

1 Targeted malaria elimination interventions reduce *Plasmodium falciparum* 2 infections up to 3 kilometers away

3
4 Jade Benjamin-Chung*^{1,2}, Haodong Li,³ Anna Nguyen¹, Gabriella Barratt Heitmann¹, Adam
5 Bennett^{4,5}, Henry Ntuku,⁴ Lisa M. Prach,⁴ Munyaradzi Tambo,⁶ Lindsey Wu⁷, Chris Drakeley⁷,
6 Roly Gosling^{4,8}, Davis Mumbengegwi⁹, Immo Kleinschmidt^{10,11,12}, Jennifer L. Smith⁴, Alan
7 Hubbard³, Mark van der Laan³, Michelle S. Hsiang^{2,4,13}

8
9 ¹ Department of Epidemiology and Population Health, Stanford University, Stanford, United States

10 ² Chan Zuckerberg Biohub, San Francisco, United States

11 ³ Division of Biostatistics, University of California, Berkeley

12 ⁴ Malaria Elimination Initiative, Global Health Group, University of California, San Francisco (UCSF) , San Francisco, United States

13 ⁵ PATH, Seattle, United States

14 ⁶ Multidisciplinary Research Centre, University of Namibia, Windhoek, Namibia

15 ⁷ Department of Infection Biology, London School of Hygiene and Tropical Medicine, London, UK

16 ⁸ Department of Disease Control, London School of Hygiene and Tropical Medicine, London, UK

17 ⁹ University of Namibia, Windhoek, Namibia

18 ¹⁰ MRC International Statistics and Epidemiology Group, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical
19 Medicine, London, UK

20 ¹¹ Wits Research Institute for Malaria, Wits/SAMRC Collaborating Centre for Multi-Disciplinary Research on Malaria, School of Pathology,
21 Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

22 ¹² Southern African Development Community Malaria Elimination Eight Secretariat, Windhoek, Namibia

23 ¹³ Department of Epidemiology and Biostatistics, UCSF, San Francisco, United States

24
25 *Corresponding author: Jade Benjamin-Chung

26 Email: jadebc@stanford.edu

27 28 Abstract

29
30 Malaria elimination interventions in low-transmission settings aim to extinguish hot spots and
31 prevent transmission to nearby areas. In malaria elimination settings, the World Health
32 Organization recommends reactive, focal interventions targeted to the area near malaria cases
33 shortly after they are detected. A key question is whether these interventions reduce
34 transmission to nearby uninfected or asymptomatic individuals who did not receive
35 interventions. Here, we measured direct effects (among intervention recipients) and spillover
36 effects (among non-recipients) of reactive, focal interventions delivered within 500m of
37 confirmed malaria index cases in a cluster-randomized trial in Namibia. The trial delivered
38 malaria chemoprevention (artemether lumefantrine) and vector control (indoor residual
39 spraying with Actellic) separately and in combination using a factorial design. We compared
40 incidence, infection prevalence, and seroprevalence between study arms among intervention
41 recipients (direct effects) and non-recipients (spillover effects) up to 3 km away from index
42 cases. We calculated incremental cost-effectiveness ratios accounting for spillover effects. The
43 combined chemoprevention and vector control intervention produced direct effects and
44 spillover effects. In the primary analysis among non-recipients within 1 km from index cases,
45 the combined intervention reduced malaria incidence by 43% (95% CI 20%, 59%). In secondary
46 analyses among non-recipients 500m-3 km from interventions, the combined intervention
47 reduced infection by 79% (6%, 95%) and seroprevalence 34% (20%, 45%). Accounting for
48 spillover effects increased the cost-effectiveness of the combined intervention by 37%. Our
49 findings provide the first evidence that targeting hot spots with combined chemoprevention
50 and vector control interventions can indirectly benefit non-recipients up to 3 km away.

51 **Significance Statement**

52

53 In settings where malaria transmission is declining and approaching elimination, new malaria
54 cases are clustered in space and time. Prior studies have found that targeting prophylactic
55 antimalarial drugs and vector control in the area around newly detected malaria cases reduced
56 community-wide malaria. Here, we found that when antimalarials and vector control were
57 delivered as a combined strategy in the area near recent cases, malaria incidence was reduced
58 up to 3 kilometers away among individuals who did not receive interventions. Accounting for
59 these benefits to non-recipients increased cost-effectiveness of the intervention. Overall, our
60 findings suggest that combined, targeted malaria interventions can reduce local transmission
61 and support their use for malaria elimination.

62 Introduction

63

64 In the past decade, there has been renewed attention towards global malaria eradication, and
65 many countries have set targets for the elimination of local malaria transmission (1). In
66 Southern Africa, eight countries hope to achieve malaria elimination by 2030 as part of the
67 Elimination Eight Initiative (E8). Yet, global progress has plateaued: annual global malaria cases
68 have increased since 2015, and in 2021, there were 59 cases per 1,000 population at risk, an
69 increase from 57 per 1,000 in 2019 (2).

70

71 The ideal malaria elimination intervention would not only prevent disease among recipients but
72 would also prevent onward transmission to nearby non-recipients through spillover effects
73 (i.e., “herd effects”, “indirect effects”) (4, 5), like some vaccines do (4, 6–12). Prior studies have
74 reported spillover effects for mass drug administration for trachoma (13, 14), school-based
75 deworming (15), insecticide treated bed nets (16–18), and chemoprevention and vector control
76 for malaria (19, 20).

77

78 When an intervention reduces disease among intervention non-recipients, accounting for
79 spillover effects can substantially increase cost-effectiveness (21, 22). Identifying cost-effective
80 interventions is crucial to the elimination and eradication enterprise because elimination efforts
81 are projected to cost significantly more than existing malaria control programs in the medium
82 term (3). Even after elimination, countries must continue to conduct intensive surveillance and
83 outbreak response for imported cases to prevent re-establishment.

