SPATIAL REPELLENTS
FOR CONTROL OF VECTOR-BORNE DISEASE

Sumba Spatial Repellent Clinical Trial Results

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Goals and Objectives

GOAL: Evaluate the public health impact of one spatial repellent (SR) product to reduce and prevent transmission of *Plasmodium* spp.

OBJECTIVES:

1. **Provide a quantitative estimate of protective efficacy (PE)**
2. **Provide inputs into program-relevant questions of optimization and application:**
   - the intervention coverage needed to reduce transmission,
   - the range of transmission contexts in which spatial repellents function
     - Low, moderate and high baseline transmission intensity
     - Susceptible and resistant mosquito populations
     - Varying vector biting behaviors (indoor/outdoor/mixed)
   - community effect (benefit) and/or diversion (increased)

3. **Confirm and measure the entomological correlates of reduced infection**
4. **Drive efforts to acquire full recommendation of SR products for inclusion in disease control programs** by generating rigorous evidence to be considered and used by public health stakeholders.

Impact of a spatial repellent product on Anopheles and non-Anopheles mosquitoes in Sumba, Indonesia

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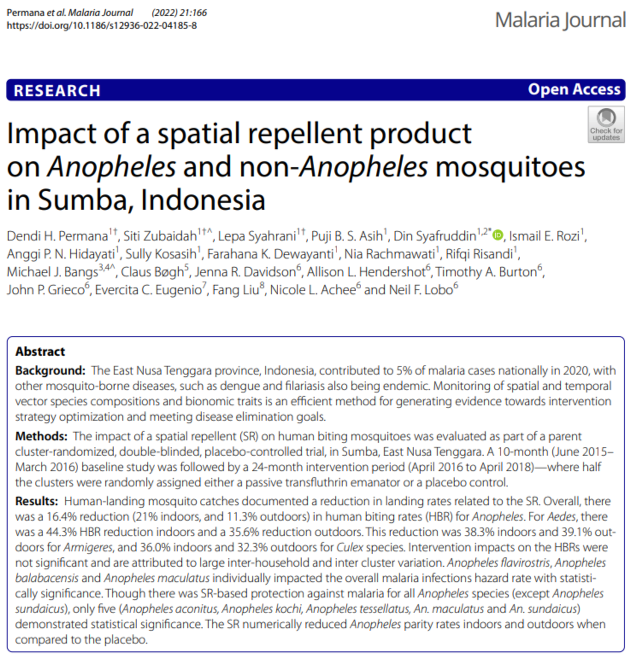

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Impact of a spatial repellent product on *Anopheles* and non-*Anopheles* mosquitoes in Sumba, Indonesia

