protocol without major protocol deviations.

5.1 Subjects who moves to a new house during the intervention follow-up period

- For a subject who moves to a different house within the same cluster, that subject will be included in both the ITT and PP analyses. The household characteristics will be updated at the time the subjects moved.
- For a subject who moves to a different house in a different cluster, the data from the subject before the subject moves will be included in the ITT analysis. All data from the subject will be included in the PP analysis, both the treatment information and the household characteristics will be updated at the time the subjects moved.

5.2 Subjects who are hospitalized for serious complicated illness (e.g. chronic illness), die, drop out, or miss scheduled visits due to reasons not related to the malaria outcome or intervention during the follow-up period

For subjects that fall under this category, the available data from the subjects (up to the time point when the subjects are hospitalized, die, or drop out; data from the scheduled visits that the subjects did not miss) will be included in both the ITT and PP analyses as the missing or absent data can be ignored (see Section 6.4 of the SAP for more details).

5.3 Subjects who do not receive (complete) intervention due to travelling outside, mis-application or partial application of the product

For the ITT analyses, these subjects will be included as is. For the PP analysis, "travel outside" (Y or N; an individual-level covariate) and the product application rate in each household (expected to be close to 100%) will be included as covariates if the data are not overly imbalanced between the Y and N categories for "travel outside", and there is practically/clinically meaningful variation in the product application rate across households and clusters.

6 Definition of new malaria infection

Following a positive malaria diagnosis, whether the next positive malaria diagnosis, either during the active or passive screening periods, is a new infection or just a remnant or a carryover from the previous malaria infection depends on the time lapse between the two malaria infections, and whether and when the first malaria infection is treated.

The treatment for malaria infection last for 3 days. Denote the first day of treatment by Day 1. A diagnosis test of malaria will take place on Day 15 +/- 3 days (that is, Day 12 to Day 18). If a positive malaria infection is detected during the diagnosis test, then the malaria infection will not be regarded as a new infection but rather a carryover and a second round of 3-day treatment will be conducted. The number of subjects that are infected but will not treated is expected to be minimal (to be confirmed at interim and final analyses of the baseline data). If there is no treatment for an infection, the subsequent positive will be regarded as a new infection only with one negative blood slide between the two positives.

The positive diagnosis that cannot be treated as a new infection will be re-coded as negative before any the following statistical analysis on malaria infection (baseline, first-time infection, overall malaria infection) is applied. Correspondingly, for the overall incidence rate calculation, the time at the risk will be adjusted by subtracting the "protection period" (the number of days from Day 1 treating a malaria infection and the post-treatment diagnosis test on Day 15 +/- 3 days).

Also noted is that the active screening of malaria occurs every 4 weeks and the passive screening occurs in between two active screenings only when a subject experiences a fever. It is possible there are only a few passive screenings upon the completion of data, leading to data imbalance between the odd-numbered visits (the active screening) and the even-numbered visits (the passive

screening). To deal with this problem if it occurs, we will apply the following approach. If the passive screening in a visit is negative on malaria, then that data point will be removed as it contains no additional info on malaria or time at risk on top of the active screenings before and after it. If the passive screening is positive, then the passive positive will be assigned to either the active screening visit immediately before the passive screening or after, whichever is closer to the passive screening in time. The same approach will be applied to the analysis of first-time overall malaria infections in Sec 7.1 and 7.2.

7 Statistical Methods

The statistical analysis and results reporting will follow the CONSORT guidelines for CRTs[1].

7.1 Primary endpoint (ITT Population)

The baseline characteristics of the enrolled subjects, households, and clusters will be summarized by treatment arm. Specifically, we will examine subject age and gender at the individual level, wall type and roof type, floor height, house open eaves, # of window, # of doors at the household levels, and cluster population and baseline overall infection incidence at the cluster level.

The primary hypothesis on PE against the first-time malaria infection will be estimated by comparing the hazard rates of first-time malaria infection between SR and placebo upon the completion of the study in the ITT population. The complementary-log-log (cloglog) regression model $\log(-\log(1-\theta_{kit})) = \beta_{0t} + \boldsymbol{x}_{ki}^{T}\beta_1 + z_k + z_{i(k)}$ will be applied [2-7]. The cloglog model is a proportional hazard model for interval-censored data. θ_{kit} is the discrete time hazard rate of subject i in cluster k at time t, and $\boldsymbol{x}_{ki}$ contains the individual-level (age, gender), household-level (number of doors, number of windows, open eaves Y or N, wall type, roof type), and cluster-level (baseline incidence rate, cluster population size, intervention group) covariates. If the data are extremely unbalanced in a categorical covariate (not in terms of the distributions between the treatment arms, but the marginal distribution of the variable itself; e.g., 99% households have the same type of walls vs 1% do not) or if a non-ignorable portion of the subjects have missing values on a covariate (due to MAR or MCAR), that covariate may be excluded in the model. $z_k \sim N(0, \sigma_1^2)$ and $z_{i(k)} \sim N(0, \sigma_2^2)$ are the random effects at the cluster, household, and individual levels respectively. The null hypothesis of PE = 0% is equivalent to $\beta = 0$, which will be tested by the Wald's test $z = \hat{\beta}/s$, where s is the estimated standard error of $\hat{\beta}$. PE is estimated by $(1 - \exp(\hat{\beta})) \times 100\%$, where $\hat{\beta}$ is the estimated regression coefficient associated with the treatment group, and $\exp(\hat{\beta})$ is the estimated hazard ratio (HR) between SR and placebo, with a 95% upper-sided CI (the hypothesis is one-sided).

There will be one formal interim analysis to test the primary hypothesis and make decision on whether stopping the trial or not. The decision boundaries are calculated for either stopping for futility or stop for efficacy using the O'Brien-Fleming error spending function [8-10]. Since we adopt the non-binding futility boundary, if it is decided the study will continue due to other considerations even if we cross the futility boundary at the interim look, there will be no inflation of type I error. In other words, the trial does not need to stop to accept the null hypothesis when the test statistic falls in the futility region at the interim stage. In addition, since trials submitted to VCAG are intended to demonstrate public health value, the committee strongly recommends that trials are not stopped early for benefit. In our design setting, even the efficacy boundary is crossed

at the interim look, the study may continue and there will be no inflation of type I error, as efficacy is already established at the interim.

The interim analysis will occur when 528 first-time infections in the core zone as defined in Remark 1 (50% information) are collected. Assuming a baseline incidence rate of 3.0 per person-year and constant average hazard rates for cohort 1 and cohort 2 post intervention, the interim analysis will occur around the end of the intervention follow-up on Cohort 1 (i.e., the end of Month 12 post randomization). The decision boundary for futility and efficacy is presented in Figure 2.

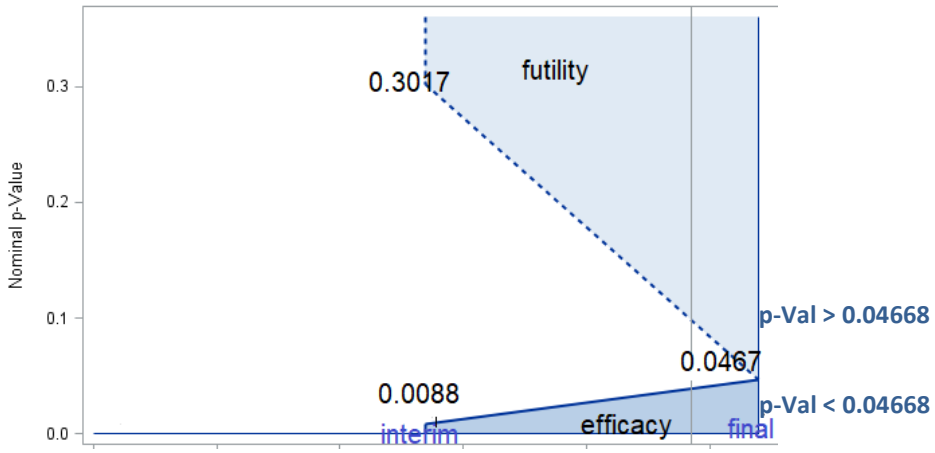


Figure 2: Boundary plot (in p-value) for testing the primary hypothesis on PE (1-sided Type-I error rate $\alpha = 0.05$, Type-II error rate $\beta = 0.2$; between-cluster CV = 47.4%, baseline incidence rate = 3 per person-year; O'Brien-Fleming error spending function)

If the result meets the stopping criterion for futility, that is, the one-sided p-value for the Wald's test on the log(HR) between SR and placebo at the interim look > 0.3017 (see Figure 2), then the study can stop for futility. Since we adopt the non-binding futility boundary, if it is decided the study will continue due to other considerations even if we cross the futility boundary at the interim look, there will be no inflation of type I error. In other words, the trial does not need to stop to accept the null hypothesis when the test statistic falls in the futility region at the interim stage. If the one-sided p-value < 0.00882, then the study can stop for efficacy; otherwise, the study will proceed. However, if it is decided that the study will continue due to other considerations even if the efficacy boundary is crossed at the interim look, there will be no inflation of type I error, as efficacy is already established at the interim.

If the one-sided p-value at the interim is > 0.00882 but <0.3017, then the study continues. At the final look, if the one-sided p-value from the Wald's test on the log(HR) between SR and placebo < 0.0467, we reject the null hypothesis, claiming SR reduces the malaria hazard rate compared to placebo in Kenya at the significance level of 5%; otherwise, we fail to reject the null hypothesis, claiming SR does not reduce the malaria hazard rate compared to placebo in Kenya.

7.2 Secondary endpoints (ITT Population)

No interim analysis will be performed on any of the secondary endpoints listed below.

PE and diversion effect of SR protection again the first-time malaria infection

The secondary hypothesis on PE against the overall new malaria infections, as defined in Sec 6, will be tested by comparing the hazard rates of the overall malaria infection between SR and placebo in the ITT population. The cloglog regression model $\log(-\log(1-\theta_{kit})) = \beta_{0t} + \boldsymbol{x}_{ki}^T\beta_1 + z_k + z_{i(k)}$ will be applied. θ_{kit} is the discrete time hazard rate of subject i from household j in cluster k at time t, and $\boldsymbol{x}_{ki}$ contains the individual-level (age, gender), household-level (number of doors, number of windows, open eaves Y or N, wall type, roof type), and cluster-level (baseline incidence rate, cluster population size, intervention group) covariates. If the data are extremely unbalanced in a categorical covariate (not in terms of the distributions between the treatment arms, but the marginal distribution of the variable itself; e.g., 99% households had the same type of walls vs 1% that did not) or if an non-ignorable portion of the subjects have missing values on a covariate (due to MAR or MCAR), that covariate maybe may be excluded in the model. $z_k \sim N(0, \sigma_1^2)$ and $z_{i(k)} \sim N(0, \sigma_2^2)$ are the random effects at the cluster, household, and individual levels respectively. The cloglog model is a proportional hazard model and thus HR does not depend on time t. The null hypothesis of PE = 0% is equivalent to $\beta = 0$, which will be tested by the Wald's test $z = \hat{\beta}/s$, where s is the estimated standard error of $\hat{\beta}$. A one-sided p-value and 95% upper-sided confidence interval (CI) for PE will be provided (the hypothesis is one-sided). If the one-sided p-value between SR and placebo < 0.05, we reject the null hypothesis, claiming SR reduces the overall malaria hazard rate compared to placebo in Kenya at the significance level of 5%; otherwise, we fail to reject the null hypothesis, claiming SR does not reduce the overall malaria hazard rate compared to placebo in Kenya.

Diversion effect

To assess the diversion effect on the first and overall malaria infection a similar model as the model used for analyzing the primary endpoint in Sec 7.1 and 7.2 will be applied. The only difference in the diversion effect assessment is the inclusion of the distance of each household in the buffer zone to the nearest intervention house in the core zone, and the interaction term between the distance and treatment arm in addition to the covariates listed in the model in Sec 7.1 and 7.2. How the malaria first-time and overall hazard rates compare in the core zones of SR relative to those of the placebo at different distance to the core zone will be quantified.

Subgroup PE analysis by age group

The above analysis of the first time and overall malaria infections in the examination of the PE and diversion effect of SR will be based on all the subjects aged 6 months to 9 years and 11 months old. The same set of analysis will also be performed by two age subgroups (≤ 59 months old; 5 years old to 9 years and 11 months old) to examine if PE and diversion effects of SR will differ by two age groups. If the results suggest a difference in PE between the two age groups, the treatment by age group interaction term will be added as a covariate to the cloglog models for the first-time and overall infection analysis to test for the statistically significant for the interaction term.

PE analysis without baseline covariates

A PE analysis on the first-time and the overall infections will be also performed by removing all the baseline covariates from the cloglog models presented Sec 7.1 and 7.2 and only keeping "intervention group" as the only covariate (in addition to visit, as a categorical predictor per the model assumptions and set-up). The hazard ratios between SR and placebo will be provided, along with 2-sided 90% CIs.

Incidence rate estimation and mid-point imputation of time to infection.

The first-time and overall malaria incidence rates per person-year during the whole intervention follow-up will be calculated by cluster for the SR and the placebo arms respectively. The first-time malaria incidence rate is defined as the ratio of the number of first-time malaria cases during the whole study vs sum of the time to event/time at risk (in year) across the individuals within the same cluster, and the overall malaria incidence rate is defined as the ratio of the number of new malaria cases during the whole study vs sum of the time to event/time at risk (in year) for each of the new cases across the individuals within the same cluster.

Since the active screenings of malaria incidences are either every 4 weeks (active screening) with passive screening taken between two active screenings if fever is reported, the actual time for contracting malaria is unknown (interval censored). Therefore, the mid-point between two consecutive screenings will be used as the time at risk for a malaria event that occurs in the latter screening. The average per-person-year first-time and overall malaria incidence rates in the SR and the placebo arms, and the incidence ratios between the two will be calculated, together with the coefficients of variation in both arms on both incidence endpoints.

With the mid-point imputed time to infection, we will also run Cox regression with the same list of covariates as in the cloglog models for the 1st-time and overall malaria infections to estimate the hazard ratios between SR and placebo. The cloglog models are based on fixed time intervals for interval censored data (every two weeks +/-3 days in this study) for each subject. If an ignorable portion of samples in the collected data deviate scheduled visit, Cox regression models will be applied to estimate the PE against the 1st-time and overall malaria infections on the mid-point imputed time to infection data.

Effects of SR on entomology

The endpoints in the entomological analysis include the HLR (number of anopheline- caught during the 12-hr interval overnight), anopheline parity rate, anopheline sporozoite positivity rate, and anopheline EIR, and the anopheline indoor density, abdominal status, and sporozoite positivity rate collected by light-trap.

The time profile plots of each of aggregated entomological endpoints will be obtained over the baseline and intervention period. An appropriate statistical model for the HLR will be identified after examining the distributional characteristics of the HLR data, which are likely to follow (zero-inflated) Poisson distribution, or (zero-inflated) negative binomial distribution if there is over-dispersion. The covariates in the models will include the fixed effects of intervention, time, cluster population size, location (inside or outside), location and intervention interaction, baseline cluster-level HLR rate; and random effects for cluster and household nested within cluster. The ratio between SR and placebo in HLR will be estimated, and the %change in HLR by SR is given by (1-HLR ratio)×100%.

Parity rate will be analyzed using a logistic regression model with the parity status (porous vs nulliparous) of a mosquito as the outcome and intervention, time, cluster population size, location (inside or outside), location and intervention interaction, baseline cluster-level parity rate; and random effects for cluster and household nested within cluster.. The model for the sporozoite positivity rate will be similar to the parity rate with sporozoite positivity (Yes or No) as the outcome . Note that if the data on parity and sporozoite positivity are highly unbalanced (not in terms of the distributions between the treatment arms, but the marginal distribution of the variable itself; e.g., 99% nulliparous or 99% negative sporozoite), then the model might lead to unstable

estimates or the model might not even converge. In such cases, only summary statistics will be provided.

EIR is defined as the number of infective mosquito bites a person receives per unit time (typically annually) and is calculated as

$$\text{HLR} \times \text{sporozoite rate} = \frac{\#\text{ of mosquitos collected}}{\#\text{ of capture nights}} \times \frac{\#\text{ of sporozoite positive mosquitos}}{\#\text{ of mosquitos tested}}.$$

We will calculate the EIR per household per cluster per unit time and provide summary statistics at baseline and per year during the intervention period by treatment group. The EIR analysis will be performed using the HLC data.

The time profile plots of light trap (LT) indoor density will be obtained over the baseline and intervention period. An appropriate statistical model will be identified after examining the distributional characteristics of the light trap indoor density which are likely to follow (zero-inflated) Poisson distribution, or (zero-inflated) negative binomial distribution if there is over-dispersion. The covariates in the models will include the fixed effects of intervention, time, cluster population size, baseline cluster-level mosquito density from the LT collection, andrandom effects for cluster and household within clusters. The ratio between SR and placebo on light trap indoor density will be estimated.

A logistic regression model will used to analyze the abdominal status to evaluate the effect of SR on blood fed rate from the LT collection. The binary outcome fed (fed + gravid + half-gravid) vs unfed) of a female anopheline mosquito will be the outcome. The model will include the cluster-level baseline blood fed rate, cluster population, time, and intervention as covariates; and cluster and household nested within cluster and household nested within cluster as random effects. The ratio of the odds of fed vs un fed between SR and placebo was estimated.

The analysis for the sporozoite positivity data from the LT analysis will be similar to the analysis of sporozoite positivity data collected by HLC.

Summary statistics will also be provided for insecticide resistance during the intervention period by treatment.

Analysis of the relationship between malaria hazard rate and entomological endpoints

To explore the relationship between the malaria hazard rate and the entomological endpoints, a similar model as the cloglog models used to address the primary objective on the first-time malaria infection and the secondary endpoint on the overall malaria infection will be applied to the epidemiological and entomological data in the clusters from which the entomological data are collected. The random effects and the individual-level and, household-level covariates will be similar to the cloglog models used for the PE analysis. The cluster-level covariates in the model will include the baseline incidence rate, cluster population size, and a covariate that captures the entomological information. Specifically, for HLR, the measurement to be paired with a malaria diagnosis in an individual is average daily HLR taken within 7 to 28 days before the diagnosis over the two-week period and over the sentinel households where entomological endpoints are collected in the same cluster to which the individual belongs. The regression coefficient associated with log(HLR) quantifies the change in the malaria hazard rate on the log scale, given one unit increase in log(HLR). For parity rate and sporozoite positivity rate, as long as there is enough data collected on these two endpoints and they are not highly unbalanced with regard to its marginal distribution (e.g., 99% mosquitos caught are nulliparous or sporozoite negative), the relationship

between the malaria hazard rate and those two will also be investigated in a similar fashion as for HLR.

Safety assessment

Summary of symptom-based adverse events (AE), severe adverse events (SAE), and death reports observed during the studies will be reviewed by the trial DSMB at predetermined checks (quarterly). Summary about AE/SAE, including mean, minimum and maximum frequencies and percentages across clusters among enrolled subjects, will be provided by the treatment arm. Statistical comparisons of the AE/SAE rates between the two arms will be conducted upon the completion of the study when there is notable difference in AE and SAEs between SR and placebo arms as needed. In such a case, two sets of statistical analysis will be run. One set will compare the proportion of having at least one occurrence in each symptom-based AE/SAE during the whole study between the two arms, and the other will compare the total number of occurrences for each AE/SAE between the two study arms. If the data collected permits meaningful statistical hypothesis testing, p-values from the treatment comparisons will be reported, with multiplicity correction via the FDR approach [11].

7.3 Supplementary analysis

Temporality of PE effects

It is expected malaria incidence changes by seasonality (rainy vs dry). To examine the temporality of malaria incidence rates and the PE effect, a supplementary analysis will performed by adding the seasonality (wet/peak) and dry/low)) and their interaction with intervention to the covariate list in the cloglog models used for analyzing the first-time and overall infections. The PE will be estimated by seasonality. Besides the binary seasonality covariate (dry vs rainy seasons), if monthly precipitation data in the study area is available, we will also examine how precipitation may affect the PE effect by including precipitation and its interaction with treatment as covariates in the model, and obtain the estimate on the effect of precipitation on malaria hazard and SR effects against malaria.