84

85 In settings approaching malaria elimination, the World Health Organization recommends
86 interventions that are “reactive” – delivered soon after a confirmed malaria case is detected –
87 and “focal” – delivered to higher risk individuals who reside near the case (23). A recent cluster-
88 randomized trial in Namibia found that reactive, focal chemoprevention and vector control
89 substantially reduced malaria incidence (24). Spillover effects of these interventions are
90 plausible: chemoprevention may reduce gametocyte biomass in recipients (25), and vector
91 control can reduce the mosquito population near malaria cases. To shed light on whether focal
92 interventions reduce transmission to nearby uninfected or asymptomatic individuals who did
93 not receive interventions, we separately estimated direct effects among intervention recipients
94 and spillover effects among nearby non-recipients. Our approach can be used to estimate
95 spillover effects of other interventions, such as malaria vaccines.

96

97 Results

98

99 Interventions

100 We analyzed data from a previously reported cluster-randomized trial of focal malaria
101 interventions conducted in Zambezi region of Namibia in 2017 (NCT02610400) (24) (Figure 1).
102 The region has low *Plasmodium falciparum* malaria transmission (26). Using a two-by-two
103 factorial design, the trial randomized 56 clusters to four arms: 1) reactive case detection
104 (RACD), 2) reactive focal mass drug administration (rfMDA) only, 3) reactive vector control
105 (RAVC) + RACD, 4) RAVC + rfMDA. rfMDA included presumptive treatment with artemether-

106 lumefrantrine to individuals in target areas (Table S1). RACD included testing with rapid
107 diagnostic tests and treatment with artemether-lumefrantrine and single-dose primaquine for
108 those who tested positive. RAVC included indoor residual spraying (IRS) with pirimiphosmethyl.
109 The trial delivered interventions in “target areas” within approximately 500 m of confirmed
110 malaria cases detected through passive surveillance.

111

112 Effects on malaria incidence

113 Primary analyses estimated effects on malaria incidence. We estimated three types of effects
114 on the cumulative incidence of locally acquired, confirmed *Pf* malaria: 1) direct effects among
115 intervention recipients in target areas within 500 m of confirmed malaria index cases, 2)
116 spillover effects among non-recipients within 1 km of index cases, and 3) total effects among all
117 individuals within 1 km of index cases (Figure 2a). We created analytic cohorts including
118 individuals residing within 1 km of each index case to capture the area and time period in which
119 we expected each intervention to reduce infections (direct effect) and secondary transmission
120 to nearby individuals (spillover effect). (Figure 1; Figure S1 see details in Materials and
121 Methods). We measured effects of the chemoprevention intervention comparing arms with
122 rfMDA vs. RACD, the vector control intervention by comparing arms with RAVC vs. no RAVC,
123 and the combined intervention by comparing the rfMDA + RAVC vs. RACD only arms.

124

125 To estimate direct effects and spillover effects, we used hierarchical targeted maximum
126 likelihood estimation, a doubly-robust, semiparametric method that adjusts for potential
127 confounders using ensemble machine learning (27). This approach is appropriate for cluster-
128 level interventions that may result in statistical dependence between outcomes (see Methods)
129 (28–30). We adjusted for covariates such as baseline malaria incidence and population size to
130 account for differences in baseline characteristics between study arms (Tables S2-3).

131

132 In analyses of direct effects among intervention recipients, the chemoprevention intervention
133 reduced malaria incidence among intervention recipients within 500m of index cases, but the
134 confidence interval included the null. There was no evidence of a direct effect for the vector
135 control or combined interventions, but precision was low (Figure 2, Table S4).

136

137 In analyses of spillover effects among intervention non-recipients up to 1 km away from
138 interventions, chemoprevention and vector control interventions reduced incidence, but
139 confidence intervals included the null. There was evidence of a spillover effect of the combined
140 intervention, which reduced malaria incidence by 43% (95% CI 21%, 58%) among non-
141 recipients.

142

143 We evaluated spillover effect heterogeneity by cluster-level malaria incidence and IRS coverage
144 prior to the trial, surface temperature, rainfall, the enhanced vegetative index, elevation, and
145 cohort-level treatment coverage, and gender. Across interventions, spillover effects were
146 consistently more protective when pre-trial incidence was below the median (Figure S2). For
147 example, the combined intervention reduced incidence by 68% (95% CI 35%, 84%) when
148 baseline incidence was lower, but there was no effect when baseline incidence was above the
149 median. Intervention spillover effects were generally stronger when environmental conditions

150 favored mosquito breeding and survival (higher rainfall, higher enhanced vegetative index, and
151 lower elevation) (Table S5). Spillover effects of the chemoprevention intervention were present
152 for men but were null for women.

153

154 We performed several sensitivity analyses. When we repeated spillover effect analyses using 2
155 and 3 km radii around index cases to capture mosquito dispersal over longer distances (31, 32),
156 results were similar (Figure S3). When using a shorter follow-up period in which intervention
157 effects may have been stronger (see Methods), results were similar for the chemoprevention
158 and vector control interventions; for the combined intervention, the spillover effect estimate
159 was closer to the null, and precision was lower (Figure S4). When we estimated direct effects
160 including the <3% of intervention recipients who resided >500m from index cases, results were
161 nearly the same (Figure S5).

162

163 Overlap in analytic cohorts may have resulted in statistical dependence between outcomes
164 (Figure 1; Table S6). When using alternative standard errors accounting for dependence (see
165 Methods), confidence intervals were wider, but there was still evidence of spillover effects and
166 total effects for the combined interventions (Table S4). When we excluded overlapping cohorts
167 from the analysis, results were similar overall (Figure S4).

168

169 Effects on malaria prevalence

170 We also estimated effects on malaria prevalence measured using qPCR in a cross-sectional
171 survey at the end of the malaria season (May to August 2017). In contrast to incidence analyses,
172 which captured any effects within the period immediately after intervention, prevalence
173 analyses captured effects of cumulative interventions near the end of the trial. Prevalence also
174 captures symptomatic and asymptomatic malaria cases that did not necessarily present at
175 health clinics. Analyses of direct effects included individuals who resided within 500 m any
176 intervention recipients; spillover effects included individuals with no intervention recipients <
177 500 m and at least one recipient within 500 m-3 km; total effects included individuals with at
178 least one intervention recipient within 3 km (Figure 2b). We estimated prevalence ratios using
179 targeted maximum likelihood estimation and adjusted standard errors for enumeration area-
180 level clustering.