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Abstract

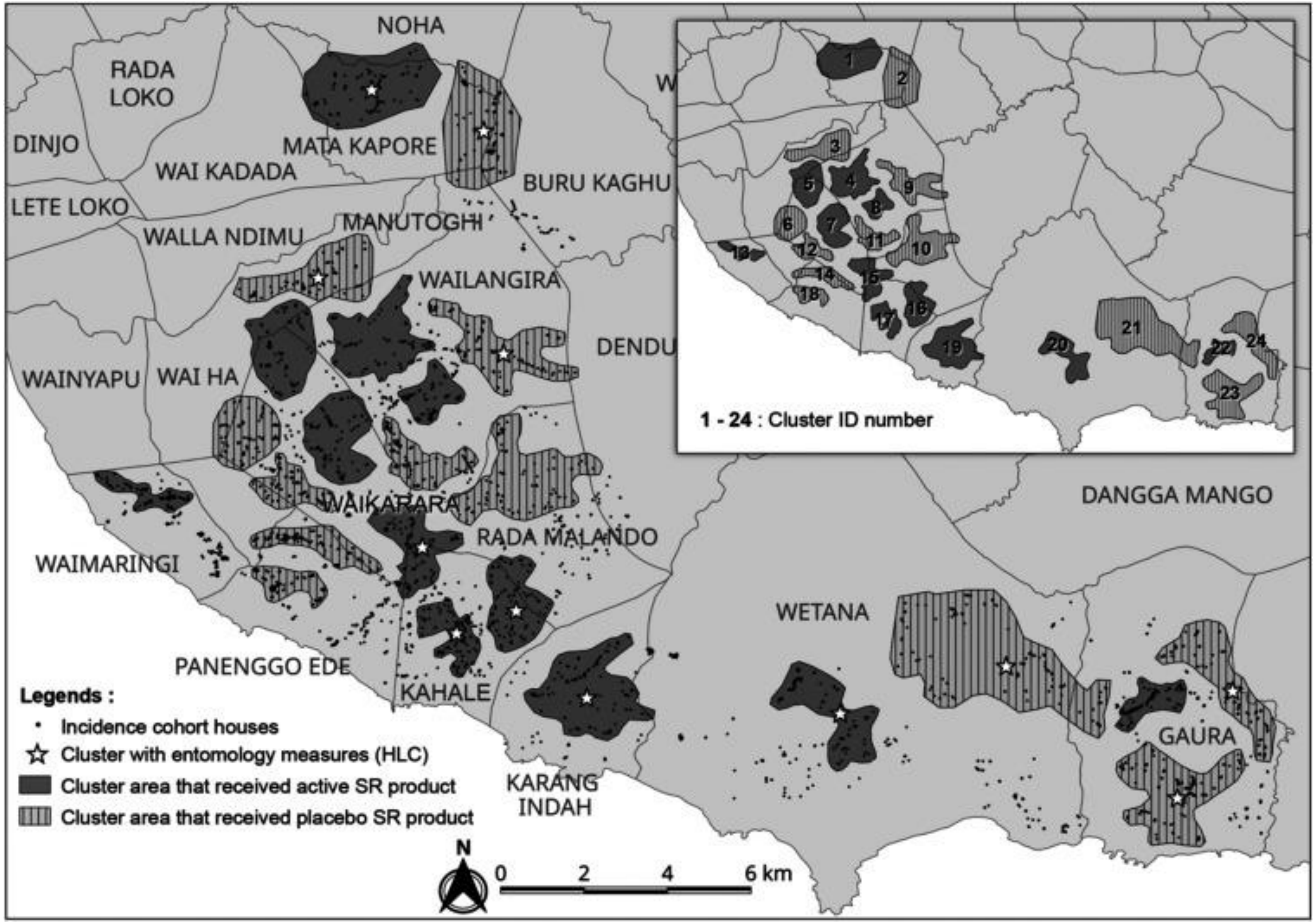
Background: The East Nusa Tenggara province, Indonesia, contributed to 5% of malaria cases nationally in 2020, with other mosquito-borne diseases, such as dengue and filariasis also being endemic. Monitoring of spatial and temporal vector species compositions and bionomic traits is an efficient method for generating evidence towards intervention strategy optimization and meeting disease elimination goals.

Methods: The impact of a spatial repellent (SR) on human biting mosquitoes was evaluated as part of a parent cluster-randomized, double-blinded, placebo-controlled trial, in Sumba, East Nusa Tenggara. A 10-month (June 2015–March 2016) baseline study was followed by a 24-month intervention period (April 2016 to April 2018)—where half the clusters were randomly assigned either a passive transfluthrin emanator or a placebo control.

Results: Human-landing mosquito catches documented a reduction in landing rates related to the SR. Overall, there was a 16.4% reduction (21% indoors, and 11.3% outdoors) in human biting rates (HBR) for *Anopheles*. For *Aedes*, there was a 44.3% HBR reduction indoors and a 35.6% reduction outdoors. This reduction was 38.3% indoors and 39.1% outdoors for *Armigeres*, and 36.0% indoors and 32.3% outdoors for *Culex* species. Intervention impacts on the HBRs were not significant and are attributed to large inter-household and inter cluster variation. *Anopheles flavirostris*, *Anopheles balabacensis* and *Anopheles maculatus* individually impacted the overall malaria infections hazard rate with statistically significance. Though there was SR-based protection against malaria for all *Anopheles* species (except *Anopheles sundaicus*), only five (*Anopheles aconitus, Anopheles kochi, Anopheles tessellatus, An. maculatus* and *An. sundaicus*) demonstrated statistical significance. The SR numerically reduced *Anopheles* parity rates indoors and outdoors when compared to the placebo.