Human behavior adjusted PE analysis

The primary and secondary analyses laid out in Sections 7.1 and 7.2 for the first-time infection, the overall infection, and the examination of relationship between the ento- and epi- endpoints will also be carried out by adjusting for the human behavior covariates the cloglog models, including “bednet usage” in the last 24 hrs (Y or N) and “travel outside” (Y or N; an individual-level covariate if such data are collected and they are balanced between the Y and N categories on “bednet usage” and “travel outside” If the data are highly unbalanced, the corresponding covariate will not be used in the analysis [Note: The bednet usage rate turns out to be 99.6% in the study, rending the PE analysis adjusted for bednet usage meaningless. The estimated PE above can be regarded as additional benefit by SR against malaria infections on top of bednet usage. No data were collected on “travel outside”, as such, this analysis cannot be run].

If it is suspected that the study subjects may not have taken the anti-malaria treatment as instructed after being diagnosed positive during the study period, a sensitivity analysis will be run to examine how PE changes with different compliance rates. Whether complying with the anti-malaria treatment or not affect how new infection are counted. For example, if a person who is malaria positive does not take the treatment as instructor, a positive diagnosis in the subsequent visit will be counted as a carry-over rather than a new infection. However, it is very unlikely accurate data on compliance as the subjects are prescribed medicine for a 3-day treatment and whether they

actually take the treatment or not is not monitored and it is quite possible that subjects do not take the medicine as instructed (e.g. saving them for future use) but insist that they have taken the treatment. In the abstract of compliance data, we apply data imputation to generate compliance status. Since there will be no information to inform whether a particular subject complies or not, the compliance status will be generated randomly for each positive diagnosis with 25% and 50% noncompliance rates, respectively. Due to the completely random imputation on the compliance status (not informed by any prior knowledge or its relationship with any of the collected variables, except for the assumed noncompliance rate), we will generate three imputed sets and run the PE analysis on each. For the same reason, the results from this sensitivity analysis can be biased and should be interpreted with caution, especially when the results across the three imputed sets vary significantly. This analysis only affects the PE against overall infections. It is also possible that subjects do not respond to the anti-malaria treatment. To consider the impact of non-respondence to drugs, among those subjects who were positive all the way to the end of study after the first-infection, we will be imputing the non-respondence status with 15% non-respondence rate. Subjects who are imputed to be a non-responder will be not part of the overall-infection PE analysis. Similar to the non-compliance imputation, this imputation is not informed by any prior knowledge or its relationship with any of the collected variables either. The results from this sensitivity analysis can be biased and should be interpreted with caution.

Adjusted HLR analysis (this analysis will not be performed for the reasons listed in the summary of the change table on page 2 of the SAP)

he adjusted HLR at a given time point is calculated as the raw HLR× the proportion of people at the risk of being bitten in each household. Specifically, in each household where the HLR data are collected in the hourly interval from 6pm to 6am, the number of people indoor, the number of people outdoor, the number of people under bednet indoor, the number of people sleeping outdoor are also collected. The adjusted HLR indoor = raw HLR × number of subjects not under the protection of bednet/ total number of indoor subject, and the adjusted HLR = raw HLR × number of subjects who sleep / total number of subject outdoor. The analysis specified for the estimating the effects SR on the raw HLR in Sec 7.2 will be applied to the adjusted HLR. This analysis will be conducted only when data collected allows for such analysis.

Per-protocol (PP) analysis

If the PP sample set differs from the ITT sample set, per the criteria listed in Sec 5, the primary analysis on the first-time infection and the secondary analysis on the overall infections as listed in Sec 7.1 and 7.2 will also performed in the PP sample set. This analysis will be conducted only when data collected allows for such analysis (e.g. subjects moving across clusters results in treatment switch, absence from treatments due to travelling or hospitalization). PP sensitivity analysis considering <100% product application rate in each household over time will be conducted. We will use cutoffs -- ≥75%, [50, 75)%, [25, 50)%, and ≤25% -- on the application rate to present different “doses” of the SR treatment and estimate PE of the SR treatment at each dosage level against placebo. We will also run include the dosage level as a continuous covariate in the model (for placebo arm, it is set at 0%), and estimate how malaria hazards changes with increasing dosage of SR. The time profile of product application rate will be plotted over time for the treatment and placebo arm.

[**Note**: There was no switch of treatment during the study course for those who moved between clusters. If a subject moved to a different cluster, the subject was dropped from the study and was

treated as a LTFU case. Travelling data were not collected and thus no information on when and how long the subjects were not protected by the product. Finally, while hospitalization data was collected, there were only 6 subjects during the intervention period, comprising <0.5% of all the enrolled subjects during intervention. In addition, except for one subject who were hospitalized for about 20 days, all the other 5 stayed in hospital for 1 to 4 days only. Given this, we expect adjusting for the absence of the product due to hospitalization– if they happened to be in the SR arm – would lead minimal changes in the PE results from those not adjusted for the ITT analysis.]

7.4 Handling of missing data

Significant effort will be made to avoid having missing values on outcome (malaria infection status and visit dates, and entomological endpoints). When missing values occur for an outcome for reasons not related to the outcome, reasons for missingness and the missing fraction by treatment arm and cluster will be reported. Per protocol, the subjects are screened actively on their malaria status (the outcome) every four weeks.

- If a subject misses one or more scheduled visits due to reasons not related to the SR product or the outcome, the subject will have missing values on the outcome that can be regarded as ignorable missingness [12] (MAR or MCAR).
- If a subject drops out study due to reasons unrelated to the SR product and/or malaria infection, then the missing observations from the subject can be regarded as ignorable missingness[11] (MAR or MCAR).

In both cases, all the available data from the subject will be included in the primary and secondary analysis, without employing any specific missing data analysis techniques, due to the ignorability of the missing mechanisms [11].

Missing baseline covariates (individual-level, household-level, and cluster-level) that are a part of the regression models for the outcome of interest will be imputed using simple hot-deck imputation methods if the missing fraction for the covariate is <5%. If the missing fraction for a covariable are ⩾5%, appropriate multiple imputation approaches will be applied. If a non-ignorable portion of the subjects have missing values on a covariate (due to missing at random or missing completely at random), that covariate may be excluded in the model.

7.5 Analysis of baseline

The per-person-year first-time and overall malaria incidence rate from the 58 recruited clusters will be calculated. Since the malaria incidences are collected on a biweekly basis, the mid-point between two visits will be imputed as the time at risk for a malaria event. The average incidence rate will be calculated, together with the coefficients of variation. The baseline analysis will occur at Month 2 and Month 4 during the baseline period internally on blinded data.

7.6 Interim analysis

A formal interim analysis during the intervention period will be to examine the primary hypothesis as outlined in Section 6.1 of this SAP. The interim analysis will be performed by an independent DSMB who will recommend whether to continue or stop a trial. The final decision to stop should always rest with the DSMC, not the investigators, or the funder.

The baseline data will be analyzed at the mid-point of the baseline period.

No other interim analyses are planned.

8 Software

Software used will be SAS for Windows, Version 9.4 or higher (SAS Institute, Cary, NC, USA) and Rstudio Version 1.0.143 or higher (RStudio, Inc, Boston, MA, USA).

9 Sample Size Determination

The sample sizes below might be adjusted based on the data collected during the 4-month baseline period. Since the adjustment will only utilize the baseline data (baseline incidence and CV) with intervention information, the Type-I error rate will not be inflated.

Primary hypothesis on first-time malaria infection

The sample size determination on the required number of households per cluster for testing the primary hypothesis on PE is based on the hazard rate comparison in the proportional hazards regression model [13-14]. With the following specifications: 1-sided type-I error rate = 5% (because the primary hypothesis is one-sided as SR is unlikely to increase the hazard rate of malaria infection compared to placebo), true PE = 30%, a between-cluster coefficient of variation (CV) of hazard rate = 48% (based on the historical data collected from Kenya), one interim analysis for efficacy and non-binding futility, with the O'Brien-Fleming error spending function when 50% information is collected, then 1056 independent first-time infections in the core zone (as defined in Remark 1)-will need to be observed to reach 80% power in testing the primary hypothesis on PE.

With a baseline first-time malaria infection hazard rate of 3.0 per person-year (ppy), 29 clusters per treatment, 28 households per cluster, factoring in a 35% loss to follow-up (LTFU) rate, are expected to yield 1056 independent first-time malaria events within 12 months follow-up period per cohort post randomization to yield 80% power. The 28 households will be split in half between the two sequential cohorts with 14 households per cohort per cluster. If, by the end of the 2-year study, 1056 independent malaria events are not reached, the study may extend until 1056 events are collected without inflating the type I error rate in the testing of the primary hypothesis.,

Appendix I provides the sample size requirement under different assumptions of baseline incidence rate (ppy) (3, 2, and 1.5) and between-cluster CV (%) (44%, 50% and 60%).

Secondary hypothesis on overall malaria infection

The sample size calculated to yield 80% power for establishing the primary hypothesis on first-time infection PE is expected to lead to 80% power when it comes to testing the secondary hypothesis on the overall malaria infection. This is because that the baseline overall malaria incidence rate is likely to be similar 3.0 per person-year (the assumed first-time incidence rate) and with a similar CV value (both are confirmed by the baseline data); in addition, there is no interim analysis on the second hypothesis and all the pre-specified Type-I error will be used toward testing the PE against overall infection upon the completion of the study.

Quantification of the diversion effect

Since there is no formal hypothesis on the diversion effect objective on the diversion effect is estimation, we focus on determining a practical feasible SS that gives a relative high precision for the estimated PE of SR in the near-zone on the malaria incidence rate. With a 48% between-cluster CV, and a baseline incidence rate of 3.0 per person year, 29 clusters with 30 HHs per cluster lead to a half width of 0.278 for the 95% CI on the log-scale, that is, the ratio between the upper bound of the 95% CI vs. the point estimate is 1.320 for a hazard ratio estimate between SR and placebo.

Factoring in a 35% LTFU rate, the required sample size is 40 households in the buffer zone per cluster. The total households will be split in half between two sequential cohorts, with 20 households per cohort per cluster.

Note: Since the sample sizes for both PE and diversion effect evaluations already factors in the LTFU rate, there is no need for replacement subjects unless the LTFU is larger than assumed. If replacement subjects are to be recruited, they should not have been exposed to the intervention until the time they are considered for replacement.

Reference

1. Marion K Campbell, Gilda Piaggio, Diana R Elbourne, Douglas G Altman (2012), Consort 2010 statement: extension to cluster randomised trials, BMJ 345:e5661
2. J. D. Kalbfleisch, R. L. Prentice (2002, 2nd ed), The Statistical Analysis of Failure Time Data, Wiley-Interscience
3. P. D. Allison (1982), Discrete-Time Methods for the Analysis of Event Histories, Sociological Methodology, 13: 61-98
4. D. Collett (2002, 2nd ed), Modelling Binary Data, Second Edition, Chapman & Hall
5. B. P. Carlin and J. S. Hodges (1999), Hierarchical proportional hazards regression models for highly stratified data, Biometrics.55(4):1162-1170
6. V. Henschell, J. Engel, D. Hölzel and U. Mansmannina (2009), A semiparametric Bayesian proportional hazards model for interval censored data with frailty effects, BMC Medical Research Methodology, 9:9
7. G. Yin and J. G. Ibrahim (2005), A Class of Bayesian Shared Gamma Frailty Models with Multivariate Failure Time Data, Biometrics, 61(1):208-216
8. Eighth VCAG meeting report (Section Conditions for early termination of trials) https://apps.who.int/iris/bitstream/handle/10665/273106/WHO-CDS-VCAG-2018.01-eng.pdf?ua=1
9. Bretz F, Koenig F, Brannath W, Glimm E, Posch M. (2009), Adaptive designs for confirmatory clinical trials. Stat Med. 28(8):1181–217.
10. Schüler S, Kieser, M, Rauch G (2017), Choice of futility boundaries for group sequential designs with two endpoints BMC Med Res Methodology. 17: 119.
11. Benjamini Y, Hochberg Y (1995). *Controlling the false discovery rate: a practical and powerful approach to multiple testing*, Journal of the Royal Statistical Society, Series B. **57** (1): 289–300
12. R. J. A. Little and D. B. Rubin (2002), Statistical Analysis with Missing Data (2nd edition), J. Wiley & Sons, New York.
13. M. Lievens, J. J. Aponte, J. Williamson, B. Mmbando, A. Mohamed, P. Bejon and A. Leach (2011), Statistical methodology for the evaluation of vaccine efficacy in a phase III multi-centre trial of the RTS,S/AS01 malaria vaccine in African children, Malaria Journal, 10:222
14. The RTS,S Clinical Trials Partnership (2011), First Results of Phase 3 Trial of RTS,S/AS01 Malaria Vaccine in African Children, The New England Journal of Medicine, 365(20): 1863-1875.

Appendix

I. Sample size under different assumptions of baseline incidence rate and between-cluster CV

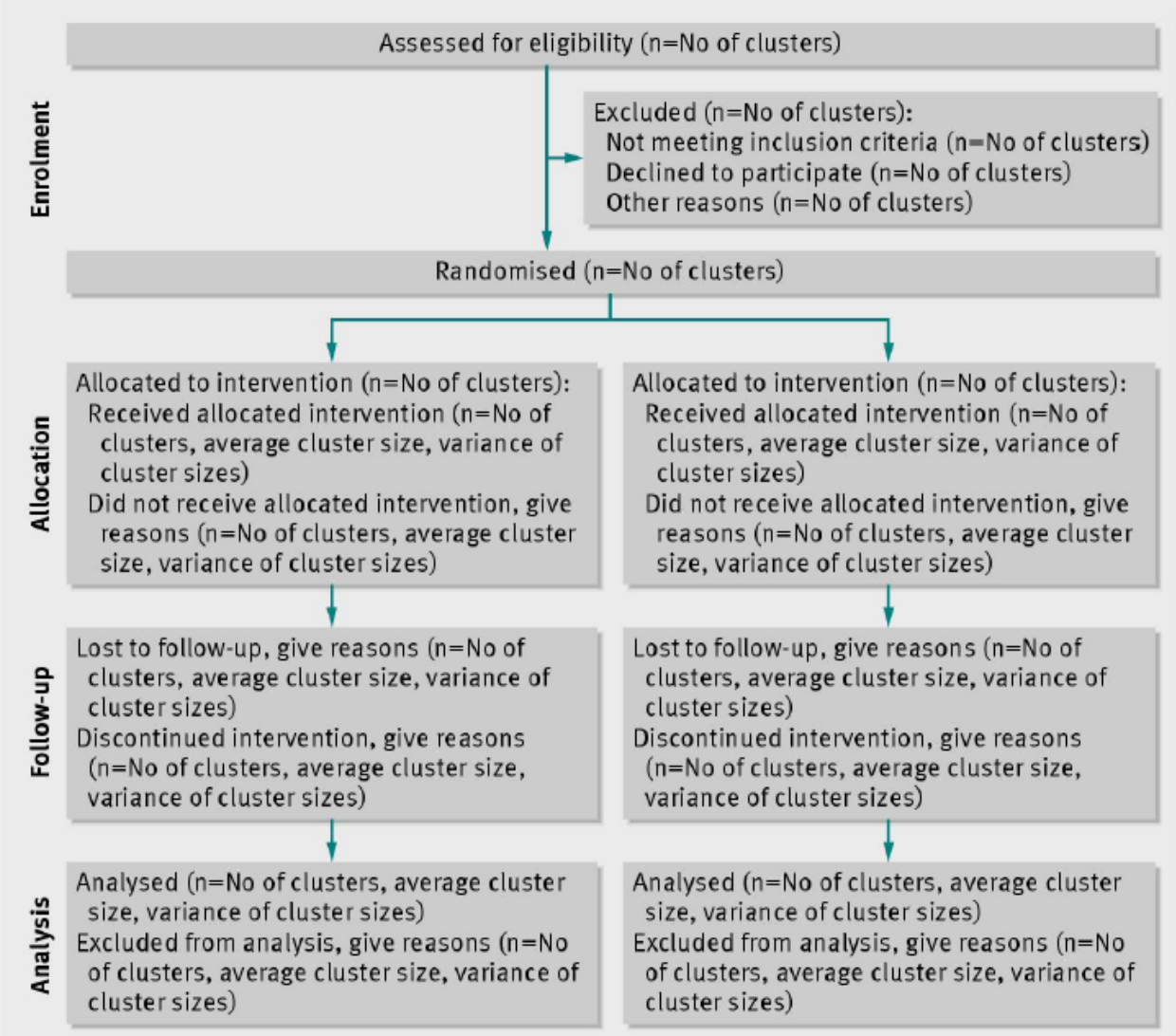
The table below shows, for different between-cluster coefficient of variation (CV) of hazard rate and different baseline incidence rate, that the required number of events and the number households per cluster (factoring in a 35% LTFU rate) for establishing the primary hypothesis on PE with 85% power with 30 clusters per arm under the 1-sided type-I error rate = 5% with true PE = 30% and one interim analysis for efficacy and non-binding futility with the O'Brien-Fleming error spending function when 50% information is collected.

Note the table was provided since the first draft of SAP to show how sample size changes under different assumptions on the parameters that affects the power/sample size calculation. The table is not updated after the dropping two clusters based on the baseline data analysis, as the trend in sample size calculations would be similar for 30 vs 29 clusters per arm. The power/sample size is updated in the main text in Sec 9 with 29 clusters per arm.

	Baseline incidence (ppy)	between-cluster CV		
		44%	50%	60%
# clusters per arm		30	30	40
# events total *		637	1467	2739
# HHs per cluster	3	16	36	51
	2	18	41	58
	1.5	21	47	65

II. Mock Tables and Figures

Figure A1: flow diagram of progress of clusters and individuals



From Campbell et al. (2012): *Consort 2010 statement: extension to cluster randomized trials*) [1]

Table A1: Summary on baseline covariates

Individual level		
	SR	**Placebo**
Age in months (mean ± SD, (min, max)) Gender (% of boys)		
Household level		
	SR	**Placebo**
house wall type (%, n) house roof type (%, n) Floor height (mean ± SD, n) house open eaves (%, n) # of windows (mean± SD, n) # of doors (mean± SD, n)		
Cluster level		
	SR	**Placebo**
Cluster population (mean ± SD, (min, max))		
Baseline overall infection incidence per person-year (mean ± SD, (min, max))		

Table A2: Protective Efficacy (PE) of SR against all infections

Look	Treatment	Baseline incidence rate	# of households	# of infections	Time at risk (in years)	hazard ratio (95% CI)	PE (95% CI)
1	SR						
	placebo						
2	SR						
	placebo						

Baseline coefficient of variation (CV) of incidence rate: xxx%

Similar tables will be provided on the 1) 1st-time malaria infections, 2) by-age group analysis on PE; and 3) the supplementary PE analysis for 1st-time, overall, and by-age group infections with no covariates included in the cloglog model.

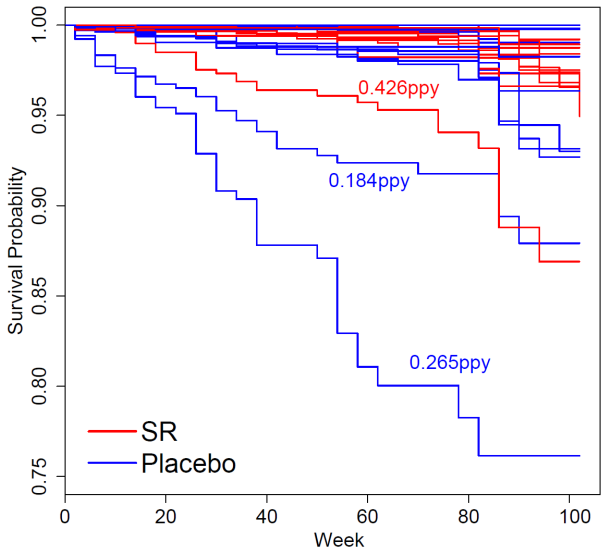
Table A3: Diversion effect of SR

Distance from the core zone	Treatment	Baseline incidence rate	# of households	# of events	Time at risk (in years)	hazard ratio (95% CI)	PE (95% CI)
d_1	SR						
	placebo						
….	SR						
	placebo						
d_K	SR						
	placebo						
	Similar tables will be provided for 1st-time malaria infection, and for overall malaria						

Table A4: Effects of SR compared to placebo on the entomological endpoints

	Mean (95% CI)		Ratio (95% CI)
Endpoint	SR	Placebo	SR vs. placebo
HLR Parity rate sporozoite positivity rate Indoor density (light trap)			

Figure A2: Kaplan Meier Curves for SR and placebo on 1st-time malaria infections



The KM curves will be generated for all recruited subjects, and also by age group (≤ 59 months old; 5 years old to 9 years and 11 months old).