181

182 There was evidence of direct effects for all interventions, but confidence intervals included the
183 null (Figure 2, Table S7). There was evidence of spillover effects: among non-recipients near
184 intervention recipients, the chemoprevention intervention reduced prevalence by 72% (95% CI
185 31%, 88%), and the combined intervention reduced it by 79% (95% CI 6%, 95%). For the
186 chemoprevention and combined interventions, spillover effects decreased in magnitude as
187 distance to the nearest intervention increased (Figure 3). There was also evidence of spillover
188 effects on prevalence of households with multiple malaria cases for the chemoprevention and
189 combined interventions (Table S8).

190

191 Effects on malaria seroprevalence

192 We also investigated whether there were effects on seroprevalence of early transcribed
193 membrane protein 5 antigen (Etramp5.Ag1), an indicator of recent malaria infection (33) that

194 was measured by Luminex in the cross-sectional survey. The chemoprevention intervention
195 reduced seroprevalence among individuals who resided within 500m of intervention recipients
196 by 25% (95% CI 14%, 34%), and the combined intervention reduced it by 34% (95% CI 10%,
197 42%) (Figure 2, Table S9). Among intervention non-recipients, the combined intervention
198 reduced seroprevalence by 34% (95% CI 20%, 45%).

199

200 Cost-effectiveness

201 To inform policy decisions, we assessed cost-effectiveness using estimates of direct effects and
202 spillover effects on prevalence. We calculated the incremental cost effectiveness ratio (ICER) by
203 dividing the difference in cost between arms by the difference in prevalent cases averted
204 between arms. We included cases averted for both individuals within 500m of any
205 interventions and those with no intervention recipients < 500 m (direct effect population) and
206 at least one recipient within 500 m-3 km (spillover effect population). Accounting for direct
207 effects and spillover effects, the incremental cost-effectiveness ratios were \$156 (95% CI \$141,
208 \$177), \$2,105 (95% CI \$1,859, \$2,430), and \$1,142 (95% CI \$944, \$1,446) for the
209 chemoprevention, vector control, and combined interventions (Table S10). Compared to the
210 trial's original incremental cost-effectiveness ratios estimates, accounting for spillover effects
211 increased cost-effectiveness by 3%, 21%, and 37% for the chemoprevention, vector control, and
212 combined interventions (34).

213

214 **Discussion**

215

216 Here, we showed that a combined intervention of reactive focal chemoprevention plus IRS
217 reduced malaria infections in intervention recipients as well as non-recipients up to 3 km away.
218 Overall, spillover effects among non-recipients were strongest for the combined intervention,
219 which was designed to reduce the parasite reservoir in both humans and mosquitoes. When
220 accounting for spillover effects, the cost-effectiveness of the combined intervention was 37%
221 higher than the prior estimate (34).

222

223 Interventions that produce spillover effects yield greater population health benefits at no
224 additional cost. A prior analysis found that the combined intervention was highly cost-effective,
225 but it did not account for possible spillover effects (34). When accounting for spillover effects,
226 interventions were 3-37% more cost-effective (34). Given that malaria elimination requires
227 substantially larger investments than malaria control (3, 35), evidence about cost savings due to
228 spillover effects is critical to policy decisions about elimination strategies.

229

230 We found stronger evidence of spillover effects of the combined chemoprevention and vector
231 control intervention over larger spatial scales than two prior studies of targeted malaria
232 interventions. In Kenya, a trial in a low-transmission area found no change in parasite
233 prevalence within 500m of serologically-defined hot spots that received targeted larviciding,
234 long-lasting insecticide treated nets, IRS, and focal mass drug administration (19). In Zambia, an
235 observational study in a high transmission setting found that IRS targeted to subdistricts with
236 higher malaria incidence and population density reduced parasite prevalence in sprayed and
237 unsprayed households within target areas; it did not measure spillover effects outside of target

238 areas (20). The interventions in our study may have been more likely to produce spillover
239 effects because they were delivered repeatedly in response to subsequent index cases. In this
240 trial, clusters received interventions up to 17 times per cluster; they were repeated annually
241 over three years in the Zambia study and once in the Kenya trial. Further, it is possible that
242 delivering interventions in response to new index cases can more effectively reduce
243 transmission than targeting interventions based on an area's incidence or seroprevalence.

244
245 For the chemoprevention intervention, there was evidence of spillover effects on prevalence
246 and suggestive evidence of spillover effects and direct effects on incidence. Incidence analyses
247 measured effects shortly after interventions, while prevalence analyses measured them at the
248 end of the transmission season. Thus, our findings may indicate that reductions in local
249 transmission accrued as additional rounds of chemoprevention interventions were delivered
250 and population intervention coverage increased. This may especially be the case for the
251 chemoprevention intervention since reductions in infectiousness of malaria cases are typically
252 short-lived following treatment, especially in the absence of concurrent vector control (36).
253 Overall, these findings suggest that reactive, focal chemoprevention can more effectively
254 reduce asymptomatic or subclinical infections among nearby non-intervention recipients than
255 RACD, particularly after repeated rounds.

256
257 For the vector control intervention, the primary analysis did not find direct effects, and the
258 spillover effect estimate included the null despite strong biologic plausibility for both types of
259 effects. We used a 6-month follow-up period to capture longer-term effects of IRS, which
260 resulted in spatiotemporal overlap between analytic cohorts (Table S6). This overlap may have
261 induced dependence between outcomes that was not fully accounted for by covariate
262 adjustment, resulting in residual bias (28). Analyses of current infection prevalence were not
263 subject to concerns about cohort overlap and were suggestive of direct effects, but confidence
264 intervals included the null, and there was no evidence of spillover effects. Finally, our pre-
265 specified subgroup analyses suggested that spillover effects of RAVC were driven by baseline
266 transmission levels and environmental conditions: spillover effects on incidence were present
267 in areas with baseline malaria incidence was <14 per 1,000 and when weather conditions
268 favored mosquito breeding and survival (temperature < 31 °C; monthly rainfall < 27 mm).