TRIAL DESIGN

Location of 24 study clusters in West and Southwest districts, Sumba. Clusters were selected for enrolling the incidence cohort, each consisting of ca. 100 households with an average distance of 500 m between clusters. A total of 48 sentinel houses from 12 clusters were selected for routine entomological human-landing catch



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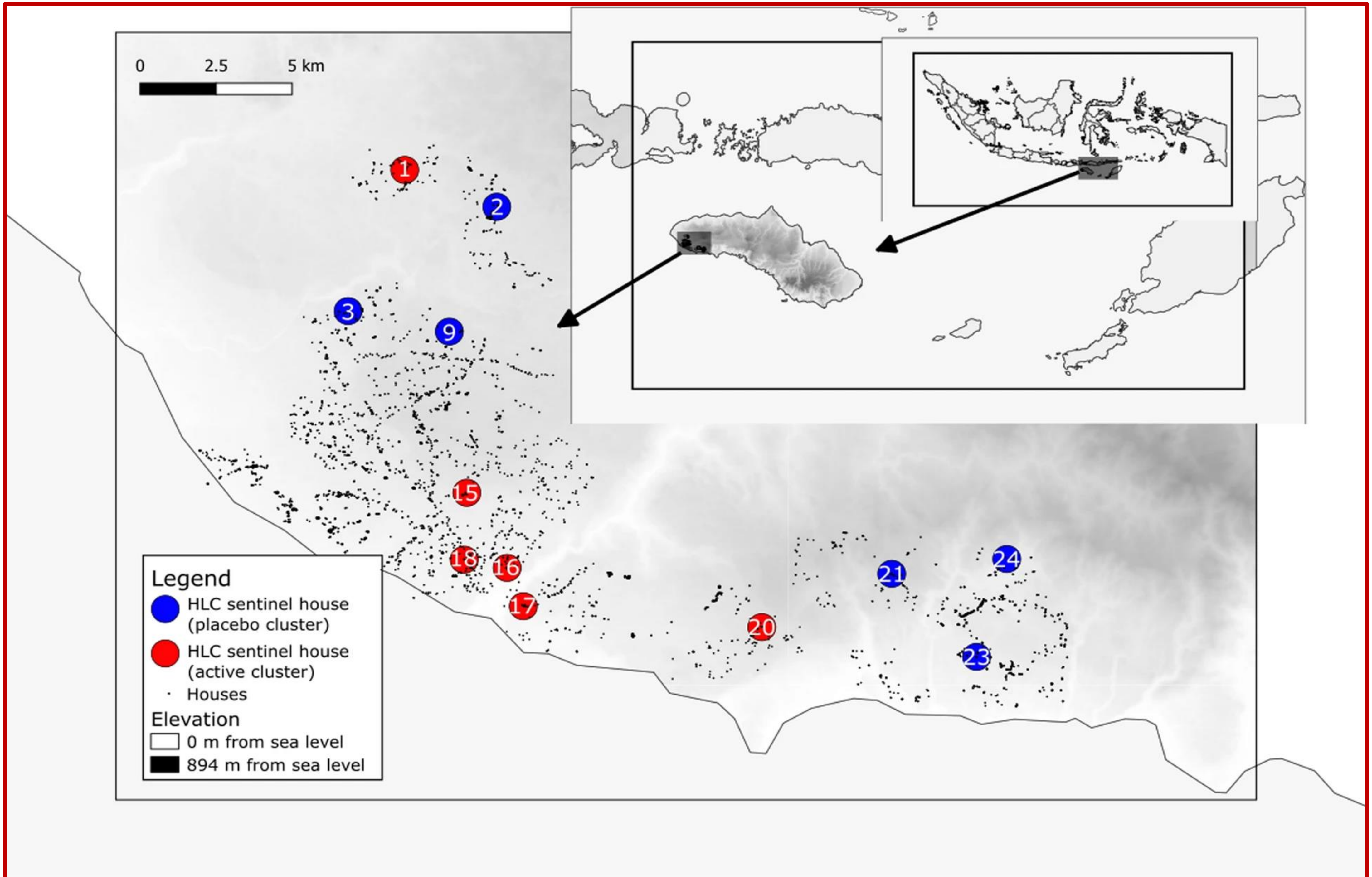
0
2.5
5 km
1
2
3
9
15
18
16
17
20
21
24
23
Legend
HLC sentinel house (placebo cluster)
HLC sentinel house (active cluster)
Houses
Elevation
0 m from sea level
894 m from sea level