Figure A3: time profile of estimated HLR (mean +SD)

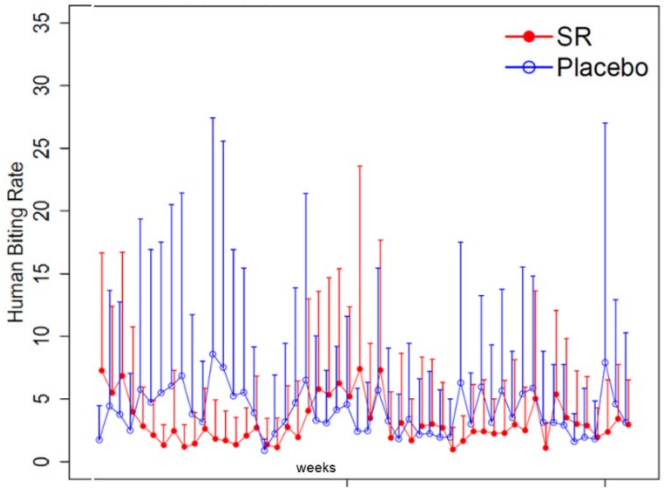


Table A5: AE and SAE Summary Statistics

	Mean (Min, Max) Frequency (Percentage) across Cluster		
	SR related*	SR	Placebo
Adverse Event/Symptoms **			
Skin irritation/Rash	Possible		
Runny nose	Possible		
Nausea/Vomiting	Possible		
Salivation/Drooling	Plausible		
Cough	Unlikely		
Eye irritation	Unlikely		
Headache	Unlikely		
Diarrhea	Unlikely		
Abdominal discomfort	Unlikely		
Difficulty Breathing	Unlikely		
Other	Unlikely		
Serious Adverse Event **			
Congenital anomaly/ Birth defect	Unlikely		
Death	Unlikely		
Persistent or Significant Disability or Incapacity	Unlikely		
Hospitalization or prolongation of existing hospitalization	Unlikely		
Other	Unlikely		

* Defined per SJC safety tests.

** AE and SAE summaries of the clinical diagnosis (disease) may be added

Table A6: Statistical Comparison on having at least AE and SAE

	Frequency (percentage)		SR vs. placebo (p-Value)	
AE	SR (N= xxx)	Placebo (N= xxx)	raw	adjusted*
Skin irritation/Rash				
Runny nose				
Nausea/Vomiting				
…..				
* FDR-adjusted p-value				

Table A7: Statistical Comparison on the total number of AE and SAE

	Frequency		SR vs. placebo (p-Value)	
AE	SR (N= xxx)	Placebo (N= xxx)	raw	adjusted*
Skin irritation/Rash				
Runny nose				
Nausea/Vomiting				
…..				
* FDR-adjusted p-value				

III. Some sample SAS and R procedures used in the analysis

Note the final codes for KM curves and estimation if PE could differ slightly from the sample codes below, which are meant to demonstrate the main procedures/commands in R and SAS to run those two types of analyses rather than to be followed strictly.

a) KM curves for each cluster. Some sample codes are given below.

```
library(interval)
fit<-icfit(Surv(left,right,type="interval2")~treatment, data=malaria)
plot(fit)
```

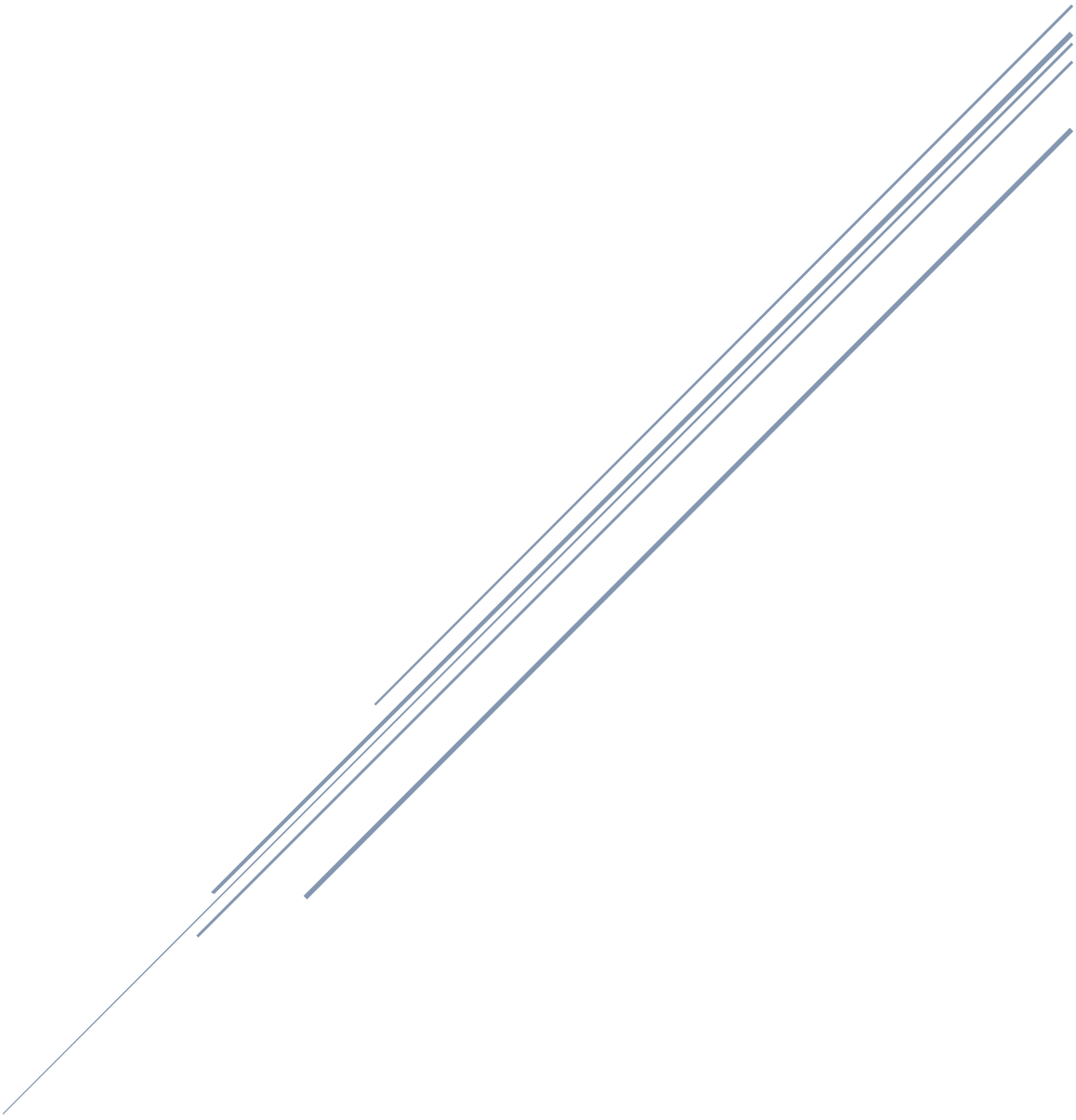
b) For estimating the PE of SR against first-time and overall malaria infection
SAS procedure `PROC glimmix` with the `cloglog` link. Each subject will have multiple rows, one for each visit. The statement `random` will be included to take account of the dependency of the subjects from the same cluster. Some sample codes are given below.

```
proc glimmix data=WORK.IMPORT NOCLPRINT method=LAPLACE;
class  Subject_ID  Cluster  Final_Diagnosis  Treatment_Allocation  Gender
Eaves_Open wallwood recoded_visit;
model Final_Diagnosis (event='POS')=
Treatment_Allocation
Gender
Eaves_Open
wallwood
age_scaled
Number_of_Doors
clusterpop_scaled
BaselineIncidence
recoded_visit/ dist=binary solution link=cloglog;
random int / subject=Cluster;
estimate 'Treatment' Treatment_Allocation 1 -1 /alpha=0.1 cl exp;
ods output estimates=treatest; run;
```

S5. Mosquito Insecticide Resistance Profile

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Ochomo EO, Gimnig JE, et al. Effect of a spatial repellent on malaria incidence in an area of western Kenya characterized by high malaria transmission, insecticide resistance and universal coverage of insecticide treated nets: a cluster-randomized, controlled trial



I. Sampling Locations

Figure 1. Sampling Location – Baseline Period

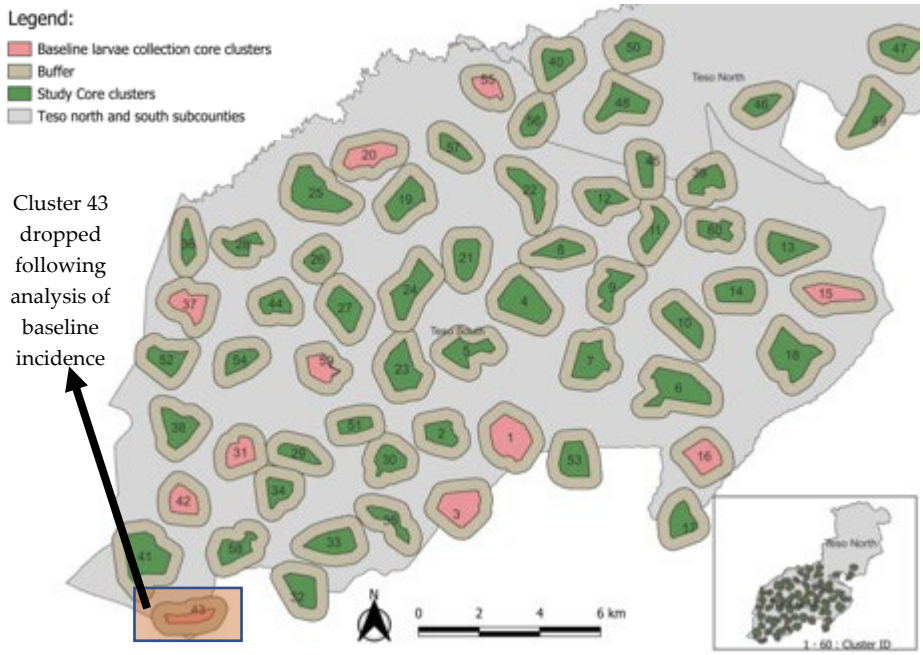
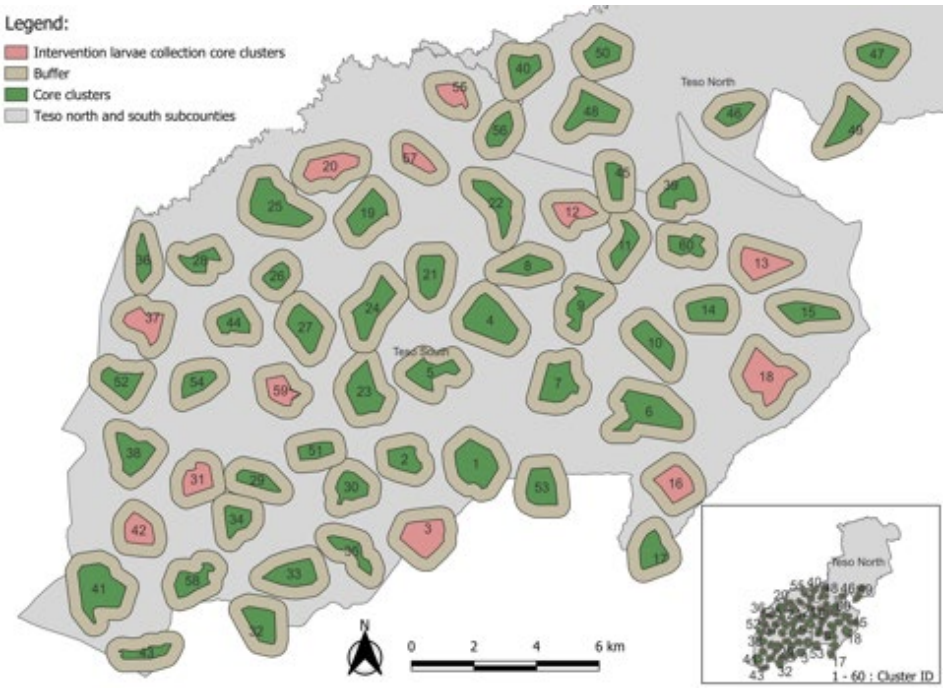


Figure 2. Sampling Location – Intervention Period



II. Methods

Anopheline mosquito larvae were reared to 3-5 day-old adults before exposure to **Permethrin (0.75)**, **Permethrin+PBO** or **transfluthrin (2ug/ml).**

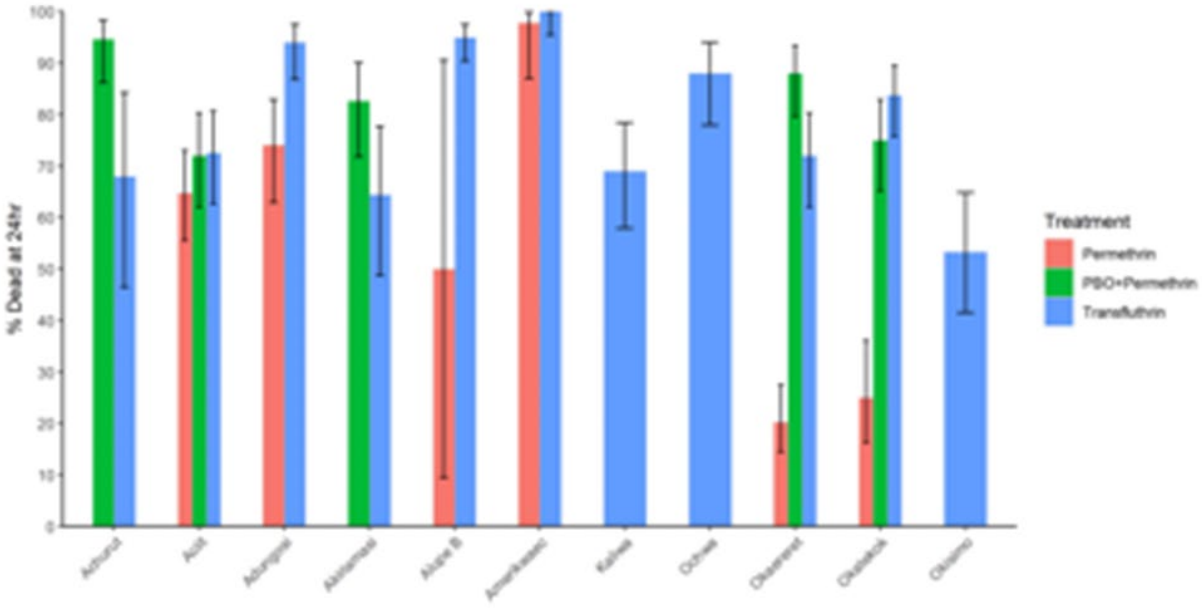
Permethrin and Permethrin+PBO exposures were conducted using standard WHO tube assays, while CDC bottle assays were utilized in testing transfluthrin. Evaluations were conducted once in 2021, to align with baseline, and once in each 2022 and 2023 during intervention phase.

III. Results

a. Baseline Outcomes:

Due to inability to consistently collect and rear-through sufficient numbers of mosquitoes (due to massive heterogeneity in distribution, productivity of larval habitats), not all three tests were conducted at each site. Assessment of transfluthrin was preferentially conducted for nearly all sites while Permethrin and Permethrin+ PBO assessment was conducted for only a few sites. Based on current WHO thresholds of susceptibility (≥98% mortality), resistance to transfluthrin was observed from assays peformed with specimens in all sites (except Amerikwai C); with one site exhibiting ~50% mortality (Okisimo). Resistance to Permethrin was observed in all sites, as expected. Exposure to PBO before Permethrin was observed to marginally increase mortality; however, mortality to Permethrin was not fully restored following PBO exposures.

Figure 3: Baseline percent mortality of *An. gambaie s.l.* exposed to permethrin (0.75), Permethrin+PBO or transfluthrin (2ug/ml)



b. Intervention Phase Outcomes:

Observed high resistance to Permethrin was consistent with previous studies assessing pyrethroid resistance in malaria vectors in the region. Pre-PBO exposure of *An. gambiae s.l.* to Permethrin increased mortality. Based on current WHO thresholds of mortality (<98%), resistance to transfluthrin was observed from assays peformed with specimens in most clusters, but no greater than that seen during baseline. *interpretation of transfluthrin resistance data should take into consideration the CDC bottle assay technique with technical-grade transfluthrin insecticide may not be optimal/suitable for the evaluation of spatial-repellent insecticides, such as tranfluthrin.*

Figure 4: Percent mortality of *An. gambiae s.l.* exposed to Permethrin (0.75), Permethrin+PBO or transfluthrin (2ug/ml) during intervention phase

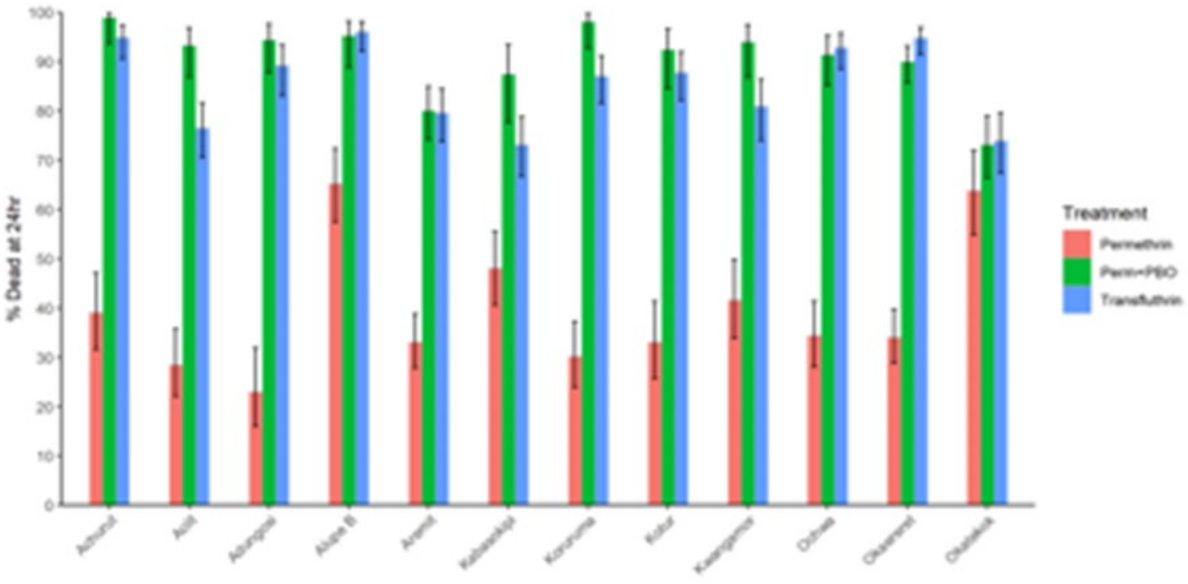


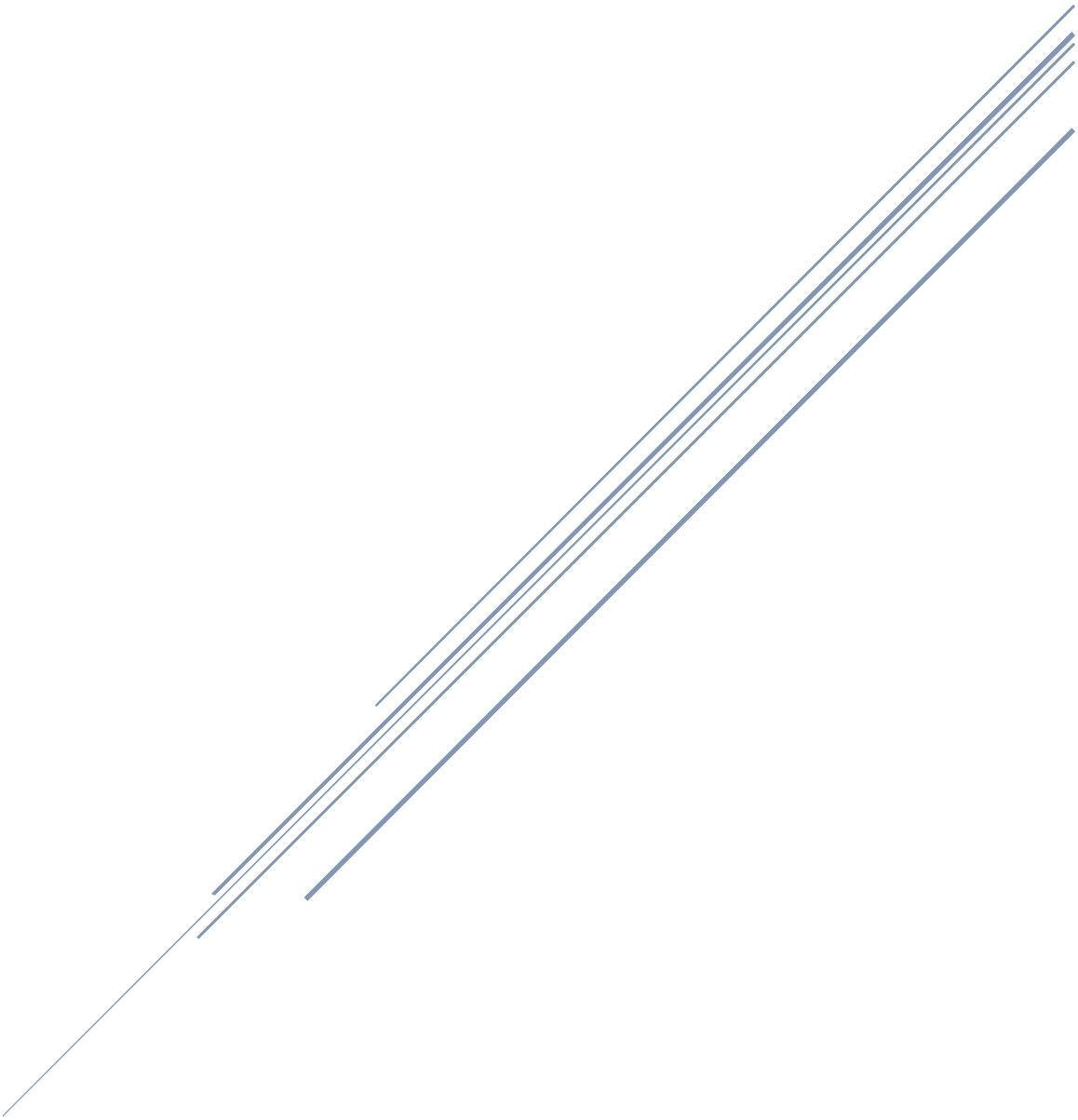
Table 1. Aggregated anopheline mosquito mortality (by cluster) from Baseline, Intervention