269
270 The combined intervention appeared to have synergist effects, reducing local transmission to
271 intervention non-recipients via spillover effects in all analyses. This may be because short-lived
272 reductions in host infectiousness following chemotherapy can be sustained over time when
273 coupled with IRS' long-lasting reductions in mosquito populations. In effect, each intervention
274 reduces the parasite reservoirs in hosts and vectors, and the combination of interventions
275 slows the replenishment of parasite reservoirs (36). This may explain why we found that
276 spillover effects were larger for prevalence of current infection, which captured effects at the
277 end of the season, rather than incidence, which captured short-term effects. Our findings are
278 consistent with two recent studies that found evidence of potential synergistic community-level
279 effects when combining community-wide chemoprevention or seasonal malaria
280 chemoprevention with IRS in high transmission settings (37, 38). Results are also consistent
281 with a modeling study that estimated that the joint effect of chemoprevention and IRS was over

282 1.5 times higher than effects of intervention alone in low-transmission settings (36). Taken
283 together, our results suggest that the combined intervention may be particularly effective as a
284 reactive intervention or outbreak response in low-transmission settings approaching
285 elimination or possibly following introduction of cases after elimination has been achieved.

286

287 Our estimates of direct and spillover effects shed light on the mechanism through which these
288 targeted interventions work in time and space. We found that spillover effect sizes were
289 generally similar to or stronger than direct effect sizes. It is possible that during the time
290 between index case detection and intervention delivery (median 13-14 days) (24), transmission
291 occurred to nearby intervention recipients. Thus, the interventions may not have been rapid
292 enough to reduce malaria among recipients but may have prevented onward transmission to
293 non-recipients further from index cases. In addition, our finding that spillover effects on
294 prevalence were stronger at shorter distances to interventions suggests that the majority of the
295 spillover effect occurred within 1km of index cases.

296

297 Our study was subject to several limitations. First, due to rare outcomes, precision was low in
298 some analyses and may have increased the chance of Type II error, especially for direct effects.
299 Second, when constructing analytic cohorts, household relocation after baseline could have
300 resulted in misclassification of households to target areas or spillover zones. Third, incidence
301 analyses could not fully rely on randomization-based inference due to cohort overlap; it is
302 possible that covariate adjustment did not fully account for imbalances between arms. In future
303 studies, using a ring trial design to test focal interventions could improve baseline balance,
304 increase precision, and minimize overlap between target areas (39).

305

306 Despite these limitations, the internal consistency between the findings of this secondary
307 analysis and the original trial, which each used different data structures and statistical methods,
308 supports the validity of our findings. Estimates of total effects in this analysis, which pooled
309 across intervention recipients and non-recipients, were consistent overall with those of the
310 original trial, which included all individuals in study clusters (intervention recipients and non-
311 recipients) (24, 40). Additional strengths include pre-specification of spillover analysis methods
312 and use of individual-level, spatially indexed data to measure spillovers.

313

314 In conclusion, we found that reactive, focal malaria interventions targeting both human and
315 mosquito parasite reservoirs reduced malaria risk, even among non-intervention recipients up
316 to 3km from index cases. Further, the combined intervention could be particularly useful in
317 responding to imported infections, which pose a persistent threat prior to and following
318 elimination. Our findings suggest that these interventions are an effective strategy for achieving
319 and maintaining malaria elimination.

320

321

322 **Materials and Methods**

323

324 Analysis overview

325 This study was a secondary analysis of a cluster-randomized trial of focal malaria interventions
326 conducted in Zambezi region of Namibia from January 1 to December 31, 2017 (NCT02610400)
327 (41, 24). Using a two-by-two factorial design, the trial randomly allocated 56 study clusters to
328 study arms: reactive case detection (RACD) only, reactive focal mass drug administration
329 (rfMDA) only, RACD + reactive vector control (RAVC), and rfMDA + RAVC. Here, we separately
330 estimated effects among intervention recipients and non-recipients to estimate direct effects
331 and spillover effects. We estimated the effects of the chemoprevention intervention (rfMDA vs.
332 RACD), the vector control intervention (RAVC vs. no RAVC), or combined interventions (rfMDA +
333 RAVC vs. RACD only), consistent with the original trial (24). The analysis plan for this study was
334 pre-specified at <https://osf.io/s8ay4/>. Deviations from the pre-analysis plan and details about
335 the study site and trial are in the Supporting Information.

336

337 Ethics statement

338 The trial protocol was approved by the Namibia Ministry of Health and Social Services (17/3/3)
339 and the Institutional Review Boards at the University of California San Francisco (15–17422) and
340 London School of Hygiene & Tropical Medicine (10411). The secondary analysis protocol was
341 approved by the Stanford University Institutional Review Board (60708).

342

343 Incidence analyses

344 The unit of intervention (index cases) and the unit of randomization (clusters) differed, so
345 cluster-level analyses would not have captured fine-scale direct effects and spillover effects. To
346 capture the person-time in which we expected each intervention to influence incident malaria
347 infections, we created analytic cohorts in space and time around each index case that triggered
348 an intervention. The primary analysis used a 1 km radius around each index case because the
349 majority of mosquito movement occurs within < 1 km.