Traditional Sumba house structure

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Traditional Sumba house structure (A) raised ∼1 m aboveground and averaging ∼70 m3 in size with thatch roof, bamboo floors, and walls (B), which offer minimal protection from mosquito entry.

RESULTS

Table 1 The effect of the SR on the human biting rate (HBR) by Anopheles species presented only for species with non-sparse data

Anopheles Species	Location	SR median (min, max)	Placebo median (min, max)	% Change (95% CI)	Raw-p value	BH* adjusted p-value
aconitus	Indoor	0 (0.43)	0 (0.6)	282.1 (59.2, 816.7)	0.003	0.060
	Outdoor	0 (0.60)	0 (0.4)	140.0 (− 4.3, 502.0)	0.062	0.413
annularis	Indoor	0 (0.8)	0 (0.13)	4.8 (− 64.1, 203.2)	0.939	0.988
	Outdoor	0 (0.12)	0 (0.16)	52.8 (− 47.7, 346.3)	0.438	0.674
barbirostris	Indoor	0 (0.3)	0(0.10)	− 16.9 (− 75.0, 175.9)	0.762	0.953
	Outdoor	0 (0.3)	0 (0.7)	− 31.8 (− 78.7, 118.3)	0.519	0.741
flavirostris	Indoor	0 (0.20)	0 (0.10)	36.7 (− 31.3, 171.8)	0.373	0.622
	Outdoor	0 (0.28)	0 (0.10)	46.4 (− 26.0, 189.4)	0.273	0.840
kochi	Indoor	0 (0.6)	0 (0.26)	− 14.0 (− 76.4, 213.5)	0.820	0.496
	Outdoor	0 (0.4)	0 (0.40)	− 26.5 (− 79.0, 156.8)	0.630	0.965
leucophyrus	Indoor	0 (0.1)	0 (0.1)	− 93.2 (− 99.90, 352.2)	0.210	0.420
	Outdoor	0 (0.1)	0 (0.3)	− 97.9 (− 100.0, 89.1)	0.093	0.310
maculatus	Indoor	0 (0.12)	0 (0.4)	112.7 (17.1, 286.4)	0.013	0.130
	Outdoor	0 (0.14)	0 (0.3)	68.7 (− 5.7, 201.8)	0.078	0.312
sundaicus	Indoor	0 (0.15)	0 (0.8)	− 83.8 (− 97.8, 16.9)	0.071	0.355
	Outdoor	0 (0.18)	0 (0.5)	− 77.7 (− 97.0, 64.8)	0.141	0.353
tessellatus	Indoor	0 (0.9)	0 (0.47)	3.9 (− 89.7, 949.2)	0.974	0.974
	Outdoor	0 (0.6)	0 (0.42)	9.7 (− 89.3, 1021.3)	0.937	1.000
vagus	Indoor	0 (0.16)	0 (0.47)	100.5 (− 26.2, 444.8)	0.173	0.384
	Outdoor	0 (0.10)	0 (0.37)	113.9 (− 21.3, 481.4)	0.136	0.389

*Benjamini–Hochberg multiplicity adjustment procedure

Human-landing mosquito catches documented a reduction in landing rates related to the SR.

A 16.4% reduction (21% indoors, and 11.3% outdoors) in human biting rates (HBR) for Anopheles.