Site Village	Cluster number	Insecticide Evaluated	Baseline	Intervention
			Number Dead/Exposed (% Dead)	Number Dead/Exposed (% Dead)
Achurut	20	Perm+PBO	71/75(94.67)	99/100(99.00)
		Permethrin	-	63/161(39.13)
		Transfluthrin	17/25(68.00)	186/196(94.90)
Aciit	59	Perm+PBO	72/100(72.00)	112/120(93.33)
		Permethrin	79/122(64.75)	51/179(28.49)
		Transfluthrin	74/102(72.55)	183/239(76.57)
Adungosi	31	Perm+PBO	-	101/107(94.39)
		Permethrin	60/81(74.07)	27/117(23.08)
		Transfluthrin	94/100(94.00)	141/158(89.24)
Alupe B	42	Perm+PBO	-	101/106(95.28)
		Permethrin	1/2(50.00)	109/167(65.27)
		Transfluthrin	170/179(94.97)	197/205(96.10)
Aremit	57	Perm+PBO	-	181/226(80.09)
		Permethrin	-	98/296(33.11)
		Transfluthrin	-	184/231(7.65)
Kabasokipi	12	Perm+PBO	-	70/80(87.50)
		Permethrin	-	87/181(48.07)
		Transfluthrin	-	161/220(73.18)
Koruruma	55	Perm+PBO	62/75(82.67)	104/106(98.11)
		Permethrin	-	58/192(30.21)
		Transfluthrin	29/45(64.44)	182/209(87.08)
Kotur	13	Perm+PBO	-	86/93(92.47)
		Permethrin	-	49/148(33.11)
		Transfluthrin	-	166/189(87.83)
Kwangamor	18	Perm+PBO	-	94/100(94.00)
		Permethrin	-	65/156(41.67)
		Transfluthrin	-	136/168(80.95)
Ochwa	16	Perm+PBO	-	128/140(91.43)
		Permethrin	-	72/209(34.45)
		Transfluthrin	66/75(88.00)	209/225(92.89)
Okaereret	37	Perm+PBO	88/100(88.00)	253/281(90.04)
		Permethrin	32/158(20.25)	105/308(34.09)
		Transfluthrin	72/100(72.00)	274/289(94.81)
Okatekok	3	Perm+PBO	75/100(75.00)	150/205(73.17)
		Permethrin	20/80(25.00)	83/130(63.85)
		Transfluthrin	103/123(83.74)	156/211(73.93)
Okisimo	15	Transfluthrin	40/75(53.33)	-
Kaliwa	1	Transfluthrin	58/84(69.05)	-
Amerikwai C	43	Permethrin	45/46(97.83)	-
		Transfluthrin	101/101(100.00)	-

S6. Safety Data

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Ochomo EO, Gimnig JE, et al. Effect of a spatial repellent on malaria incidence in an area of western Kenya characterized by high malaria transmission, insecticide resistance and universal coverage of insecticide treated nets: a cluster-randomized, controlled trial



The safety results in the baseline and during the intervention period based on the final data in the Kenya study from the analysis listed in the table below are presented.

	Analysis	
1	Total number of AE (adverse events) and SAE (Serious AEs) by symptom in each cluster	secondary
2	Total number of AEs (adverse events) and SAEs (Serious AEs) by symptom by treatment (spatial repellent/SR vs placebo) and zone (buffer vs core)	secondary
3	Frequency and percentage of subjects that experienced at least one episode of AE by symptom in each cluster	secondary
4	Frequency and percentage of subjects that experienced at least one episode of SAE by symptom in each cluster	secondary
5	Histograms of the total number of AEs per cluster by treatment	secondary
The analysis was performed on the baseline data and intervention data, respectively.		

Summary Safety Results during the Baseline Period (1,866 subjects)

B.1 Among the observed symptoms, cough and running nose were the top 2 symptoms in both total occurrences (664 and 549, respectively), followed by headache (356), skin irritation/ rash (299), abdominal discomfort (215), nausea /vomiting (208), diarrhea (162), eye irritation (34). Difficulty breathing and severe malaria related symptoms were (<10 occurrences) across the 58 clusters at baseline in the core and buffer zones of the SR and placebo arms combined. In addition, there were 421 occurrences of "other" symptoms associated with, for example, septic wounds secondary to scabies and dental cavity.

B.2 Similar patterns on the symptoms as stated in **B.1**, but broken down by buffer/core and SR/placebo, were observed. The SR clusters at baseline somehow have more occurrence of AE symptoms than the placebo symptoms. There was significant variation in the total numbers of AE in both the SR and placebo clusters at baseline (Part I Tables 1 to 5; Figures 1 and 2).

B.3 Among the observed symptoms, cough and running nose were the top 2 symptoms with the highest average prevalence rates across the 58 clusters at 27.8% and 21.2% (%percentage of subjects in a cluster with at least one episode of a symptom). The prevalence rate was 15% for headache, 13% for skin irritation/rash, 10% for abdominal discomfort, 10% for nausea/ vomiting, 7.6% for diarrhea, and 1.73% for eye irritation; prevalence rate was < 0.5% for each of the rest of the symptoms (Part I Table 6).

B.4 There were 13 occurrences of SAE symptoms at baseline overall (buffer + core, SR + placebo), with 1 Abdominal Discomfort, 1 Nausea / Vomiting, 2 Vomiting everything, 3 Severe Malaria - Prostration / Very weak, unable to stand, 1 Severe Malaria - Severe Pallor, 1 Severe Malaria - Unconsciousness / Drowsiness, 1 Severe Malaria: Convulsions / Seizures, and 3 Other. Broken down by buffer/core and SR/placebo, there were 4 occurrences in 3 core SR clusters, 5 occurrences in 4 core SR clusters, 2 occurrences in 3 core placebo clusters, 2 occurrences in 1 buffer placebo clusters (Part I Tables 7 to 11).

B.5 Regarding the prevalence of the SAE symptoms at the cluster level (%percentage of subjects with at least one episode of an SAE symptom in a cluster), the largest was 2.9% associated with Severe Malaria - Prostration / Very weak, unable to stand (Part I Table 12).

Summary Safety Results during the Intervention Period (3,733 Subjects)

I.1 Among the observed symptoms, cough and running nose were the top 2 AE symptoms in both total occurrences (2465 and 2051, respectively), followed by skin irritation/ rash (877), headache (607), diarrhea

(550), abdominal discomfort (361), nausea /vomiting (327), eye irritation (152), Difficulty breathing (14), and severe malaria related symptoms had < 5 occurrences across the 58 clusters at intervention in the core and buffer zones of the SR and placebo arms combined. In addition, there were 777 occurrences of "other" symptoms associated with, for example, septic wounds secondary to scabies and dental cavity (Part II Table 1).

I.2 Running nose and cough remained as the top 2 AE symptoms, broken down by buffer/core and SR/placebo, so did the top 8 symptoms and "other" in terms of occurrence frequency (Part II Tables 2 to 5).

I.3 Comparing the SR and placebo clusters in the core zone on the AE symptoms, except for headache, where the occurrence frequency was slightly lower in the 29 SR clusters, all the other 7 top symptoms and "other" had notably more occurrences in the 29 SR clusters compared to the 29 placebo clusters, where the total numbers of subjects were about the same between the SR and placebo groups. Comparing the SR and placebo clusters in the buffer zone on the AE symptoms, all the other 7 top symptoms and "other" had notably more occurrences in the 29 SR clusters compared to the 29 placebo clusters, where the total numbers of subjects were about the same between the SR and placebo groups. As stated in **B.3**, the SR clusters tended to have more AE occurrences than placebo clusters even at baseline. Thus, the higher numbers of AEs during the interventions in the SR clusters in both the core and buffer zones were likely associated with the higher baseline numbers. In addition, no formal statistical tests were performed, we cannot conclude whether the increases in AE symptoms in the SR clusters during the interventions were statistically significant or not, especially if the analysis would adjust for baseline. Also noted is that there was significant variation in the total numbers of AE in both the SR and placebo clusters at baseline (Part II Tables 2 to 5; Figures 3 and 4).

I.4 Among the observed symptoms, cough and running nose were the top 2 symptoms with the highest average prevalence across the 58 clusters at 37.42% and 30.7% (%percentage of subjects with at least one episode of a symptom in a cluster). The average cluster-level prevalence rate was 16% for skin irritation/rash, 11.2% for headache,11.85% for diarrhea, 7.93% for abdominal discomfort, 7.43% for nausea/vomiting, and 3.56% for eye irritation; prevalence rate was < 0.5% for each of the rest of the symptoms (Part II Table 6). Compared to baseline, the prevalence rates for the top 2 symptoms were notably numerically higher while those for the rest of the AE symptom were either slightly higher, slightly lower, or similar.

I.5 There were 22 occurrences of SAE symptoms during the intervention period overall (buffer + core, SR + placebo), with 2 headache, 5 Nausea / Vomiting, 1 Severe Malaria - Prostration / Very weak, unable to stand, 3 Severe Malaria - Unconsciousness / Drowsiness, 1 Severe Malaria: Convulsions / Seizures, 2 Severe Malaria: Dark Urine, and 8 Other. Broken down by buffer/core and SR/placebo, there were 3 occurrences in 2 core SR clusters, 7 occurrences in 4 buffer SR cluster, 1 occurrence in 1 core placebo cluster, 11 occurrences in 5 buffer placebo clusters (Part II Tables 7 to 11).

I.6 Regarding the prevalence of the SAE symptoms at the cluster level (%percentage of subjects with at least one episode of a SAE symptom in a cluster), the largest was 3% (2 subject in the whole cluster out of 66 subjects, buffer + core) associated with Nausea / Vomiting, the rest was either 1.5% or 1.6% (1 subjects out of a whole cluster, buffer + core) (Part II Table 12).

Detailed Safety Results

The AE and SAE summary results are provided in the following Tables and Figures. Note that there was no SAE occurrence in the core zones of 29 placebo clusters during the intervention period, so Part II has one table less compared to Part I.

		Table #	Contents
Part I Baseline	**AE**	1	number of AEs per symptom per cluster
		2	number of AEs per symptom per cluster for **Core** zones with **SR**
		3	number of AEs per symptom per cluster for **Buffer** zones with **SR**
		4	number of AEs per symptom per cluster for **Core** zones with **Placebo**
		5	number of AEs per symptom per cluster for **Buffer** zones with **Placebo**
		6	frequency and percentage of subjects per cluster having at least one AE episode by symptom
	SAE	7	number of SAEs per symptom per cluster
		8	number of SAEs per symptom per cluster for **Core** zones with **SR**
		9	number of SAEs per symptom per cluster for **Buffer** zones with **SR**
		10	number of SAEs per symptom per cluster for **Core** zones with **Placebo**
		11	number of SAEs per symptom per cluster for **Buffer** zones with **Placebo**
		12	frequency and percentage of subjects per cluster having at least one SAE episode by symptom
		Table #	**Contents**
Part II Intervention	**AE**	1	number of AEs per symptom per cluster
		2	number of AEs per symptom per cluster for **Core** zones with **SR**
		3	number of AEs per symptom per cluster for **Buffer** zones with **SR**
		4	number of AEs per symptom per cluster for **Core** zones with **Placebo**
		5	number of AEs per symptom per cluster for **Buffer** zones with **Placebo**
		6	frequency and percentage of subjects per cluster having at least one AE episode by symptom
	SAE	7	number of SAEs per symptom per cluster
		8	number of SAEs per symptom per cluster for **Core** zones with **SR**
		9	number of SAEs per symptom per cluster for **Buffer** zones with **SR**
		10	number of SAEs per symptom per cluster for C**ore** zones with **Placebo**
		11	number of SAEs per symptom per cluster for **Buffer** zones with **Placebo**
		12	frequency and percentage of subjects per cluster having at least one SAE episode by symptom

Figure 1: total number of AEs in placebo clusters (baseline)

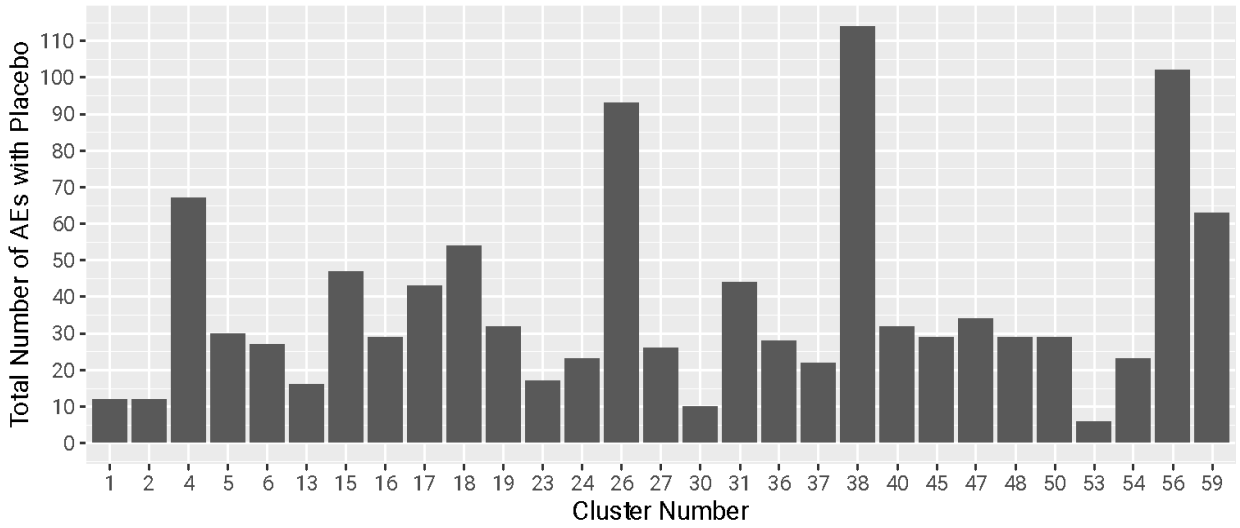


Figure 2: total number of AEs in SR clusters (baseline)

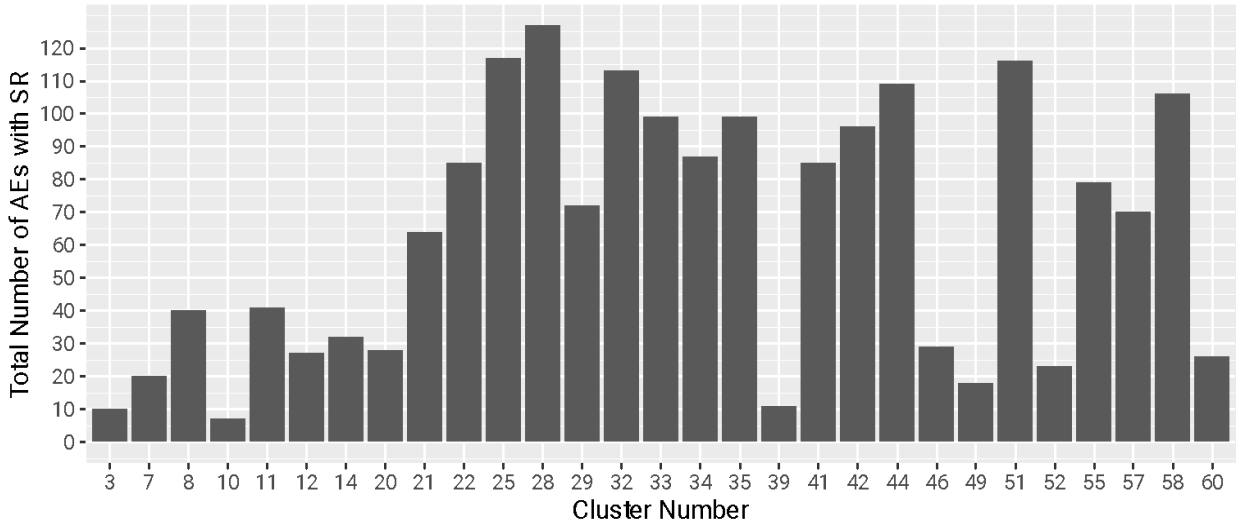


Figure 3: total number of AEs in placebo clusters (intervention)