350

351 We pre-specified cohort follow-up length based on the period in which we expected each
352 intervention to reduce malaria among intervention recipients (direct effects) and non-recipients
353 (spillover effects). For comparisons of rfMDA and RACD interventions, the direct effect follow-
354 up period was 35 days, the length of intrinsic incubation period for *Pf* malaria (8). The spillover
355 effect follow-up period was 21 to 56 days; the 3-week lag period allowed for gametocyte
356 clearance in the treated individual, sporozoite development in mosquitos, and development of
357 detectable merozoites in humans. For RAVC interventions, the direct effects follow-up period
358 was 6 months since IRS can remain effective for an entire transmission season (9). The spillover
359 effects follow-up period was from day 17 to 6 months. We conducted a sensitivity analysis with
360 alternative follow-up lengths (rfMDA and RACD direct effects: day 0-21; spillover effects: day
361 21-42; RAVC direct effects day 0-7; spillover effects day 17-90). Additional details are in the
362 Supporting Information.

363

364 Statistical models for incidence

365 To compare incidence between arms, we used hierarchical targeted maximum likelihood
366 estimation (TMLE), a double robust, semi-parametric approach appropriate for cluster-level
367 exposures (27). TMLE estimates both an outcome regression and a propensity score (the
368 probability of treatment conditional on covariates) and updates the initial parameter estimate

369 using information in the propensity score. Compared to other parametric models for clustered
370 data (e.g., mixed effects models, generalized estimating equations), hierarchical TMLE imposes
371 fewer assumptions and may be more efficient for randomized trials (42). We fit outcome and
372 propensity score models using an ensemble machine learning algorithm (the Superlearner) (43).
373 We adjusted standard errors to account for potential correlation due to overlap between some
374 cohorts using a model of cohort-level influence curves analogous to variance-covariance
375 models used in cross-random effects models (See details in Supporting Information) (44, 45).

376

377 Because incidence analyses did not rely on cluster randomization, we adjusted for covariates
378 that were correlated with the outcome (likelihood ratio test p-value < 0.2) (46). Propensity
379 score models adjusted for the following baseline variables: cluster-level indoor residual spray
380 coverage, malaria incidence, median monthly rainfall, median enhanced vegetative index, and
381 median daytime land surface temperature in the season prior to the trial, population size, and
382 median elevation. Outcome models adjusted for individual- and cluster-level covariates.

383 Individual-level covariates included sex, age, calendar month of intervention, distance from an
384 individual's residence to the residence of the index case that triggered an intervention, number
385 of interventions an individual previously received, number of previously intervention recipients
386 within 0.5, 1, 2, and 3 km of the individual's residence (from the start of the trial to the start of
387 the cohort's observation period), and population size within 0.5, 1, 2, and 3 km of the
388 individual's residence. Cluster-level covariates included those in the propensity score models as
389 well as mean distance to the nearest neighboring household, mean distance to the nearest
390 healthcare facility, and mean time from index case detection to intervention.

391

392 Prevalence analyses

393 To capture effects of cumulative interventions at the end of the malaria transmission season,
394 we estimated effects on prevalence using data from a cross-sectional survey. Direct effects
395 analyses included individuals who resided near any intervention recipients within 500 m of their
396 residence, spillover effects analyses included individuals with no intervention recipients < 500
397 m and at least one recipient within 500 m-3 km, and total effects included individuals with at
398 least one intervention recipient within 3 km.

399

400 Statistical models for prevalence

401 Prevalence analyses used data from the cross-sectional survey conducted at the end of the
402 malaria transmission season in 2017. We used targeted maximum likelihood estimation (47)
403 with individual-level data with the same learners included in incidence analyses. We accounted
404 for correlation within enumeration area-level clusters using cluster-level influence curve-based
405 standard errors. The covariate set included the same cluster-level covariates included in
406 incidence analyses and the following individual-level covariates: age, sex, occupation, recent
407 travel, household slept under a bed net, slept outdoors in the past two weeks, and the total
408 population, number of intervention recipients, number of intervention recipients in the same
409 study arm, the number of intervention recipients in a different study arm, and the proportion of
410 intervention recipients with the same treatment within 500 m, 1 km, 2 km, and 3 km of
411 sampled individuals. We screened for covariates using the same approach described for
412 incidence analyses.

413

414 Cost-effectiveness analysis

415 We estimated incremental cost effectiveness ratios (ICER) incorporating direct effects and
416 spillover effects. To facilitate comparison with the original cost-effectiveness estimates for the
417 trial (34), we used estimated effects on prevalence measured by qPCR. ICERs estimated using
418 incidence would not be directly comparable between this study and the original trial because
419 we used a cohort-level analysis, but the original trial used a cluster-level analysis. We used
420 previously published estimates of total intervention costs in 2017 in US dollars (34). To obtain
421 the number of prevalent cases averted, we multiplied the difference in prevalence between
422 arms among intervention recipients and non-recipients by the estimated population size
423 included in direct effects and spillover effects analyses. We calculated the ICER by dividing the
424 difference in cost between arms by the difference in prevalent cases averted between arms
425 among individuals who were located within 500m of any intervention recipients and individuals
426 who resided within 500m to 3 km of interventions.

427

428 Data and Code Availability

429 Data from the original trial is available at
430 https://clinepidb.org/ce/app/workspace/analyses/DS_f559aee789. Replication scripts are
431 available at <https://github.com/jadebc/malaria-focal-spillover-public>.

432

433

434 **Author Contributions:** JBC and MH conceptualized the study. JBC, AB, AH, MVDL, and MH
435 developed the analysis plan. HN, LMP, MT, LW, CD, RG, DM, IK, and MH contributed data. JBC,
436 HL, AN, and GBH processed data. JBC and HL conducted the analysis. JBC wrote the manuscript,
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438