Table 2 The effect of per-species HBR on PE against overall malaria infections

Anopheles species	Collection location	PE difference* (%)	95% CI	Raw 2-sided p-value	BH# adjusted p-value
aconitus	Indoor	− 4.19	− 9.10, 0.73	0.095	0.136
	Outdoor	− 5.90	− 10.85, − 0.97	0.019	0.057
	Indoor + outdoor	− 6.75	− 11.52, − 1.95	0.006	0.026
annularis	Indoor	− 6.00	− 11.46, 0.48	0.033	0.090
	Outdoor	− 0.92	− 6.50, 4.65	0.744	0.797
	Indoor + outdoor	− 4.43	− 9.37, 0.52	0.079	0.125
barbirostris	Indoor	− 5.7	− 11.63, 0.26	0.061	0.102
	Outdoor	− 6.15	− 12.55, 0.22	0.058	0.102
	Indoor + outdoor	− 15.18	− 29.50, − 0.88	0.038	0.088
flavirostris	Indoor	− 1.95	− 6.80, 2.94	0.438	0.505
	Outdoor	− 2.78	− 7.73, 2.24	0.278	0.348
	Indoor + outdoor	− 3.43	− 8.57, 1.70	0.188	0.245
kochi	Indoor	− 8.88	− 15.24, − 2.50	0.006	0.023
	Outdoor	− 9.04	− 16.1, − 1.95	0.012	0.036
	Indoor + outdoor	− 6.20	− 12.15, − 0.26	0.04	0.086
leucosphyrus	Indoor	− 14.57	− 31.16, 2.08	0.086	0.129
	Outdoor	− 6.15	− 24.87, 12.52	0.519	0.577
	Indoor + outdoor	− 9.91	− 22.55, 2.69	0.124	0.169
maculatus	Indoor	− 7.78	− 12.96, − 2.55	0.004	0.02
	Outdoor	− 10.51	− 15.37, − 5.60	< 0.0001	< 0.003
	Indoor + outdoor	− 9.17	− 14.03, − 4.77	< 0.0001	< 0.003
sundaicus	Indoor	6.89	0.13, 13.61	0.046	0.086
	Outdoor	7.19	0.43, 13.96	0.037	0.093
	Indoor + outdoor	5.84	0.17, 11.53	0.044	0.088
tessellatus	Indoor	− 8.2	− 13.49, − 2.92	0.002	0.02
	Outdoor	− 4.19	− 6.91, − 1.55	0.002	0.015
	Indoor + outdoor	− 7.88	− 12.73, − 3.01	0.002	0.012
vagus	Indoor	0.39	− 4.48, 5.27	0.876	0.906
	Outdoor	− 2.14	− 7.42, 3.10	0.421	0.505
	Indoor + outdoor	0.17	− 4.62, 4.96	0.944	0.944