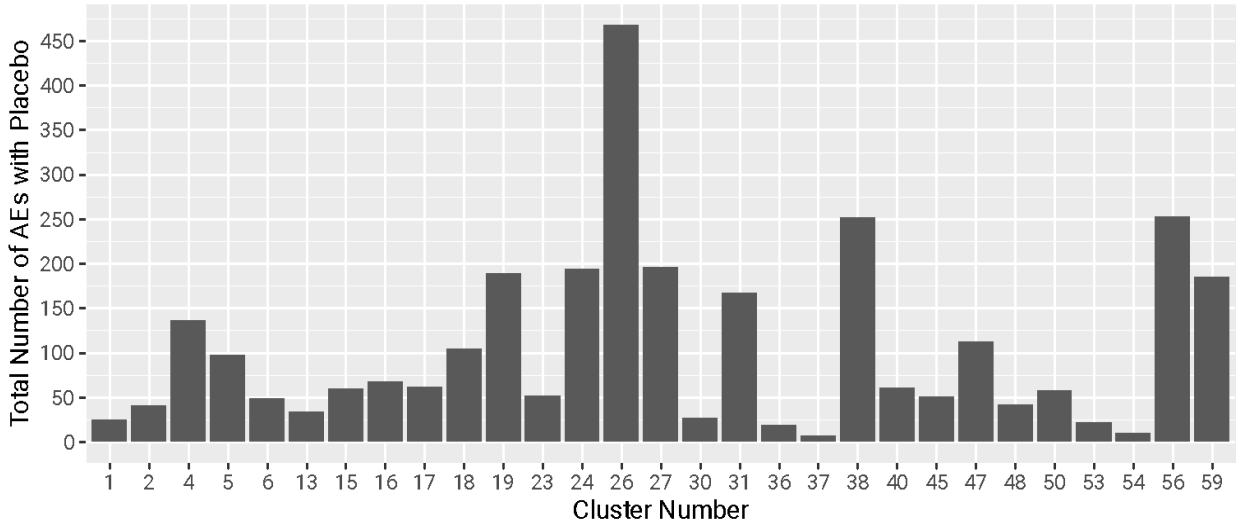
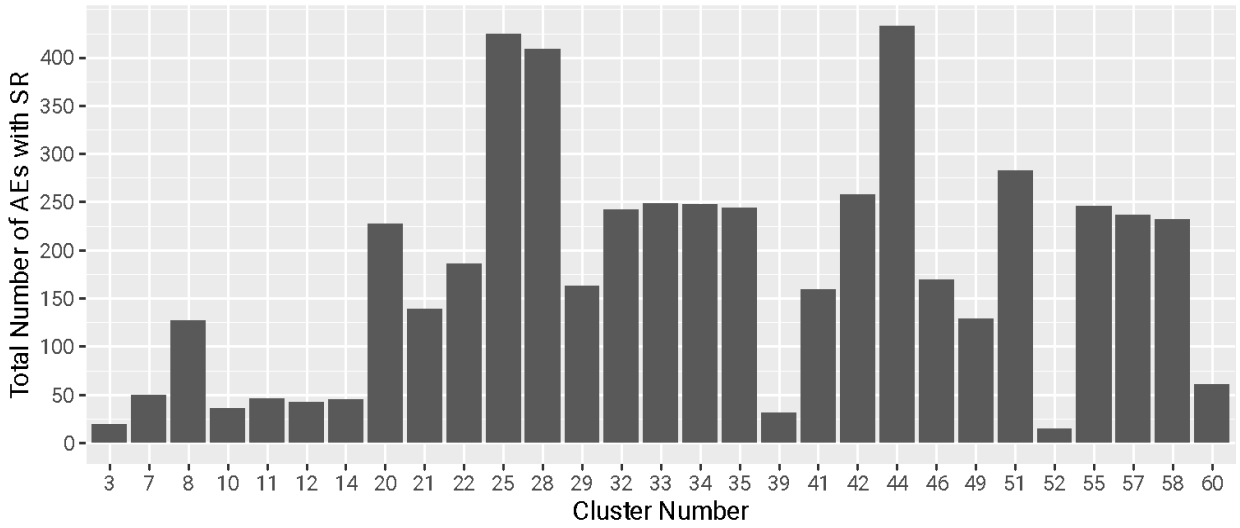


Figure 4: total number of AEs in SR clusters (intervention)



Part I
Baseline

Table 1: number of AEs per symptom per cluster (cluster number highlighted in red are SR clusters)

Cluster	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
1	34	7	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
2	33	6	3	0	2	0	0	0	0	0	1	0	0	0	0	0	0	0	0
3	32	5	3	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
4	31	17	14	1	5	8	1	0	8	3	0	0	0	0	0	0	0	0	10
5	33	3	5	0	0	7	1	3	4	0	0	0	0	0	0	0	0	0	7
6	34	8	3	0	3	1	3	0	6	1	0	0	0	0	0	0	0	0	2
7	34	4	2	0	1	2	2	3	3	0	0	0	0	0	0	0	0	0	3
8	32	14	4	1	5	4	3	0	4	0	0	0	0	0	0	0	0	0	5
10	31	0	0	0	0	1	3	1	1	0	0	1	0	0	0	0	0	0	0
11	32	13	4	0	6	1	2	1	4	0	0	0	0	0	0	0	0	0	10
12	32	6	2	0	2	5	0	0	3	0	0	0	0	0	0	0	0	0	9
13	33	2	1	0	2	3	0	0	6	0	0	0	0	0	0	0	0	0	2
14	29	13	0	0	2	2	2	3	4	1	0	0	0	0	0	0	0	0	5
15	28	9	6	0	3	10	1	2	8	1	0	0	0	0	0	0	0	0	7
16	29	9	5	0	1	4	3	1	2	1	0	0	0	0	0	0	0	0	3
17	28	12	8	0	1	4	2	4	0	2	0	1	0	0	0	0	0	0	9
18	29	14	6	1	5	11	3	2	3	2	0	0	0	0	0	0	0	0	7
19	33	5	5	0	6	0	4	2	5	1	0	0	0	0	0	0	0	0	4
20	33	6	2	0	5	5	2	1	6	0	0	0	0	0	0	0	0	0	1
21	31	15	16	0	6	8	1	3	2	2	0	0	0	0	0	0	0	0	11
22	33	28	13	1	4	7	4	0	20	1	0	0	1	0	0	0	0	0	6
23	33	1	5	0	0	3	0	1	6	0	0	0	0	0	0	0	0	0	1
24	33	2	2	0	2	2	2	4	7	1	0	0	0	0	0	0	0	0	1
25	34	18	28	0	8	23	4	7	14	1	0	0	0	0	0	0	0	0	14
26	33	22	34	0	5	7	7	2	5	3	0	0	0	0	0	0	0	0	8
27	35	4	4	0	3	2	0	2	7	0	0	0	0	0	0	1	0	0	3
28	33	24	28	0	11	20	14	6	10	2	0	0	0	0	0	0	0	0	12
29	33	19	15	1	7	2	7	3	10	0	0	0	0	0	0	0	0	0	8
30	35	3	2	0	1	0	0	1	0	1	0	0	0	0	0	0	0	0	2
31	32	11	11	0	5	1	2	5	2	0	0	0	0	0	0	0	0	0	7
32	35	29	39	0	3	10	4	5	3	0	0	0	0	0	0	0	0	0	20
33	34	24	22	0	2	17	10	8	2	0	0	0	0	0	0	0	0	0	14
34	31	19	30	0	0	5	8	7	6	0	0	0	0	0	0	0	0	0	12
35	32	14	27	0	0	17	7	8	6	0	0	0	0	0	0	0	0	0	20
36	27	4	0	0	7	2	3	2	5	0	0	0	0	0	0	0	0	0	5
37	32	4	0	0	5	3	2	0	6	0	0	0	0	0	0	0	0	0	2
38	34	17	19	0	13	10	8	8	20	1	0	0	0	1	1	0	0	0	16
39	30	2	0	0	1	1	0	1	1	0	0	0	0	0	0	0	0	0	5
40	32	7	1	0	3	0	6	2	10	0	0	0	0	0	0	0	0	0	3
41	32	24	16	0	3	5	4	2	9	1	0	0	0	0	0	0	0	0	21
42	32	22	20	0	8	4	4	2	10	1	1	0	0	0	1	0	0	0	23
44	35	28	32	0	4	11	7	4	10	0	0	0	0	0	1	0	1	0	11

45	32	2	0	0	3	0	8	1	11	0	0	0	0	0	0	0	0	0	4
46	33	1	0	0	2	8	7	2	3	0	0	0	0	0	0	0	0	0	6
47	34	7	3	0	2	3	3	4	4	2	0	0	0	0	0	0	0	0	6
48	31	4	0	0	7	1	5	2	7	0	0	0	0	0	0	0	0	0	3
49	30	3	3	0	2	2	2	1	2	0	0	0	0	0	0	0	0	0	3
50	32	10	3	0	2	0	5	1	6	1	0	0	0	0	0	0	0	0	1
51	31	18	21	1	15	7	13	8	7	0	0	0	0	0	0	0	0	0	26
52	35	7	0	0	4	2	1	4	3	1	0	0	0	0	0	0	0	0	1
53	31	0	0	0	0	2	1	0	3	0	0	0	0	0	0	0	0	0	0
54	32	3	0	0	3	5	2	6	2	0	0	0	0	0	0	0	0	0	2
55	33	29	11	0	0	7	6	6	11	0	0	0	0	0	0	0	0	0	9
56	34	33	21	0	1	8	3	7	17	3	1	0	0	0	0	0	0	0	8
57	31	18	16	0	5	11	4	0	10	0	0	0	0	0	0	0	0	0	6
58	33	20	17	0	7	9	6	5	18	1	1	1	0	0	0	0	0	0	21
59	30	10	12	0	7	2	5	5	13	0	0	0	0	0	0	0	0	0	9
60	33	5	1	0	5	4	1	4	0	0	1	0	0	0	0	0	0	0	5
	# of subjects	**Cough**	**Runny Nose**	**Difficulty Breathing**	**Abdominal Discomfort**	**Skin Irritation / Rash**	**Nausea / Vomiting**	**Diarrhea**	**Headache**	**Eye Irritation**	**Vomiting everything**	**Respiratory Distress**	**Salivation (drooling)**	**Severe Malaria - Unconsciousness / Drowsiness**	**Severe Malaria - Prostration / Very weak, unable to stand**	**Severe Malaria - Convulsions / Seizures**	**Severe Malaria - Severe Pallor**	**Severe Malaria - Dark Urine**	**Other**
min	27	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
max	35	33	39	1	15	23	14	8	20	3	1	1	1	1	1	1	1	0	26
median	32	9	4.5	0	3	4	3	2	5.5	0	0	0	0	0	0	0	0	0	6
mean	32.17	11.45	9.47	0.1	3.71	5.16	3.59	2.79	6.14	0.59	0.09	0.05	0.02	0.02	0.05	0.02	0.02	0	7.26
sd	1.85	8.85	10.46	0.31	3.22	5.13	3.16	2.49	4.91	0.86	0.28	0.22	0.13	0.13	0.22	0.13	0.13	0	6.36
total	1866	664	549	6	215	299	208	162	356	34	5	3	1	1	3	1	1	0	421

Table 2: number of AEs per symptom per cluster for Core zones with SR

Cluster	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
3	19	4	3	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
7	20	1	1	0	0	2	1	3	2	0	0	0	0	0	0	0	0	0	1
8	19	9	1	1	3	2	2	0	0	0	0	0	0	0	0	0	0	0	3
10	17	0	0	0	0	1	3	1	1	0	0	1	0	0	0	0	0	0	0
11	18	6	4	0	3	1	1	0	1	0	0	0	0	0	0	0	0	0	6
12	19	4	2	0	0	3	0	0	2	0	0	0	0	0	0	0	0	0	5
14	17	10	0	0	1	1	1	0	4	0	0	0	0	0	0	0	0	0	2
20	20	4	1	0	2	4	1	1	3	0	0	0	0	0	0	0	0	0	0
21	18	8	6	0	6	4	0	1	2	1	0	0	0	0	0	0	0	0	6
22	19	14	4	1	3	5	4	0	15	0	0	0	1	0	0	0	0	0	4
25	20	14	16	0	5	13	3	3	10	1	0	0	0	0	0	0	0	0	9
28	19	16	16	0	6	10	6	1	6	1	0	0	0	0	0	0	0	0	4
29	20	9	8	0	4	1	2	3	5	0	0	0	0	0	0	0	0	0	6
32	19	16	24	0	0	5	1	1	1	0	0	0	0	0	0	0	0	0	11
33	20	13	12	0	2	12	6	3	1	0	0	0	0	0	0	0	0	0	10
34	17	14	19	0	0	2	4	5	2	0	0	0	0	0	0	0	0	0	9
35	20	6	13	0	0	10	4	4	3	0	0	0	0	0	0	0	0	0	15
39	19	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	4
41	18	15	9	0	2	5	4	1	4	0	0	0	0	0	0	0	0	0	16
42	18	14	14	0	7	1	3	2	4	1	1	0	0	0	1	0	0	0	11
44	21	17	21	0	2	4	7	3	8	0	0	0	0	0	0	0	0	0	8
46	19	1	0	0	1	5	6	0	1	0	0	0	0	0	0	0	0	0	4
49	16	2	1	0	2	1	2	0	1	0	0	0	0	0	0	0	0	0	2
51	18	9	11	0	4	3	10	6	2	0	0	0	0	0	0	0	0	0	16
52	19	5	0	0	3	2	0	4	2	0	0	0	0	0	0	0	0	0	0
55	19	14	9	0	0	4	4	3	5	0	0	0	0	0	0	0	0	0	8
57	20	11	11	0	3	5	4	0	7	0	0	0	0	0	0	0	0	0	5
58	20	11	10	0	4	4	4	4	13	1	1	0	0	0	0	0	0	0	14
60	19	3	1	0	2	2	0	2	0	0	1	0	0	0	0	0	0	0	3
	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
min	16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
max	21	17	24	1	7	13	10	6	15	1	1	1	1	0	1	0	0	0	16
median	19	9	6	0	2	3	3	1	2	0	0	0	0	0	0	0	0	0	5
mean	18.86	8.66	7.48	0.07	2.28	3.9	2.86	1.76	3.66	0.17	0.1	0.03	0.03	0	0.03	0	0	0	6.31
sd	1.16	5.39	7.14	0.26	2.03	3.39	2.5	1.77	3.79	0.38	0.31	0.19	0.19	0	0.19	0	0	0	4.86
total	547	251	217	2	66	113	83	51	106	5	3	1	1	0	1	0	0	0	183

Table 3: number of AEs per symptom per cluster for Buffer zones with SR

Cluster	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
3	13	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	14	3	1	0	1	0	1	0	1	0	0	0	0	0	0	0	0	0	2
8	13	5	3	0	2	2	1	0	4	0	0	0	0	0	0	0	0	0	2
10	14	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11	14	7	0	0	3	0	1	1	3	0	0	0	0	0	0	0	0	0	4
12	13	2	0	0	2	2	0	0	1	0	0	0	0	0	0	0	0	0	4
14	12	3	0	0	1	1	1	3	0	1	0	0	0	0	0	0	0	0	3
20	13	2	1	0	3	1	1	0	3	0	0	0	0	0	0	0	0	0	1
21	13	7	10	0	0	4	1	2	0	1	0	0	0	0	0	0	0	0	5
22	14	14	9	0	1	2	0	0	5	1	0	0	0	0	0	0	0	0	2
25	14	4	12	0	3	10	1	4	4	0	0	0	0	0	0	0	0	0	5
28	14	8	12	0	5	10	8	5	4	1	0	0	0	0	0	0	0	0	8
29	13	10	7	1	3	1	5	0	5	0	0	0	0	0	0	0	0	0	2
32	16	13	15	0	3	5	3	4	2	0	0	0	0	0	0	0	0	0	9
33	14	11	10	0	0	5	4	5	1	0	0	0	0	0	0	0	0	0	4
34	14	5	11	0	0	3	4	2	4	0	0	0	0	0	0	0	0	0	3
35	12	8	14	0	0	7	3	4	3	0	0	0	0	0	0	0	0	0	5
39	11	1	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	1
41	14	9	7	0	1	0	0	1	5	1	0	0	0	0	0	0	0	0	5
42	14	8	6	0	1	3	1	0	6	0	0	0	0	0	0	0	0	0	12
44	14	11	11	0	2	7	0	1	2	0	0	0	0	0	1	0	1	0	3
46	14	0	0	0	1	3	1	2	2	0	0	0	0	0	0	0	0	0	2
49	14	1	2	0	0	1	0	1	1	0	0	0	0	0	0	0	0	0	1
51	13	9	10	1	11	4	3	2	5	0	0	0	0	0	0	0	0	0	10
52	16	2	0	0	1	0	1	0	1	1	0	0	0	0	0	0	0	0	1
55	14	15	2	0	0	3	2	3	6	0	0	0	0	0	0	0	0	0	1
57	11	7	5	0	2	6	0	0	3	0	0	0	0	0	0	0	0	0	1
58	13	9	7	0	3	5	2	1	5	0	0	1	0	0	0	0	0	0	7
60	14	2	0	0	3	2	1	2	0	0	0	0	0	0	0	0	0	0	2
Cluster	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
min	11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
max	16	15	15	1	11	10	8	5	6	1	0	1	0	0	1	0	1	0	12
median	14	7	5	0	1	2	1	1	3	0	0	0	0	0	0	0	0	0	3
mean	13.52	6.1	5.34	0.07	1.79	3	1.55	1.52	2.66	0.21	0	0.03	0	0	0.03	0	0.03	0	3.62
sd	1.12	4.38	5.11	0.26	2.23	2.9	1.86	1.64	1.99	0.41	0	0.19	0	0	0.19	0	0.19	0	3.06
total	392	177	155	2	52	87	45	44	77	6	0	1	0	0	1	0	1	0	105

Table 4: number of AEs per symptom per cluster for Core zones with Placebo

Cluster	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
1	18	4	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	20	3	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
4	19	11	9	1	4	7	1	0	5	1	0	0	0	0	0	0	0	0	8
5	19	2	2	0	0	2	0	2	3	0	0	0	0	0	0	0	0	0	3
6	20	5	3	0	2	1	3	0	5	1	0	0	0	0	0	0	0	0	1
13	19	0	0	0	0	1	0	0	5	0	0	0	0	0	0	0	0	0	1
15	18	5	3	0	1	5	0	2	2	1	0	0	0	0	0	0	0	0	3
16	19	6	4	0	1	1	1	1	1	0	0	0	0	0	0	0	0	0	3
17	18	9	4	0	1	2	0	2	0	2	0	0	0	0	0	0	0	0	6
18	19	11	2	1	3	10	0	2	2	2	0	0	0	0	0	0	0	0	6
19	20	3	2	0	3	0	1	1	2	1	0	0	0	0	0	0	0	0	1
23	19	0	0	0	0	2	0	0	5	0	0	0	0	0	0	0	0	0	0
24	20	1	1	0	1	2	1	1	5	1	0	0	0	0	0	0	0	0	0
26	20	11	17	0	5	6	4	1	3	3	0	0	0	0	0	0	0	0	6
27	21	2	4	0	2	1	0	1	6	0	0	0	0	0	0	0	0	0	2
30	21	2	1	0	1	0	0	1	0	1	0	0	0	0	0	0	0	0	1
31	19	5	6	0	3	1	1	2	0	0	0	0	0	0	0	0	0	0	4
36	13	2	0	0	3	2	1	2	1	0	0	0	0	0	0	0	0	0	3
37	21	4	0	0	3	1	2	0	3	0	0	0	0	0	0	0	0	0	1
38	20	9	9	0	10	7	3	5	11	1	0	0	0	1	1	0	0	0	8
40	19	4	0	0	3	0	0	2	6	0	0	0	0	0	0	0	0	0	2
45	18	2	0	0	3	0	6	1	8	0	0	0	0	0	0	0	0	0	2
47	19	3	0	0	1	2	2	2	4	0	0	0	0	0	0	0	0	0	2
48	17	2	0	0	0	0	1	1	3	0	0	0	0	0	0	0	0	0	2
50	19	6	2	0	2	0	4	1	5	1	0	0	0	0	0	0	0	0	1
53	19	0	0	0	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0
54	18	2	0	0	1	4	0	2	2	0	0	0	0	0	0	0	0	0	2
56	18	12	6	0	0	6	2	2	7	2	0	0	0	0	0	0	0	0	3
59	17	8	10	0	3	0	3	3	6	0	0	0	0	0	0	0	0	0	6
	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
min	13	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
max	21	12	17	1	10	10	6	5	11	3	1	0	0	1	1	0	0	0	8
median	19	4	2	0	1	1	1	1	3	0	0	0	0	0	0	0	0	0	2
mean	18.86	4.62	3	0.07	1.97	2.21	1.28	1.28	3.48	0.59	0.03	0	0	0.03	0.03	0	0	0	2.66
sd	1.55	3.61	4.01	0.26	2.08	2.68	1.56	1.13	2.75	0.82	0.19	0	0	0.19	0.19	0	0	0	2.38
total	547	134	87	2	57	64	37	37	101	17	1	0	0	1	1	0	0	0	77