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440

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442

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454

455

456

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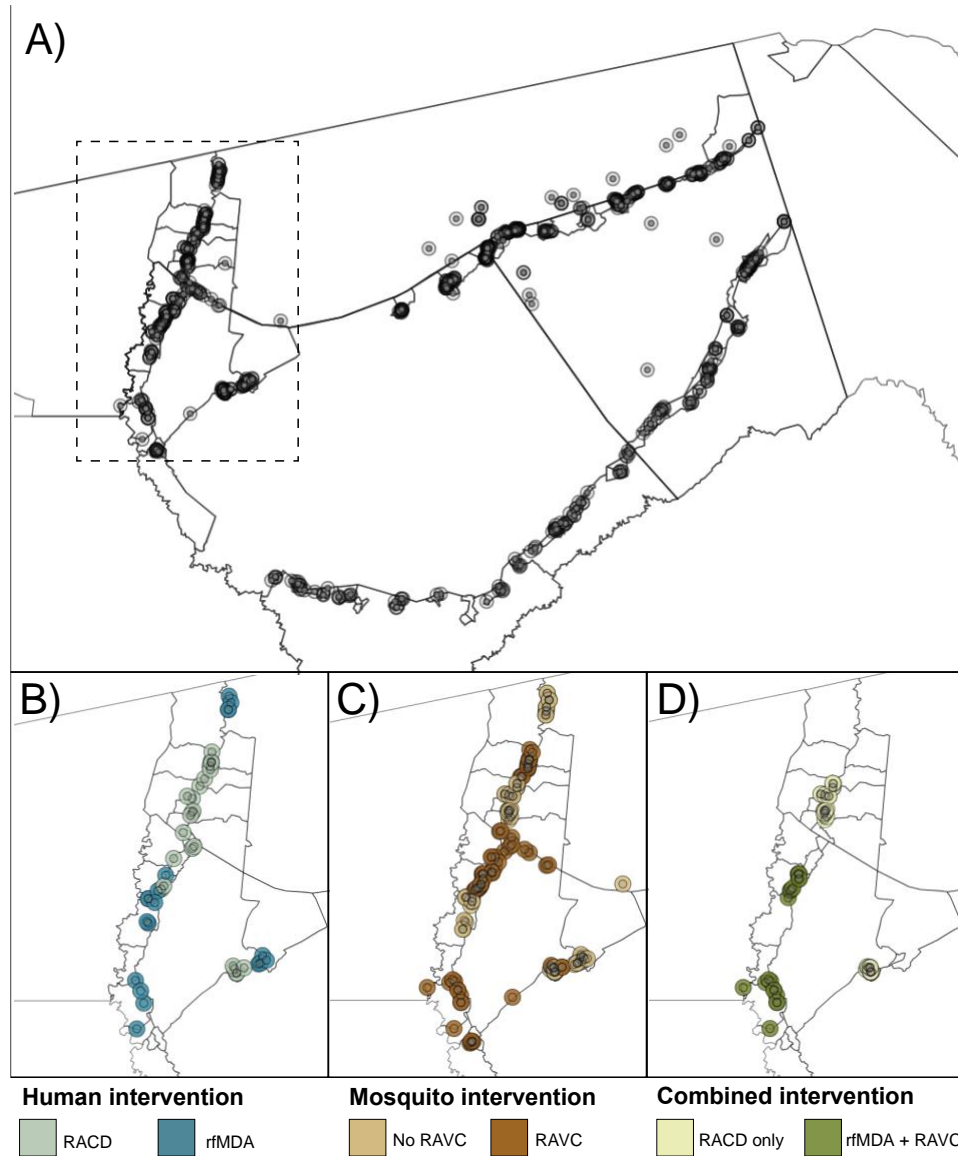
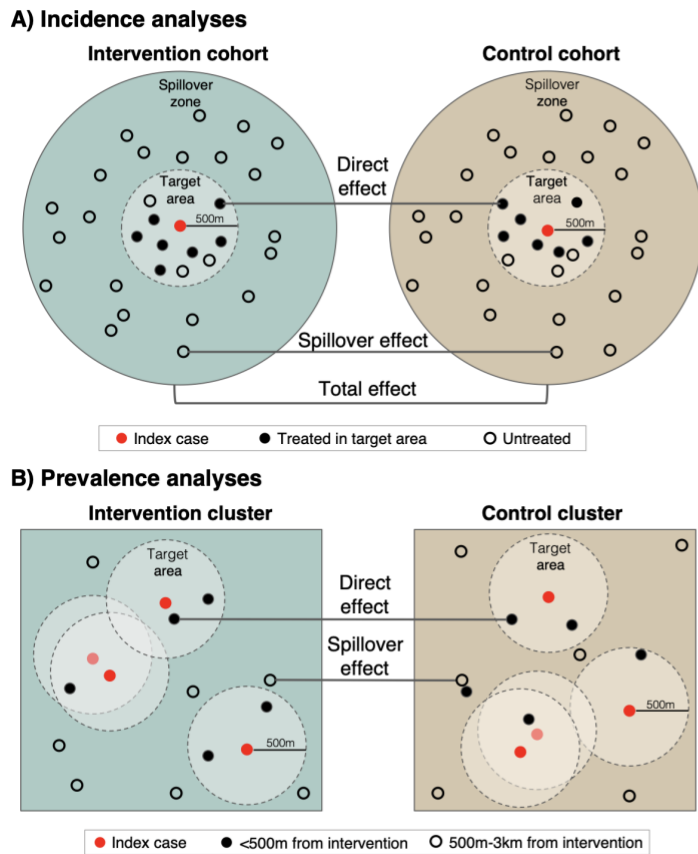