*Benjamini–Hochberg multiplicity adjustment procedure

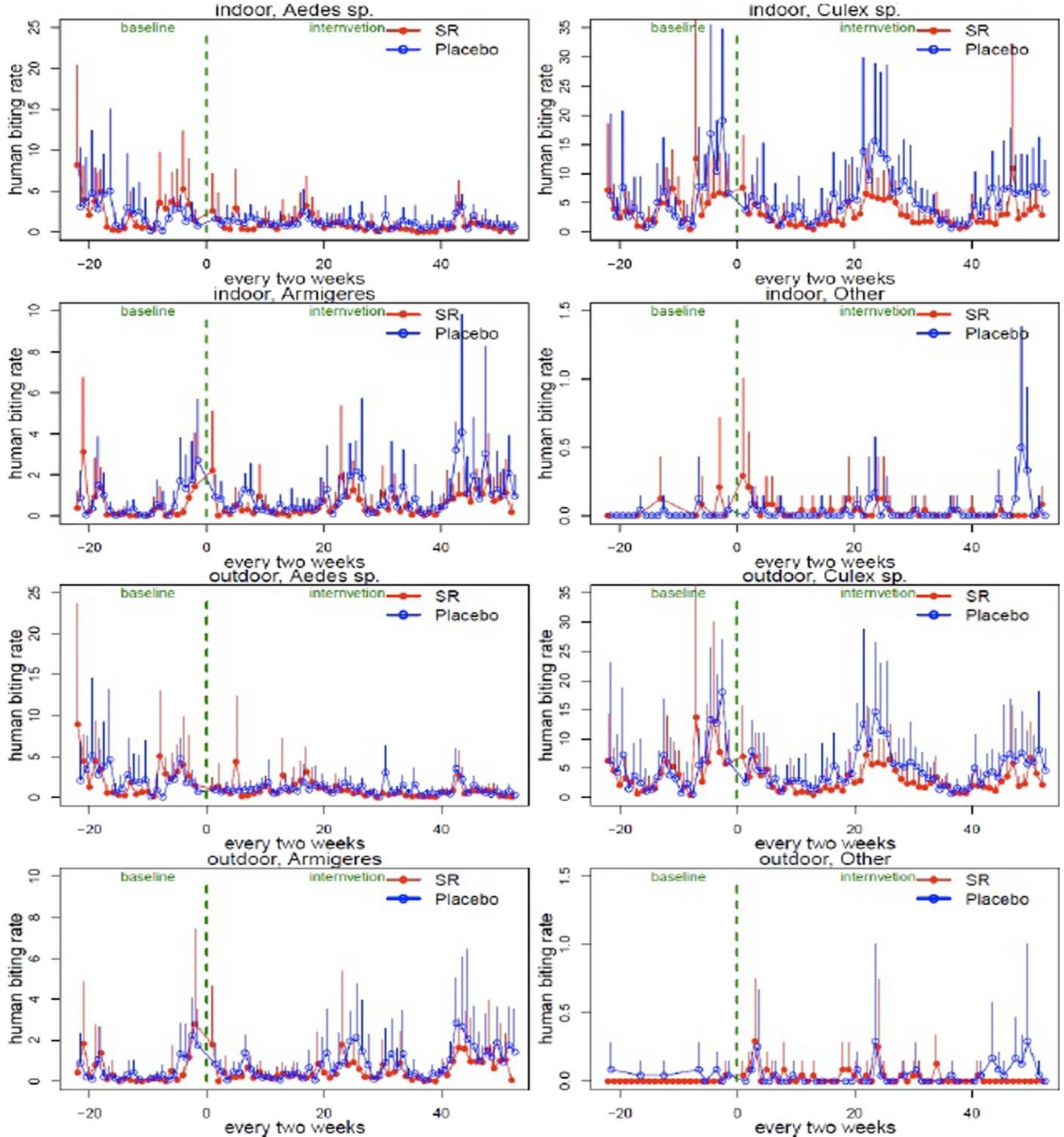
The PE differences are only approximate (based on first-order Taylor Expansion)

The interpretation is as follow: If a HBR increases by $e^1 - 1 = 1.72$-folds, then the PE of SR again overall malaria infection changes by PE difference %

Anopheles flavirostris, An. balabacensis and *An.* maculatus individually impacted the overall malaria infections hazard rate with statistically significance.

Though there was SR-based protection against malaria for all Anopheles species (except An. sundaicus), only five (An. aconitus, An. kochi, An.tessellatus, An. maculatus and An. sundaicus) demonstrated statistical significance.

The SR numerically reduced Anopheles parity rates indoors and outdoors when compared to the placebo.



For Aedes, there was a 44.3% HBR reduction indoors and a 35.6% reduction outdoors.

This reduction was 38.3% indoors and 39.1% outdoors for Armigeres, and 36.0% indoors and 32.3% outdoors for Culex species.

Table 3 Effect of the SR on parity, nulliparity and unknown parity status during the intervention period

	Location	SR	Placebo	% Change (95% CI)
Parity rate	Indoor	0.41 ± 0.44	0.41 ± 0.45	− 10.2 (− 62.1, 113.2)
	Outdoor	0.40 ± 0.44	0.43 ± 0.45	− 25.9 (− 68.8, 75.6)
Nulliparity rate	Indoor	0.16 ± 0.29	0.12 ± 0.26	58.3 (− 37.0, 298.0)
	Outdoor	0.17 ± 0.30	0.11 ± 0.25	54.9 (− 37.6, 284.3)