Table 5: number of AEs per symptom per cluster for Buffer zones with Placebo

Cluster	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
1	16	3	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
2	13	3	3	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	12	6	5	0	1	1	0	0	3	2	0	0	0	0	0	0	0	0	2
5	14	1	3	0	0	5	1	1	1	0	0	0	0	0	0	0	0	0	4
6	14	3	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	1
13	14	2	1	0	2	2	0	0	1	0	0	0	0	0	0	0	0	0	1
15	10	4	3	0	2	5	1	0	6	0	0	0	0	0	0	0	0	0	4
16	10	3	1	0	0	3	2	0	1	1	0	0	0	0	0	0	0	0	0
17	10	3	4	0	0	2	2	2	0	0	0	1	0	0	0	0	0	0	3
18	10	3	4	0	2	1	3	0	1	0	0	0	0	0	0	0	0	0	1
19	13	2	3	0	3	0	3	1	3	0	0	0	0	0	0	0	0	0	3
23	14	1	5	0	0	1	0	1	1	0	0	0	0	0	0	0	0	0	1
24	13	1	1	0	1	0	1	3	2	0	0	0	0	0	0	0	0	0	1
26	13	11	17	0	0	1	3	1	2	0	0	0	0	0	0	0	0	0	2
27	14	2	0	0	1	1	0	1	1	0	0	0	0	0	0	1	0	0	1
30	14	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
31	13	6	5	0	2	0	1	3	2	0	0	0	0	0	0	0	0	0	3
36	14	2	0	0	4	0	2	0	4	0	0	0	0	0	0	0	0	0	2
37	11	0	0	0	2	2	0	0	3	0	0	0	0	0	0	0	0	0	1
38	14	8	10	0	3	3	5	3	9	0	0	0	0	0	0	0	0	0	8
40	13	3	1	0	0	0	6	0	4	0	0	0	0	0	0	0	0	0	1
45	14	0	0	0	0	0	2	0	3	0	0	0	0	0	0	0	0	0	2
47	15	4	3	0	1	1	1	2	0	2	0	0	0	0	0	0	0	0	4
48	14	2	0	0	7	1	4	1	4	0	0	0	0	0	0	0	0	0	1
50	13	4	1	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0
53	12	0	0	0	0	1	0	0	2	0	0	0	0	0	0	0	0	0	0
54	14	1	0	0	2	1	2	4	0	0	0	0	0	0	0	0	0	0	0
56	16	21	15	0	1	2	1	5	10	1	1	0	0	0	0	0	0	0	5
59	13	2	2	0	4	2	2	2	7	0	0	0	0	0	0	0	0	0	3
	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
min	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
max	16	21	17	0	7	5	6	5	10	2	1	1	0	0	0	1	0	0	8
median	13	3	2	0	1	1	1	0	2	0	0	0	0	0	0	0	0	0	1
mean	13.1	3.52	3.1	0	1.38	1.21	1.48	1.03	2.48	0.21	0.03	0.03	0	0	0	0.03	0	0	1.93
sd	1.63	4.14	4.23	0	1.63	1.4	1.6	1.4	2.64	0.56	0.19	0.19	0	0	0	0.19	0	0	1.81
total	380	102	90	0	40	35	43	30	72	6	1	1	0	0	0	1	0	0	56

Table 6: frequency and percentage of subjects per cluster having at least one AE episode by symptom (cluster number highlighted in red are SR clusters)

Cluster	# of subjects	Cough		Runny Nose		Difficulty Breathing		Abdominal Discomfort		Skin Irritation / Rash		Nausea / Vomiting		Diarrhea		Headache		Eye Irritation		Vomiting everything		Respiratory Distress		Salivation (drooling)		Severe Malaria - Unconsciousness / Drowsiness		Severe Malaria - Prostration / Very weak, unable to stand		Severe Malaria - Convulsions / Seizures		Severe Malaria - Severe Pallor		Severe Malaria - Dark Urine		Other	
		#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%
1	34	7	20.6	4	11.8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2.9
2	33	6	18.2	3	9.1	0	0	2	6.1	0	0	0	0	0	0	0	0	0	0	1	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	32	5	15.6	3	9.4	0	0	0	0	0	0	0	0	0	0	1	3.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	3.1
4	31	15	48.4	11	35.5	1	3.2	5	16.1	7	23	1	3.2	0	0	6	19.4	2	6.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	26
5	33	3	9.1	5	15.2	0	0	0	0	6	18	1	3	3	9.1	4	12.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	18
6	34	8	23.5	3	8.8	0	0	3	8.8	1	2.9	3	8.8	0	0	5	14.7	1	2.9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	5.9
7	34	4	11.8	2	5.9	0	0	1	2.9	2	5.9	2	5.9	2	5.9	3	8.8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	8.8
8	32	11	34.4	4	12.5	1	3.1	4	12.5	4	13	3	9.4	0	0	3	9.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	16
10	31	0	0	0	0	0	0	0	0	1	3.2	3	9.7	1	3.2	1	3.2	0	0	0	0	1	3.2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11	32	11	34.4	3	9.4	0	0	6	18.8	1	3.1	2	6.3	1	3.1	3	9.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	22
12	32	5	15.6	2	6.3	0	0	2	6.3	5	16	0	0	0	0	3	9.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	25
13	33	2	6.1	1	3	0	0	2	6.1	3	9.1	0	0	0	0	5	15.2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	6.1
14	29	9	31	0	0	0	0	2	6.9	2	6.9	2	6.9	2	6.9	4	13.8	1	3.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	17
15	28	7	25	6	21.4	0	0	2	7.1	8	29	1	3.6	1	3.6	6	21.4	1	3.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	25
16	29	9	31	5	17.2	0	0	1	3.4	4	14	3	10.3	1	3.4	2	6.9	1	3.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	10
17	28	11	39.3	7	25	0	0	1	3.6	4	14	2	7.1	4	14.3	0	0	2	7.1	0	0	1	3.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	29
18	29	12	41.4	5	17.2	1	3.4	5	17.2	8	28	2	6.9	2	6.9	3	10.3	2	6.9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	17
19	33	5	15.2	5	15.2	0	0	6	18.2	0	0	4	12.1	2	6.1	4	12.1	1	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	12
20	33	6	18.2	2	6.1	0	0	5	15.2	5	15	2	6.1	1	3	6	18.2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	3
21	31	13	41.9	12	38.7	0	0	5	16.1	6	19	1	3.2	3	9.7	2	6.5	2	6.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	26
22	33	19	57.6	10	30.3	1	3	3	9.1	5	15	4	12.1	0	0	12	36.4	1	3	0	0	0	0	1	3	0	0	0	0	0	0	0	0	0	0	0	0	5	15
23	33	1	3	4	12.1	0	0	0	0	2	6.1	0	0	1	3	5	15.2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	3
24	33	2	6.1	2	6.1	0	0	2	6.1	1	3	2	6.1	3	9.1	5	15.2	1	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	3
25	34	12	35.3	17	50	0	0	6	17.6	19	56	4	11.8	7	20.6	11	32.4	1	2.9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	12	35
26	33	13	39.4	22	66.7	0	0	5	15.2	6	18	4	12.1	2	6.1	5	15.2	3	9.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	24
27	35	4	11.4	4	11.4	0	0	3	8.6	2	5.7	0	0	2	5.7	5	14.3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2.9	0	0	0	0	3	8.6
28	33	18	54.5	20	60.6	0	0	9	27.3	14	42	10	30.3	6	18.2	8	24.2	2	6.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10	30
29	33	13	39.4	11	33.3	1	3	7	21.2	2	6.1	6	18.2	3	9.1	7	21.2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	18
30	35	3	8.6	2	5.7	0	0	1	2.9	0	0	0	0	1	2.9	0	0	1	2.9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	5.7
31	32	9	28.1	9	28.1	0	0	5	15.6	1	3.1	2	6.3	5	15.6	2	6.3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	22
32	35	21	60	27	77.1	0	0	2	5.7	9	26	4	11.4	5	14.3	3	8.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	18	51
33	34	20	58.8	18	52.9	0	0	2	5.9	13	38	10	29.4	7	20.6	2	5.9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11	32
34	31	12	38.7	18	58.1	0	0	0	0	5	16	7	22.6	5	16.1	5	16.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10	32
35	32	12	37.5	16	50	0	0	0	0	15	47	6	18.8	7	21.9	5	15.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	47
36	27	4	14.8	0	0	0	0	7	25.9	2	7.4	3	11.1	2	7.4	5	18.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	15
37	32	4	12.5	0	0	0	0	4	12.5	3	9.4	2	6.3	0	0	6	18.8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	6.3
38	34	15	44.1	13	38.2	0	0	10	29.4	9	27	8	23.5	7	20.6	17	50	1	2.9	0	0	0	0	0	0	1	2.9	1	2.9	0	0	0	0	0	0	0	0	14	41
39	30	2	6.7	0	0	0	0	1	3.3	1	3.3	0	0	1	3.3	1	3.3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	17
40	32	5	15.6	1	3.1	0	0	3	9.4	0	0	5	15.6	2	6.3	9	28.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	9.4
41	32	17	53.1	12	37.5	0	0	2	6.3	3	9.4	3	9.4	2	6.3	6	18.8	1	3.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	47
42	32	16	50	13	40.6	0	0	7	21.9	3	9.4	4	12.5	2	6.3	9	28.1	1	3.1	1	3.1	0	0	0	0	0	0	1	3.1	0	0	0	0	0	0	0	0	15	47
44	35	20	57.1	20	57.1	0	0	3	8.6	10	29	7	20	3	8.6	8	22.9	0	0	0	0	0	0	0	0	0	0	1	2.9	0	0	1	2.9	0	0	0	0	8	23
45	32	2	6.3	0	0	0	0	3	9.4	0	0	7	21.9	1	3.1	10	31.3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	13

46	33	1	3	0	0	0	0	2	6.1	6	18	5	15.2	1	3	3	9.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	18
47	34	7	20.6	2	5.9	0	0	2	5.9	3	8.8	3	8.8	4	11.8	4	11.8	2	5.9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	18
48	31	4	12.9	0	0	0	0	6	19.4	1	3.2	4	12.9	2	6.5	7	22.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	6.5
49	30	3	10	3	10	0	0	2	6.7	2	6.7	2	6.7	1	3.3	2	6.7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	6.7
50	32	9	28.1	3	9.4	0	0	2	6.3	0	0	4	12.5	1	3.1	4	12.5	1	3.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	3.1
51	31	11	35.5	14	45.2	1	3.2	11	35.5	6	19	11	35.5	6	19.4	6	19.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	16	52
52	35	7	20	0	0	0	0	3	8.6	1	2.9	1	2.9	4	11.4	2	5.7	1	2.9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2.9
53	31	0	0	0	0	0	0	0	0	2	6.5	1	3.2	0	0	3	9.7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
54	32	3	9.4	0	0	0	0	3	9.4	5	16	2	6.3	5	15.6	2	6.3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	6.3
55	33	19	57.6	9	27.3	0	0	0	0	5	15	6	18.2	6	18.2	6	18.2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	9	27
56	34	22	64.7	15	44.1	0	0	1	2.9	7	21	3	8.8	6	17.6	11	32.4	2	5.9	1	2.9	0	0	0	0	0	0	0	0	0	0	0	0	0	6	18
57	31	13	41.9	11	35.5	0	0	4	12.9	8	26	3	9.7	0	0	8	25.8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	19
58	33	15	45.5	10	30.3	0	0	6	18.2	7	21	6	18.2	4	12.1	12	36.4	1	3	1	3	1	3	0	0	0	0	0	0	0	0	0	0	0	0	14	42
59	30	8	26.7	9	30	0	0	3	10	1	3.3	5	16.7	2	6.7	10	33.3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	23
60	33	5	15.2	1	3	0	0	5	15.2	4	12	1	3	4	12.1	0	0	0	0	1	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	12

	# of subjects	Cough		Runny Nose		Difficulty Breathing		Abdominal Discomfort		Skin Irritation / Rash		Nausea / Vomiting		Diarrhea		Headache		Eye Irritation		Vomiting everything		Respiratory Distress		Salivation (drooling)		Severe Malaria - Unconsciousness / Drowsiness		Severe Malaria - Prostration / Very weak, unable to stand		Severe Malaria - Convulsions / Seizures		Severe Malaria - Severe Pallor		Severe Malaria - Dark Urine		Other	
		#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%
min	27	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
max	35	22	64.7	27	77.1	1	3.4	11	35.5	19	56	11	35.5	7	21.9	17	50	3	9.1	1	3.1	1	3.6	1	3	1	2.9	1	3.1	1	2.9	1	2.9	0	0	18	52
median	32	8	25.85	4	12.3	0	0	3	8.6	3	9.4	3	8.8	2	6.3	5	14.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	17
mean	32.17	9	27.77	6.9	21.2	0.1	0.3	3.22	10.1	4.3	13	3.2	10	2	7.61	5	15.4	0.55	1.73	0.1	0.26	0.1	0.17	0	0.1	0.02	0.05	0.05	0.15	0.02	0.05	0	0.05	0	0	6	19
sd	1.85	6	18.04	6.8	20.5	0.3	1	2.61	8.2	4.1	12	2.7	8.18	2	6.62	3.5	10.7	0.78	2.45	0.3	0.85	0.2	0.73	0.1	0.4	0.13	0.38	0.22	0.66	0.13	0.38	0.1	0.38	0	0	4.6	14

Table 7: number of SAEs per symptom per cluster (cluster number highlighted in red are SR clusters)

Cluster	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
4	31	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
21	31	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
27	35	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
29	33	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
38	34	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0
42	32	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
44	35	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0
51	31	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
58	33	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
60	33	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0

Table 8: number of SAEs per symptom per cluster for Core zones with SR

Cluster	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
42	18	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
58	20	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
60	19	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0

Table 9: number of SAEs per symptom per cluster for Buffer zones with SR

Cluster	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
21	13	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
29	13	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
44	14	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0
51	13	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

Table 10: number of SAEs per symptom per cluster for Core zones with Placebo

Cluster	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
4	19	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
38	20	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0

Table 11: number of SAEs per symptom per cluster for Buffer zones with Placebo

Cluster	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
27	14	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0

Table 12: frequency and percentage of subjects per cluster having at least one SAE episode by symptom (cluster number highlighted in red are SR clusters)

Cluster	# of subjects	Cough		Runny Nose		Difficulty Breathing		Abdominal Discomfort		Skin Irritation / Rash		Nausea / Vomiting		Diarrhea		Headache		Eye Irritation		Vomiting everything		Respiratory Distress		Salivation (drooling)		Severe Malaria - Unconsciousness / Drowsiness		Severe Malaria - Prostration / Very weak, unable to stand		Severe Malaria - Convulsions / Seizures		Severe Malaria - Severe Pallor		Severe Malaria - Dark Urine		Other	
		#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%
4	31	0	0	0	0	0	0	1	3.2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
21	31	0	0	0	0	0	0	0	0	0	0	1	3.2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
27	35	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2.9	0	0	0	0
29	33	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	3
38	34	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2.9	1	2.9	0	0	0	0	0	0
42	32	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	3.1	0	0	0	0	1	3.1
44	35	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2.9	0	0	1	2.9	0	0
51	31	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	3.2
58	33	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0
60	33	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Part II
Intervention

Table 1: number of AEs per symptom per cluster (cluster number highlighted in red are SR clusters)

Cluster	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
1	63	10	8	0	2	1	0	1	2	0	0	0	0	0	0	0	0	0	1
2	64	17	17	0	2	0	0	1	1	1	0	0	0	0	0	0	0	0	2
3	63	7	9	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	2
4	67	38	26	0	0	31	0	8	2	10	0	0	0	0	0	0	0	0	21
5	63	29	16	0	4	16	1	17	8	0	0	0	0	0	0	0	0	0	7
6	67	31	1	0	2	6	1	2	3	0	0	0	0	0	0	0	0	0	3
7	66	30	1	0	3	4	2	3	6	0	0	0	0	0	0	0	0	0	1
8	64	32	29	2	0	33	1	8	0	5	0	0	0	0	0	0	0	0	17
10	67	17	0	1	4	2	1	3	3	0	0	0	0	0	0	0	0	0	5
11	65	21	7	0	7	2	1	2	1	1	0	0	0	0	0	0	0	0	4
12	62	25	4	0	1	1	0	6	1	0	0	0	0	0	0	0	0	0	4
13	62	19	1	0	0	1	0	3	3	1	0	0	0	0	0	0	0	0	6
14	67	31	3	0	0	2	0	3	2	1	0	0	0	0	0	0	0	0	3
15	64	18	16	0	1	6	5	3	1	2	0	0	0	0	0	0	0	0	8
16	65	17	20	0	2	8	2	3	2	0	0	0	0	0	0	0	0	0	14
17	64	9	14	0	4	11	3	4	2	0	0	0	0	1	1	1	0	0	12
18	64	32	29	0	2	10	4	10	2	1	0	0	0	0	0	0	0	0	15
19	65	38	44	1	12	24	5	11	47	4	0	0	1	0	0	0	0	0	2
20	66	53	50	1	22	17	8	9	49	9	0	0	1	0	0	0	0	0	8
21	67	32	18	0	1	53	1	6	1	11	0	0	0	0	0	0	0	0	16
22	67	45	54	0	7	30	4	18	16	0	0	0	0	0	0	0	0	0	12
23	66	12	23	0	1	5	0	6	2	0	0	0	0	0	0	0	0	0	3
24	66	48	51	0	14	19	4	6	39	8	0	0	0	0	0	0	0	0	5
25	64	130	153	0	22	44	8	22	15	8	0	0	0	0	0	0	0	0	23
26	68	154	144	0	22	52	19	14	28	14	0	0	0	0	0	0	0	0	21
27	66	41	38	0	23	12	6	3	63	5	0	0	0	0	0	0	0	0	5
28	64	114	125	0	21	67	15	21	26	5	0	0	0	0	0	0	0	0	15
29	66	58	44	0	6	1	7	10	8	0	0	0	0	0	0	0	0	0	29
30	67	12	11	0	2	0	1	0	0	0	0	0	0	0	0	0	0	0	1
31	61	57	49	2	4	2	6	10	7	0	0	0	0	0	0	0	0	0	30
32	62	70	70	0	2	32	8	16	7	7	0	0	0	0	0	0	0	0	30
33	68	93	50	0	5	22	10	23	11	2	0	0	0	0	0	0	0	0	33
34	66	78	64	1	4	32	10	21	7	4	0	0	0	0	0	0	0	0	27
35	64	68	62	0	7	32	9	24	12	8	0	0	0	0	0	0	0	0	22
36	68	8	0	0	0	3	0	5	0	0	0	0	0	0	0	0	0	0	3
37	65	1	0	0	0	3	0	0	3	0	0	0	0	0	0	0	0	0	0
38	63	69	39	1	20	29	21	24	17	6	0	1	0	0	0	0	0	0	25
39	61	13	3	0	0	1	0	6	1	0	0	0	0	0	0	0	0	0	7
40	68	18	10	1	4	2	4	8	3	0	0	0	0	1	0	0	0	1	9
41	63	50	28	0	7	9	12	18	11	2	0	0	0	0	0	0	0	0	22
42	66	74	42	1	24	19	14	15	25	3	0	0	1	0	0	0	0	0	40
44	63	131	132	1	23	57	15	23	23	11	0	0	0	0	0	0	0	0	17

45	68	14	8	0	2	5	5	5	1	3	0	0	0	1	0	0	0	1	6
46	66	37	47	0	7	16	21	14	9	1	0	0	0	0	0	0	0	0	18
47	66	21	26	0	5	8	11	12	15	0	0	0	0	0	0	0	0	0	14
48	65	11	4	0	8	3	1	5	1	0	0	0	0	0	0	0	0	0	9
49	65	39	37	1	3	5	11	9	5	6	0	0	0	0	0	0	0	0	13
50	66	20	13	0	2	4	4	4	2	1	0	0	0	0	0	0	0	0	8
51	66	94	77	0	5	2	23	20	10	0	0	0	0	0	0	0	0	0	52
52	66	3	0	0	0	4	0	3	2	0	0	0	0	0	0	0	0	0	3
53	58	12	0	0	3	3	0	1	0	0	0	0	0	0	0	0	0	0	3
54	65	1	0	0	0	4	0	1	3	0	0	0	0	0	0	0	0	0	1
55	67	74	63	0	10	30	10	20	28	1	0	0	0	0	0	0	0	0	10
56	64	73	88	0	3	31	3	12	19	3	0	0	0	0	0	0	0	0	21
57	66	54	84	0	8	38	5	17	17	2	0	0	1	0	0	0	0	0	11
58	68	67	53	0	11	17	12	18	16	6	0	0	0	0	0	0	0	0	32
59	65	60	41	0	4	3	13	10	17	0	0	0	0	0	0	0	0	0	37
60	65	35	5	1	3	3	0	3	2	0	0	0	0	0	0	0	0	0	9
	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
min	58	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
max	68	154	153	2	24	67	23	24	63	14	1	1	1	1	1	1	0	1	52
median	65	32	26	0	4	7	4	8	4	1	0	0	0	0	0	0	0	0	9.5
mean	65.05	42.5	35.36	0.24	6.22	15.12	5.64	9.48	10.47	2.62	0.02	0.02	0.07	0.05	0.02	0.02	0	0.03	13.4
sd	2.06	34.5	37.13	0.51	7.16	16.67	6.19	7.41	13.47	3.57	0.13	0.13	0.26	0.22	0.13	0.13	0	0.18	11.59
total	3773	2465	2051	14	361	877	327	550	607	152	1	1	4	3	1	1	0	2	777