Figure 1. Map of target areas and spillover zones in the study site

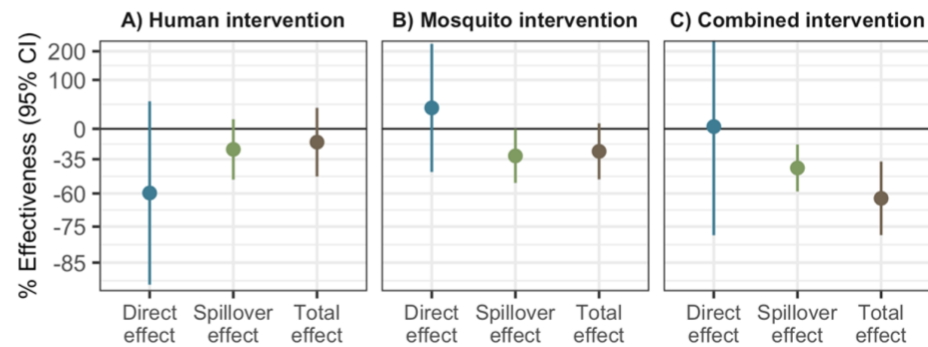
a) All index cases during the study period. The centroid of each circle is the residence location of a treated index case. Inner circles indicate 500m target areas where interventions were delivered. Outer circles indicate the 1km radius around each index case in which spillover effects were estimated in primary analyses. The dashed line indicates insets in panels B-D showing index cases during the follow-up periods with the largest number of treated index cases. For each comparison of study arms, panels b-d depict examples of analytic cohorts from a single follow-up period (i.e., subsample of person-time) in a subset of the study area. **b)** Inset of study area with index cases in the RACD and rfMDA arms (5-week period: April 25, 2017 – May 30, 2017). **c)** Inset of study area with index cases in the no RAVC and RAVC arms (6-month period: January 1, 2017 - June 30, 2017). **d)** Inset of study area with index cases in the RAVC and rfMDA+RAVC arms (6-month period: January 1, 2017 - June 30, 2017).

RACD: reactive case detection
 rfMDA: reactive focal mass drug administration
 RAVC: reactive focal vector control

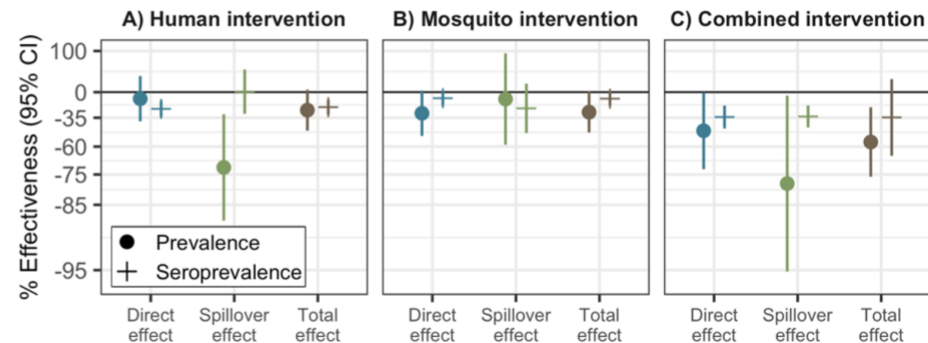
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C) Effects on incidence



D) Effects on prevalence

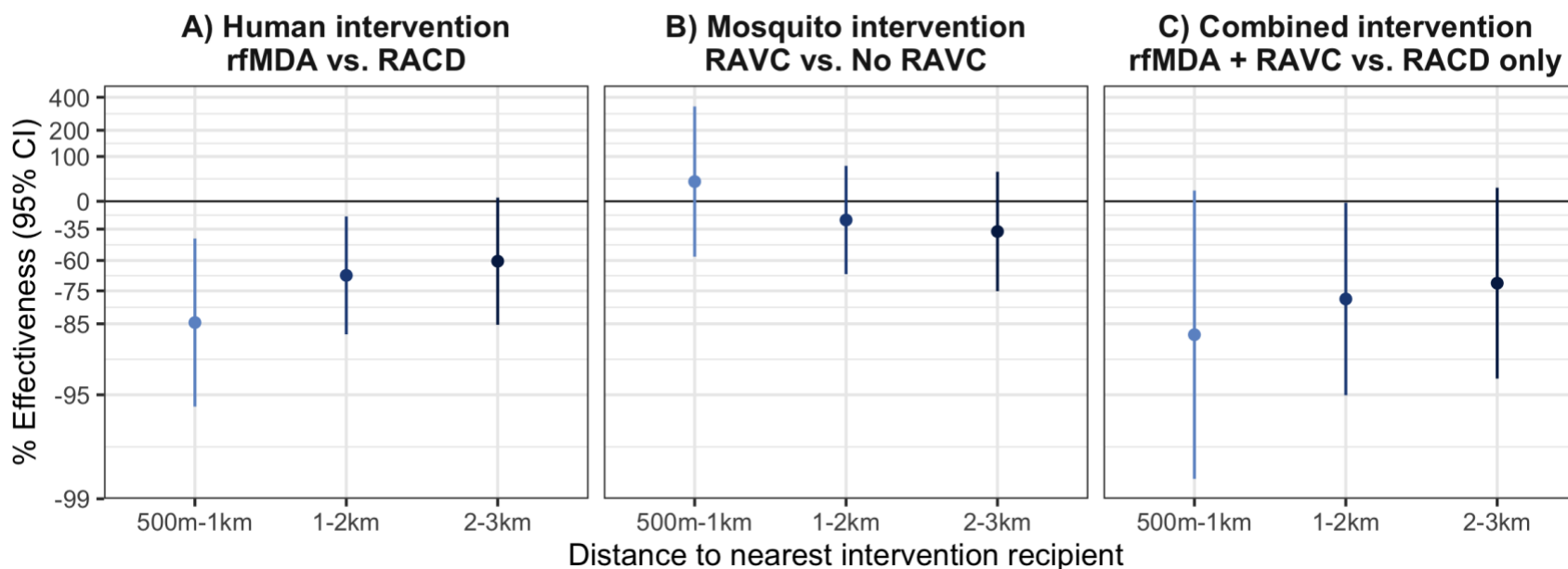


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Figure 2. Effects of reactive, focal malaria interventions

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8 a) Definition of effects in incidence analyses. b) Definition of effects in prevalence analyses. c) Effects on incidence estimated with hierarchical
9 TMLE. All incidence outcome models were fit with cohort-level data except for models of spillover effects of rfMDA vs. RACD and rfMDA + RAVC
10 vs. RACD only. Models were adjusted for covariates that were screened separately for each model using a likelihood ratio test. Confidence
11 intervals shown here do not account for potential outcome correlation. For rfMDA and RACD arms, the incidence analysis includes the period
12 from 0-35 days following index case detection for direct effects and 21-56 days for spillover effects. For rfMDA+RAVC and RAVC only arms, the