Table 5 Species specific parity rates during the SR intervention implementation

Species	Total number/ Parity(%)	
	Placebo	Intervention
Anopheles aconitus	216/71.41	2071/78.24
Anopheles annularis	562/54.46	112/60.32
Anopheles barbirostris	513/68.54	89/82.85
Anopheles flavirostris	681/78.25	1007/87.22
Anopheles indefinitus	14/50	4/85.71
Anopheles kochi	647/85.59	118/91.04
Anopheles maculatus	133/66.79	280/67.67
Anopheles subpictus s.l	81/85.71	7/82.72
Anopheles sundaicus	95/73.68	171/74.74
Anopheles tessellatus	785/83.86	223/86.62
Anopheles vagus	921/50.9	444/76.76

Table 4 The relationship between parity rates and malaria infection

	Collection location	Hazard ratio	95% CI
First-time infection			
Parity rate	Indoor	1.006	(0.999, 1.013)
	Outdoor	1.004	(0.997, 1.010)
	Indoor + outdoor	1.006	(0.999, 1.013)
Nulliparity rate	Indoor	0.989	(0.976, 1.001)
	Outdoor	0.995	(0.984, 1.007)
	Indoor + outdoor	0.985	(0.973, 0.998)
Overall infection			
Parity rate	Indoor	1.003	(0.999, 1.007)
	Outdoor	1.001	(0.998, 1.005)
	Indoor + outdoor	1.005	(1.001, 1.009)
Nulliparity rate	Indoor	0.994	(0.988, 1.001)
	Outdoor	0.995	(0.989, 1.001)
	Indoor + outdoor	0.990	(0.984, 0.996)

Interpretation on hazard ratio: the hazard of malaria infection changes by (1-HR) × 100% with 1% unit changes in the rate

Table 6 Frequency of sporozoite positivity status

Treatment allocation	Pf	Pv	Unclear	Uninfected	Sporozoite positivity Rate = (Pf + Pv)/(Pf + Pv + unclear + uninfected)
Baseline					
SR	12	9	0	4706	0.44%
Placebo	12	9	0	6244	0.34%
Post-intervention					
SR	3	8	0	8130	0.14%
Placebo	6	1	1	9615	0.07%

Table 7 The effect of the SR on the HBR (bpn) of non-*Anopheles* mosquitoes

Species	Location	(Mean ± SD)		% Reduction (SR vs. placebo) (95% CI)	p-Value
		SR	Placebo		
All	Indoor	4.33 ± 7.45	7.27 ± 9.26	43.1 (− 2.2, 68.3)	0.0589
	Outdoor	4.29 ± 6.25	6.59 ± 8.35	38.7 (− 10.1, 65.8)	0.1015
Aedes sp.	Indoor	0.86 ± 2.17	1.09 ± 1.91	44.3 (1.5, 67.0)	0.0443
	Outdoor	0.86 ± 2.21	0.99 ± 1.87	35.6 (− 14.6, 63.8)	0.1348
Armigeres sp.	Indoor	0.55 ± 1.48	0.90 ± 2.41	38.3 (− 37.2, 72.2)	0.2365
	Outdoor	0.13 ± 1.39	0.85 ± 2.26	39.1 (− 34.0, 72.3)	0.2178
Culex sp.	Indoor	2.88 ± 6.30	1.23 ± 8.34	36.0 (− 58.2, 74.1)	0.3336
	Outdoor	2.87 ± 5.09	4.72 ± 7.46	32.3 (− 67.4, 72.6)	0.3986
Others	Indoor	0.034 ± 0.269	0.038 ± 0.302	NA*	NA*
	Outdoor	0.030 ± 0.196	0.037 ± 0.309	NA*	NA*

*Model-based analysis was not performed (a large amount 0's); no statistically significant % change is expected

Intervention impacts on the HBRs were not significant and are attributed to large inter-household and inter cluster variation.

Conclusion

1. Evidence demonstrating that Anopheles vectors bite both indoors and outdoors indicates that currently implemented indoor-based vector control tools may not be sufficient to eliminate malaria.
2. The documented impact of the SR intervention on Aedes, Armigeres and Culex species points to its importance in combatting other vector borne diseases.
3. Studies to determine the impact of spatial repellents on other mosquito-borne diseases is recommended.

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