Table 2: number of AEs per symptom per cluster for Core zones with SR

Cluster	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
3	26	4	2	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
7	28	16	0	0	0	0	0	1	3	0	0	0	0	0	0	0	0	0	0
8	27	15	10	2	0	12	0	3	0	2	0	0	0	0	0	0	0	0	5
10	28	5	0	1	1	1	0	2	1	0	0	0	0	0	0	0	0	0	2
11	26	10	4	0	4	1	1	0	0	1	0	0	0	0	0	0	0	0	2
12	27	7	1	0	1	1	0	2	0	0	0	0	0	0	0	0	0	0	1
14	27	10	1	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	2
20	26	24	15	0	3	8	2	1	10	3	0	0	0	0	0	0	0	0	3
21	28	11	12	0	0	28	1	1	0	7	0	0	0	0	0	0	0	0	10
22	27	20	24	0	5	13	0	4	5	0	0	0	0	0	0	0	0	0	7
25	27	58	61	0	10	17	3	9	8	3	0	0	0	0	0	0	0	0	11
28	26	48	50	0	7	27	8	9	13	1	0	0	0	0	0	0	0	0	6
29	26	20	18	0	4	0	2	3	1	0	0	0	0	0	0	0	0	0	9
32	24	27	26	0	1	13	4	6	5	3	0	0	0	0	0	0	0	0	10
33	28	45	32	0	0	10	4	10	4	2	0	0	0	0	0	0	0	0	15
34	27	30	24	1	4	13	5	13	4	2	0	0	0	0	0	0	0	0	13
35	27	33	27	0	2	18	5	15	2	3	0	0	0	0	0	0	0	0	12
39	23	2	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	2
41	25	26	14	0	1	6	8	9	7	1	0	0	0	0	0	0	0	0	9
42	28	32	17	1	5	9	2	7	7	2	0	0	0	0	0	0	0	0	13
44	27	44	60	0	8	24	7	11	10	7	0	0	0	0	0	0	0	0	5
46	27	17	20	0	2	5	7	6	0	1	0	0	0	0	0	0	0	0	7
49	27	16	13	1	1	1	7	4	1	1	0	0	0	0	0	0	0	0	4
51	28	41	35	0	1	0	11	11	6	0	0	0	0	0	0	0	0	0	19
52	29	2	0	0	0	2	0	2	0	0	0	0	0	0	0	0	0	0	0
55	27	28	23	0	3	13	4	7	8	1	0	0	0	0	0	0	0	0	6
57	27	22	22	0	4	20	3	4	8	2	0	0	0	0	0	0	0	0	3
58	28	28	16	0	6	4	5	5	11	1	0	0	0	0	0	0	0	0	11
60	27	14	0	0	1	1	0	2	1	0	0	0	0	0	0	0	0	0	4
	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
min	23	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
max	29	58	61	2	10	28	11	15	13	7	1	0	0	0	0	0	0	0	19
median	27	20	16	0	1	6	2	4	3	1	0	0	0	0	0	0	0	0	6
mean	26.83	22.59	18.17	0.21	2.55	8.52	3.07	5.14	4	1.52	0.03	0	0	0	0	0	0	0	6.62
sd	1.26	14.64	17.1	0.49	2.72	8.76	3.15	4.21	4.02	1.84	0.19	0	0	0	0	0	0	0	4.96
total	778	655	527	6	74	247	89	149	116	44	1	0	0	0	0	0	0	0	192

Table 3: number of AEs per symptom per cluster for Buffer zones with SR

Cluster	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
3	37	3	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
7	38	14	1	0	3	4	2	2	3	0	0	0	0	0	0	0	0	0	1
8	37	17	19	0	0	21	1	5	0	3	0	0	0	0	0	0	0	0	12
10	39	12	0	0	3	1	1	1	2	0	0	0	0	0	0	0	0	0	3
11	39	11	3	0	3	1	0	2	1	0	0	0	0	0	0	0	0	0	2
12	35	18	3	0	0	0	0	4	1	0	0	0	0	0	0	0	0	0	3
14	40	21	2	0	0	2	0	3	1	0	0	0	0	0	0	0	0	0	1
20	40	29	35	1	19	9	6	8	39	6	0	0	1	0	0	0	0	0	5
21	39	21	6	0	1	25	0	5	1	4	0	0	0	0	0	0	0	0	6
22	40	25	30	0	2	17	4	14	11	0	0	0	0	0	0	0	0	0	5
25	37	72	92	0	12	27	5	13	7	5	0	0	0	0	0	0	0	0	12
28	38	66	75	0	14	40	7	12	13	4	0	0	0	0	0	0	0	0	9
29	40	38	26	0	2	1	5	7	7	0	0	0	0	0	0	0	0	0	20
32	38	43	44	0	1	19	4	10	2	4	0	0	0	0	0	0	0	0	20
33	40	48	18	0	5	12	6	13	7	0	0	0	0	0	0	0	0	0	18
34	39	48	40	0	0	19	5	8	3	2	0	0	0	0	0	0	0	0	14
35	37	35	35	0	5	14	4	9	10	5	0	0	0	0	0	0	0	0	10
39	38	11	3	0	0	1	0	4	1	0	0	0	0	0	0	0	0	0	5
41	38	24	14	0	6	3	4	9	4	1	0	0	0	0	0	0	0	0	13
42	38	42	25	0	19	10	12	8	18	1	0	0	1	0	0	0	0	0	27
44	36	87	72	1	15	33	8	12	13	4	0	0	0	0	0	0	0	0	12
46	39	20	27	0	5	11	14	8	9	0	0	0	0	0	0	0	0	0	11
49	38	23	24	0	2	4	4	5	4	5	0	0	0	0	0	0	0	0	9
51	38	53	42	0	4	2	12	9	4	0	0	0	0	0	0	0	0	0	33
52	37	1	0	0	0	2	0	1	2	0	0	0	0	0	0	0	0	0	3
55	40	46	40	0	7	17	6	13	20	0	0	0	0	0	0	0	0	0	4
57	39	32	62	0	4	18	2	13	9	0	0	0	1	0	0	0	0	0	8
58	40	39	37	0	5	13	7	13	5	5	0	0	0	0	0	0	0	0	21
60	38	21	5	1	2	2	0	1	1	0	0	0	0	0	0	0	0	0	5
Cluster	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
min	35	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
max	40	87	92	1	19	40	14	14	39	6	0	0	1	0	0	0	0	0	33
median	38	25	25	0	3	10	4	8	4	0	0	0	0	0	0	0	0	0	9
mean	38.34	31.72	27.14	0.1	4.79	11.31	4.1	7.31	6.83	1.69	0	0	0.1	0	0	0	0	0	10.1
sd	1.32	20.51	24.65	0.31	5.61	10.81	3.92	4.45	8.17	2.17	0	0	0.31	0	0	0	0	0	8.13
total	1112	920	787	3	139	328	119	212	198	49	0	0	3	0	0	0	0	0	293

Table 4: number of AEs per symptom per cluster for Core zones with Placebo

Cluster	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
1	26	3	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1
2	28	9	7	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0
4	28	21	15	0	0	14	0	5	2	3	0	0	0	0	0	0	0	0	11
5	27	10	5	0	1	11	0	4	1	0	0	0	0	0	0	0	0	0	1
6	28	14	1	0	1	2	0	1	0	0	0	0	0	0	0	0	0	0	0
13	25	9	1	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0	3
15	28	5	8	0	0	4	2	2	1	0	0	0	0	0	0	0	0	0	4
16	28	7	13	0	0	2	2	2	2	0	0	0	0	0	0	0	0	0	8
17	27	5	5	0	2	4	2	2	0	0	0	0	0	0	0	0	0	0	6
18	28	14	8	0	1	2	1	2	1	0	0	0	0	0	0	0	0	0	7
19	28	13	24	0	6	11	3	3	22	1	0	0	1	0	0	0	0	0	2
23	28	5	9	0	1	1	0	1	2	0	0	0	0	0	0	0	0	0	1
24	27	9	29	0	7	7	2	3	14	5	0	0	0	0	0	0	0	0	2
26	28	70	60	0	7	19	8	5	10	3	0	0	0	0	0	0	0	0	8
27	28	16	16	0	7	7	4	1	28	2	0	0	0	0	0	0	0	0	1
30	27	6	3	0	2	0	1	0	0	0	0	0	0	0	0	0	0	0	0
31	24	27	23	0	3	2	0	3	2	0	0	0	0	0	0	0	0	0	14
36	28	2	0	0	0	2	0	1	0	0	0	0	0	0	0	0	0	0	2
37	26	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
38	26	25	13	0	4	10	7	6	7	2	0	0	0	0	0	0	0	0	9
40	28	12	6	0	2	1	2	5	2	0	0	0	0	0	0	0	0	0	4
45	29	11	6	0	2	4	4	3	0	2	0	0	0	0	0	0	0	0	3
47	27	10	9	0	3	3	7	7	5	0	0	0	0	0	0	0	0	0	6
48	28	4	2	0	4	1	1	1	0	0	0	0	0	0	0	0	0	0	4
50	28	10	4	0	1	4	3	2	1	0	0	0	0	0	0	0	0	0	4
53	25	6	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
54	27	1	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	1
56	26	33	30	0	1	14	1	6	6	1	0	0	0	0	0	0	0	0	9
59	28	27	22	0	2	2	8	4	9	0	0	0	0	0	0	0	0	0	18
	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
min	24	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
max	29	70	60	0	7	19	8	7	28	5	0	0	1	0	0	0	0	0	18
median	28	10	7	0	1	2	1	2	1	0	0	0	0	0	0	0	0	0	3
mean	27.21	13.28	11.03	0	2	4.41	2	2.45	4.14	0.69	0	0	0.03	0	0	0	0	0	4.48
sd	1.18	13.7	12.97	0	2.27	5.1	2.56	2.05	6.79	1.26	0	0	0.19	0	0	0	0	0	4.51
total	789	385	320	0	58	128	58	71	120	20	0	0	1	0	0	0	0	0	130

Table 5: number of AEs per symptom per cluster for Buffer zones with Placebo

Cluster	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
1	37	7	7	0	2	0	0	1	2	0	0	0	0	0	0	0	0	0	0
2	36	8	10	0	2	0	0	1	0	0	0	0	0	0	0	0	0	0	2
4	39	17	11	0	0	17	0	3	0	7	0	0	0	0	0	0	0	0	10
5	36	19	11	0	3	5	1	13	7	0	0	0	0	0	0	0	0	0	6
6	39	17	0	0	1	4	1	1	3	0	0	0	0	0	0	0	0	0	3
13	37	10	0	0	0	1	0	2	1	1	0	0	0	0	0	0	0	0	3
15	36	13	8	0	1	2	3	1	0	2	0	0	0	0	0	0	0	0	4
16	37	10	7	0	2	6	0	1	0	0	0	0	0	0	0	0	0	0	6
17	37	4	9	0	2	7	1	2	2	0	0	0	0	1	1	1	0	0	6
18	36	18	21	0	1	8	3	8	1	1	0	0	0	0	0	0	0	0	8
19	37	25	20	1	6	13	2	8	25	3	0	0	0	0	0	0	0	0	0
23	38	7	14	0	0	4	0	5	0	0	0	0	0	0	0	0	0	0	2
24	39	39	22	0	7	12	2	3	25	3	0	0	0	0	0	0	0	0	3
26	40	84	84	0	15	33	11	9	18	11	0	0	0	0	0	0	0	0	13
27	38	25	22	0	16	5	2	2	35	3	0	0	0	0	0	0	0	0	4
30	40	6	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
31	37	30	26	2	1	0	6	7	5	0	0	0	0	0	0	0	0	0	16
36	40	6	0	0	0	1	0	4	0	0	0	0	0	0	0	0	0	0	1
37	39	0	0	0	0	3	0	0	2	0	0	0	0	0	0	0	0	0	0
38	37	44	26	1	16	19	14	18	10	4	0	1	0	0	0	0	0	0	16
40	40	6	4	1	2	1	2	3	1	0	0	0	0	1	0	0	0	1	5
45	39	3	2	0	0	1	1	2	1	1	0	0	0	1	0	0	0	1	3
47	39	11	17	0	2	5	4	5	10	0	0	0	0	0	0	0	0	0	8
48	37	7	2	0	4	2	0	4	1	0	0	0	0	0	0	0	0	0	5
50	38	10	9	0	1	0	1	2	1	1	0	0	0	0	0	0	0	0	4
53	33	6	0	0	2	3	0	1	0	0	0	0	0	0	0	0	0	0	2
54	38	0	0	0	0	4	0	0	2	0	0	0	0	0	0	0	0	0	0
56	38	40	58	0	2	17	2	6	13	2	0	0	0	0	0	0	0	0	12
59	37	33	19	0	2	1	5	6	8	0	0	0	0	0	0	0	0	0	19
	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
min	33	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
max	40	84	84	2	16	33	14	18	35	11	0	1	0	1	1	1	0	1	19
median	38	10	9	0	2	4	1	3	2	0	0	0	0	0	0	0	0	0	4
mean	37.72	17.41	14.38	0.17	3.1	6	2.1	4.07	5.97	1.34	0	0.03	0	0.1	0.03	0.03	0	0.07	5.59
sd	1.58	17.72	18.11	0.47	4.66	7.56	3.32	4.13	9.07	2.48	0	0.19	0	0.31	0.19	0.19	0	0.26	5.23
total	1094	505	417	5	90	174	61	118	173	39	0	1	0	3	1	1	0	2	162

Table 6: frequency and percentage of subjects per cluster having at least one AE episode by symptom (cluster number highlighted in red are SR clusters)

Cluster	# of subjects	Cough		Runny Nose		Difficulty Breathing		Abdominal Discomfort		Skin Irritation / Rash		Nausea / Vomiting		Diarrhea		Headache		Eye Irritation		Vomiting everything		Respiratory Distress		Salivation (drooling)		Severe Malaria - Unconsciousness / Drowsiness		Severe Malaria - Prostration / Very weak, unable to stand		Severe Malaria - Convulsions / Seizures		Severe Malaria - Severe Pallor		Severe Malaria - Dark Urine		Other	
		#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%
1	63	8	12.7	8	12.7	0	0	2	3.2	1	1.6	0	0	1	1.6	2	3.2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1.6
2	64	14	21.9	12	18.8	0	0	2	3.1	0	0	0	0	1	1.6	1	1.6	1	1.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	3.1
3	63	7	11.1	8	12.7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	3.2
4	67	24	35.8	22	32.8	0	0	0	0	24	36	0	0	7	10.4	2	3	9	13.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	22
5	63	25	39.7	11	17.5	0	0	4	6.3	13	21	1	1.6	15	23.8	7	11.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	9.5
6	67	24	35.8	1	1.5	0	0	2	3	5	7.5	1	1.5	2	3	3	4.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	4.5
7	66	24	36.4	1	1.5	0	0	3	4.5	4	6.1	2	3	3	4.5	6	9.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1.5
8	64	22	34.4	19	29.7	2	3.1	0	0	22	34	1	1.6	7	10.9	0	0	4	6.3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	17	27
10	67	14	20.9	0	0	1	1.5	4	6	2	3	1	1.5	3	4.5	3	4.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	7.5
11	65	18	27.7	7	10.8	0	0	6	9.2	2	3.1	1	1.5	2	3.1	1	1.5	1	1.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	6.2
12	62	21	33.9	4	6.5	0	0	1	1.6	1	1.6	0	0	6	9.7	1	1.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	6.5
13	62	15	24.2	1	1.6	0	0	0	0	1	1.6	0	0	3	4.8	3	4.8	1	1.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	9.7
14	67	23	34.3	2	3	0	0	0	0	2	3	0	0	3	4.5	2	3	1	1.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	4.5
15	64	13	20.3	12	18.8	0	0	1	1.6	6	9.4	5	7.8	3	4.7	1	1.6	2	3.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	7.8
16	65	15	23.1	14	21.5	0	0	2	3.1	6	9.2	2	3.1	3	4.6	2	3.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	11	17
17	64	8	12.5	12	18.8	0	0	3	4.7	7	11	3	4.7	4	6.3	2	3.1	0	0	0	0	0	0	0	0	0	0	1	1.6	1	1.6	1	1.6	0	0	11	17
18	64	22	34.4	18	28.1	0	0	2	3.1	5	7.8	4	6.3	7	10.9	2	3.1	1	1.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	12	19
19	65	22	33.8	33	50.8	1	1.5	9	13.8	17	26	5	7.7	10	15.4	28	43.1	4	6.2	0	0	0	0	1	1.5	0	0	0	0	0	0	0	0	0	0	2	3.1
20	66	35	53	29	43.9	1	1.5	15	22.7	14	21	8	12.1	8	12.1	27	40.9	8	12.1	0	0	0	0	1	1.5	0	0	0	0	0	0	0	0	0	0	8	12
21	67	19	28.4	13	19.4	0	0	1	1.5	31	46	1	1.5	3	4.5	1	1.5	10	14.9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	16	24
22	67	27	40.3	33	49.3	0	0	7	10.4	19	28	3	4.5	10	14.9	12	17.9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10	15
23	66	9	13.6	17	25.8	0	0	1	1.5	4	6.1	0	0	5	7.6	2	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	4.5
24	66	29	43.9	29	43.9	0	0	12	18.2	15	23	3	4.5	5	7.6	25	37.9	7	10.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	7.6
25	64	51	79.7	56	87.5	0	0	15	23.4	30	47	8	12.5	20	31.3	12	18.8	6	9.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	18	28
26	68	53	77.9	47	69.1	0	0	16	23.5	29	43	15	22.1	12	17.6	20	29.4	9	13.2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	19	28
27	66	29	43.9	27	40.9	0	0	17	25.8	10	15	6	9.1	3	4.5	32	48.5	5	7.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	7.6
28	64	44	68.8	51	79.7	0	0	15	23.4	37	58	11	17.2	17	26.6	20	31.3	5	7.8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	13	20
29	66	30	45.5	28	42.4	0	0	6	9.1	1	1.5	7	10.6	10	15.2	7	10.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	25	38
30	67	11	16.4	9	13.4	0	0	2	3	0	0	1	1.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1.5
31	61	29	47.5	29	47.5	1	1.6	4	6.6	2	3.3	5	8.2	7	11.5	6	9.8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	19	31
32	62	39	62.9	34	54.8	0	0	2	3.2	25	40	7	11.3	14	22.6	6	9.7	5	8.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	17	27
33	68	48	70.6	32	47.1	0	0	5	7.4	18	27	9	13.2	20	29.4	9	13.2	2	2.9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	23	34
34	66	42	63.6	34	51.5	1	1.5	4	6.1	21	32	10	15.2	16	24.2	6	9.1	4	6.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	21	32
35	64	35	54.7	37	57.8	0	0	6	9.4	22	34	8	12.5	14	21.9	8	12.5	8	12.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	19	30
36	68	6	8.8	0	0	0	0	0	0	3	4.4	0	0	5	7.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	4.4
37	65	1	1.5	0	0	0	0	0	0	3	4.6	0	0	0	0	3	4.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
38	63	38	60.3	27	42.9	1	1.6	16	25.4	20	32	18	28.6	16	25.4	12	19	5	7.9	0	0	1	1.6	0	0	0	0	0	0	0	0	0	0	0	0	19	30
39	61	13	21.3	3	4.9	0	0	0	0	1	1.6	0	0	6	9.8	1	1.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	9.8
40	68	14	20.6	9	13.2	1	1.5	4	5.9	2	2.9	4	5.9	7	10.3	3	4.4	0	0	0	0	0	0	0	0	1	1.5	0	0	0	0	0	0	1	1.5	7	10
41	63	32	50.8	22	34.9	0	0	6	9.5	8	13	9	14.3	15	23.8	8	12.7	2	3.2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	18	29
42	66	35	53	26	39.4	1	1.5	21	31.8	16	24	10	15.2	12	18.2	17	25.8	3	4.5	0	0	0	0	1	1.5	0	0	0	0	0	0	0	0	0	0	25	38
44	63	51	81	55	87.3	1	1.6	15	23.8	30	48	13	20.6	17	27	18	28.6	10	15.9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14	22
45	68	11	16.2	7	10.3	0	0	2	2.9	5	7.4	5	7.4	5	7.4	1	1.5	3	4.4	0	0	0	0	0	0	1	1.5	0	0	0	0	0	0	1	1.5	6	8.8

46	66	23	34.8	27	40.9	0	0	5	7.6	12	18	15	22.7	10	15.2	6	9.1	1	1.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	12	18
47	66	16	24.2	19	28.8	0	0	5	7.6	7	11	9	13.6	10	15.2	13	19.7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	13	20
48	65	9	13.8	4	6.2	0	0	6	9.2	3	4.6	1	1.5	5	7.7	1	1.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	12
49	65	26	40	26	40	1	1.5	3	4.6	4	6.2	10	15.4	9	13.8	5	7.7	6	9.2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	12	19
50	66	18	27.3	9	13.6	0	0	2	3	3	4.5	4	6.1	4	6.1	2	3	1	1.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	12
51	66	47	71.2	44	66.7	0	0	5	7.6	2	3	18	27.3	12	18.2	7	10.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	30	46
52	66	3	4.5	0	0	0	0	0	0	4	6.1	0	0	3	4.5	2	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	3
53	58	10	17.2	0	0	0	0	3	5.2	2	3.4	0	0	1	1.7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	3.4
54	65	1	1.5	0	0	0	0	0	0	3	4.6	0	0	1	1.5	3	4.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1.5
55	67	35	52.2	36	53.7	0	0	9	13.4	19	28	9	13.4	15	22.4	17	25.4	1	1.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	12
56	64	38	59.4	41	64.1	0	0	3	4.7	26	41	3	4.7	11	17.2	14	21.9	2	3.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	16	25
57	66	35	53	44	66.7	0	0	8	12.1	23	35	5	7.6	13	19.7	11	16.7	2	3	0	0	0	0	1	1.5	0	0	0	0	0	0	0	0	10	15
58	68	39	57.4	35	51.5	0	0	11	16.2	13	19	9	13.2	13	19.1	10	14.7	6	8.8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	25	37
59	65	37	56.9	29	44.6	0	0	4	6.2	3	4.6	11	16.9	10	15.4	11	16.9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	31	48
60	65	26	40	5	7.7	1	1.5	3	4.6	3	4.6	0	0	3	4.6	2	3.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	9	14

	# of subjects	Cough		Runny Nose		Difficulty Breathing		Abdominal Discomfort		Skin Irritation / Rash		Nausea / Vomiting		Diarrhea		Headache		Eye Irritation		Vomiting everything		Respiratory Distress		Salivation (drooling)		Severe Malaria - Unconsciousness / Drowsiness		Severe Malaria - Prostration / Very weak, unable to stand		Severe Malaria - Convulsions / Seizures		Severe Malaria - Severe Pallor		Severe Malaria - Dark Urine		Other	
		#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%
min	58	1	1.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
max	68	53	81	56	87.5	2	3.1	21	31.8	37	58	18	28.6	20	31.3	32	48.5	10	15.9	1	1.6	1	1.6	1	1.5	1	1.6	1	1.6	1	1.6	0	0	1	1.5	31	48
median	65	24	35.3	19	28.5	0	0	3.5	5.55	5.5	8.5	3.5	5.3	7	10.35	4	6.25	1	1.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8.5	13
mean	65.05	24	37.42	20	30.7	0.2	0.3	5.17	7.93	11	16	4.8	7.43	8	11.85	7.3	11.2	2.33	3.56	0	0.03	0	0.03	0.1	0.1	0.05	0.08	0.02	0.03	0.02	0.03	0	0	0	0.05	11	16
sd	2.06	14	20.71	16	24.4	0.5	0.7	5.3	8.1	10	16	5	7.62	6	8.49	7.9	12	3.04	4.64	0.1	0.21	0.1	0.21	0.3	0.4	0.22	0.34	0.13	0.21	0.13	0.21	0	0	0.2	0.28	8	12

Table 7: number of SAEs per symptom per cluster

Cluster	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
3	63	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
17	64	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	1
18	64	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
28	64	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
32	62	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
40	68	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
45	68	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
46	66	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	2
47	66	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
48	65	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
51	66	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2

Table 8: number of SAEs per symptom per cluster for Core zones with SR

Cluster	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
28	26	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
51	28	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1

Table 9: number of SAEs per symptom per cluster for Buffer zones with SR

Cluster	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
3	37	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
32	38	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
46	39	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	2
51	38	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1

Table 10: number of SAEs per symptom per cluster for Core zones with Placebo

Cluster	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
47	27	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

Table 11: number of SAEs per symptom per cluster for Buffer zones with Placebo

Cluster	# of subjects	Cough	Runny Nose	Difficulty Breathing	Abdominal Discomfort	Skin Irritation / Rash	Nausea / Vomiting	Diarrhea	Headache	Eye Irritation	Vomiting everything	Respiratory Distress	Salivation (drooling)	Severe Malaria - Unconsciousness / Drowsiness	Severe Malaria - Prostration / Very weak, unable to stand	Severe Malaria - Convulsions / Seizures	Severe Malaria - Severe Pallor	Severe Malaria - Dark Urine	Other
17	37	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	1
18	36	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
40	40	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
45	39	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
48	37	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0

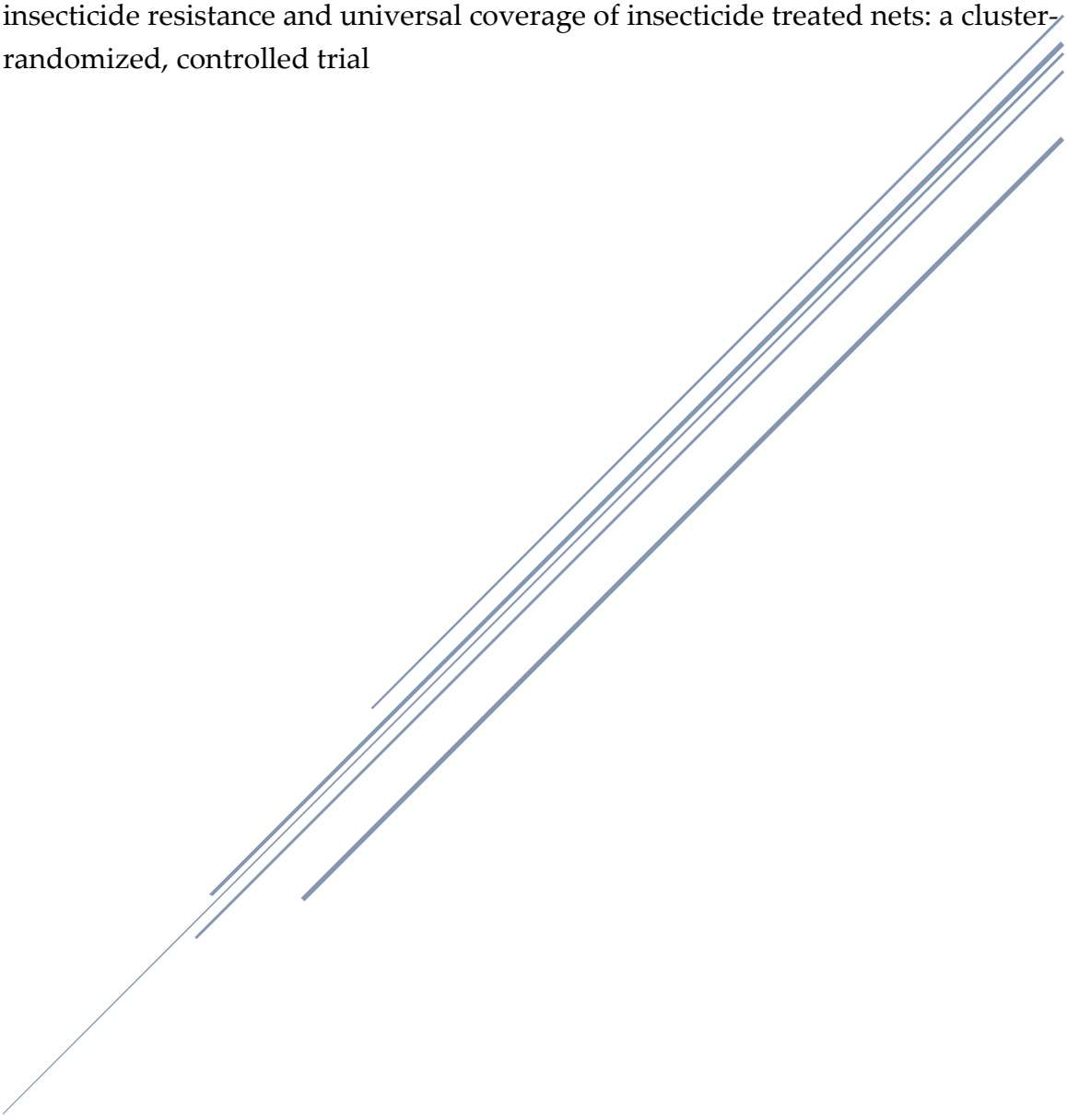
Table 12: frequency and percentage of subjects per cluster having at least one SAE episode by symptom (cluster number highlighted in red are SR clusters)

Cluster	# of subjects	Cough		Runny Nose		Difficulty Breathing		Abdominal Discomfort		Skin Irritation / Rash		Nausea / Vomiting		Diarrhea		Headache		Eye Irritation		Vomiting everything		Respiratory Distress		Salivation (drooling)		Severe Malaria - Unconsciousness / Drowsiness		Severe Malaria - Prostration / Very weak, unable to stand		Severe Malaria - Convulsions / Seizures		Severe Malaria - Severe Pallor		Severe Malaria - Dark Urine		Other	
		#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%
3	63	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1.6
17	64	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1.6	1	1.6	1	1.6	0	0	0	0	1	1.6
18	64	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1.6
28	64	0	0	0	0	0	0	0	0	0	0	1	1.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
32	62	0	0	0	0	0	0	0	0	0	0	1	1.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
40	68	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1.5	0	0	0	0	0	0	1	1.5	0	0
45	68	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1.5	0	0	0	0	0	0	1	1.5	0	0
46	66	0	0	0	0	0	0	0	0	0	0	1	1.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1.5
47	66	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1.5
48	65	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
51	66	0	0	0	0	0	0	0	0	0	0	2	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	3

S7. Rationale for One-Sided Primary Hypothesis

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Ochomo EO, Gimnig JE, et al. Effect of a spatial repellent on malaria incidence in an area of western Kenya characterized by high malaria transmission, insecticide resistance and universal coverage of insecticide treated nets: a cluster-randomized, controlled trial



The primary hypothesis as specified in the protocol and statistical analysis plan (SAP) is one-sided; that is, H_0: SR does not reduce first-time malaria infection hazard rate compared to placebo, vs H_1: SR reduces first-time malaria infection hazard rate compared to placebo). The study protocol was published (Ochomo, et. al, Trials 23 (1), 260) and the SAP was reviewed and approved by the VCAG panel at WHO. The 20th VCAG meeting report (https://www.who.int/publications/i/item/9789240096677) that covers the study results was based on the 1-sided hypothesis, as pre-specified in the protocol and SAP[#]. Below, we provide the rationale for using the 1-sided hypothesis in the protocol and SAP at the study design phase.

While there is a non-zero possibility that SR may increase malaria infection, it is part of the null hypothesis and is of no interest to us. To be consistent with the one-sided hypothesis, the p-value for testing the hypothesis is also one-sided. We tested this superiority hypothesis using a one-sided p-value in a similar manner as in:

- https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)00056-2/fulltext
- https://jamanetwork.com/journals/jama/fullarticle/2432163

In addition, superiority and non-inferiority trials are more widely used nowadays than before. The link below provides some discussions on using one-sided hypothesis testing.

- 2004, BMJ: https://ebm.bmj.com/content/9/2/38
- 2008, Clinical Trial https://doi.org/10.1177/1740774508098590
- 2016, Eur J Epidemiol https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4877414/

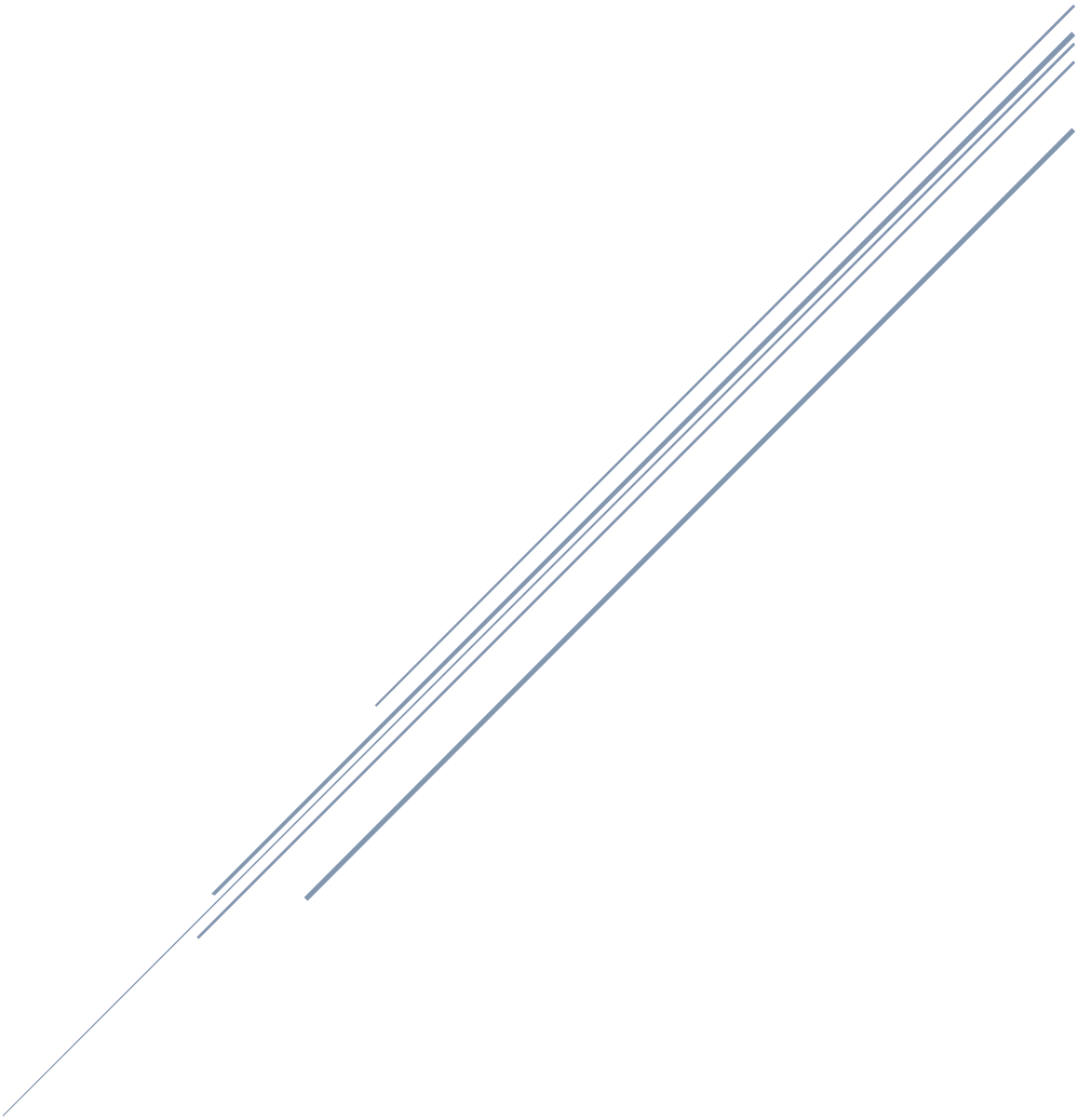
Regarding our justification for the 1-sided test, here we draw from the practices and standards used in clinical drug trials, for which the vector control community is forging to meet similar standards of rigor, specifically the following paper: Fisher LD (J Biopharm Stat. 1991) in "*The use of one-sided tests in drug trials: an FDA advisory committee member's perspective*" states that "T*he use of one-sided or two-sided tests in drug trials to evaluate new compounds is considered. For drugs that may be tested against placebos, with* ***two positive trials required*** *(as in the United States), it is argued that from both a regulatory and pharmaceutical industry perspective,* ***one-sided tests at the 0.05 significance level are appropriate****. In situations where only one trial against placebo may be done (for example, survival trials), one-sided tests at the 0.025 level are appropriate in many cases. For active control trials, it is argued that two-sided tests are usually appropriate*."

Finally, regarding whether 2-sided p-values vs 1-sided p-values, there is no formal guidance in the "*Consort 2010 statement: extension to cluster randomized trials"* or the FDA or EU guidance on clinical trials. Ludbrook J (2013; Clin Exp Pharmacol Physiol) states in *"Should we use one-sided or two-sided p values in tests of significance?"* that "*Distinguished statisticians, the authors of statistical texts, the authors of guidelines for human and animal experimentation and the editors of biomedical journals give confusing advice, or none at all, about the choice between one- and two-sided P values*."

S8. Protocol Deviations

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Ochomo EO, Gimnig JE, et al. Effect of a spatial repellent on malaria incidence in an area of western Kenya characterized by high malaria transmission, insecticide resistance and universal coverage of insecticide treated nets: a cluster-randomized, controlled trial



No.	Summary of protocol deviation	Measures taken to address deviation	Impact on the study outcomes
C1-1	Nineteen compounds that previously had participants participating in baseline were re-randomized to participate in C1. Eight participants from these compounds who met the age limit required for enrollment were consented to participate in C1. This deviated from protocol (ver 8, 01 Sep 2021).	All compounds that participated in baseline were subsequently removed from randomized list of C1 compounds. Baseline participants who had been consented were screened, and if eligible, enrolled. Protocol amendment was submitted to ethical review boards to allow compounds used in baseline to participate in C1 or C2.	This had no impact on study outcomes
C1-2	Delay in sharing AE/SAE dataset with DSMB for safety assessment. Dataset should have ranged Oct 18, 2021 to Jan 17, 2020. Dataset was not shared until Apr 2022.	A tracker and notification system for safety assessment was developed. The deviation was reported to the study ethical review boards and sponsor.	Given that no concerns were noted throughout the study, this did not impact the overall outcome.
C2-1	Study was supposed to randomize and consent participants in 14 compounds in core and 20 participants in buffer of every clusterb. In 4 of 58 clusters, 5 participants were over-consented. Clusters 45, 53, 52 over-consented by one participant each in core. Cluster 38 over-consented by 2 participants in buffer.	All the consented participants were screened and those who were eligible were enrolled in the study. The deviation was reported to the study regulating ethical review boards and the sponsor.	The study over enrolled beyond the required sample size. No impact on trial outcomes.
C2-2	Participant on malaria prophylaxis (cotrimoxazole) was enrolled on 27 Oct 2022 which was noticed two weeks later in an unscheduled sick visit. Study requires exclusion participants on malaria prophylaxis	Participant was discontinued from study participation. The deviation was reported to the study regulating ethical review boards and the sponsor.	The sample size was reduced but did not affect the study outcomes as we had built in a 35% lost to follow up rate.
C2-3	Two participants who participated in C1 were randomized and consented to participate in C2 contrary to protocol (ver9, 18th Apr 2022). Two participants moved from compound where they participated during C1 to different compound in C2.	Participants were excluded from participating in C2 since we already had their 12 months data collected in C1. Deviation was reported to the study regulating ethical review boards and the sponsor.	The sample size was reduced but did not affect the study outcomes as we had built in a 35% lost to follow up rate.
C2-4	A study participant tested positive for sickle cell disease which requires proguanil, a malaria prophylaxis. The study requires exclusin of participants on malaria prophylaxis	Participant was enrolled into sickle cell care including malaria prophylaxis. Participant was excluded from subsequent study participation. Deviation was reported to study regulating ethical review boards and sponsor.	The sample size was reduced but did not affect the study outcomes as we had built in a 35% lost to follow up rate.