13 analysis includes the period from 0-6 months following index case detection for direct effects and 17 days to 6 months for spillover effects. Total
14 effects analyses include the person-time for the direct effects and spillover effects analyses. For incidence analyses, direct effects include treated
15 in target zone, spillover effects include intervention non-recipients up to 1km from an index case, and total effects include all individuals
16 (intervention recipients and non-recipients) up to 1km from index case. **d)** Effects on prevalence estimated with TMLE using individual-level data;
17 standard errors were adjusted for clustering at the enumeration area level. Models were unadjusted because there were fewer than 10 malaria
18 cases per variable. Direct effects include individuals who resided within 500m of any intervention recipients, spillover effects include individuals
19 with no intervention recipients < 500m and any intervention recipients 500m-3km, and total effects include individuals with any intervention
20 recipients <3km during the study. In **c)** and **d)**, % effectiveness was calculated as the ratio of incidence or prevalence between study arms minus
21 1 x 100%. The upper bound of the 95% CI for the combined intervention direct effect was truncated from its original value of 381%.
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25 **Figure 3. Spillover effects of reactive, focal malaria interventions on prevalence by distance to nearest intervention recipient**

26 Spillover effects include individuals with no intervention recipients < 500m and any intervention recipients within different distance radii. **a)**

27 Includes effects of the human intervention by comparing arms with rfMDA vs. those with RACD. **b)** Includes effects of the mosquito intervention

28 by comparing arms with RAVC vs. those without RAVC. **c)** Includes effects of the combined intervention by comparing arms with rfMDA vs. RACD

29 and rfMDA + RAVC vs. RACD only. Effects on prevalence estimated with TMLE using individual-level data; standard errors were adjusted for

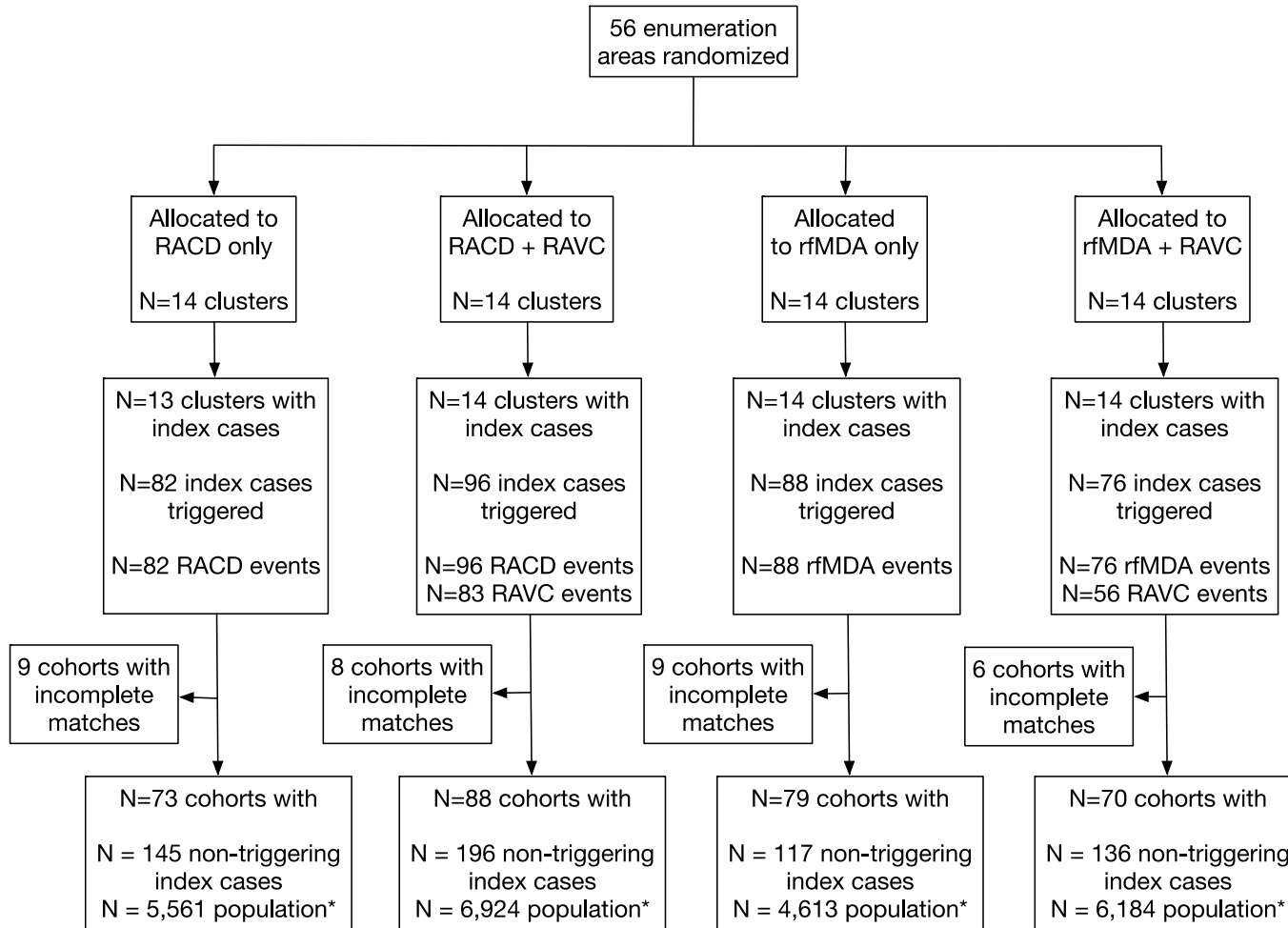
30 clustering at the enumeration area level. Models were adjusted for covariates that were screened separately for each model using a likelihood

31 ratio test. Models were unadjusted because there were fewer than 10 malaria cases per variable. % Effectiveness was calculated as the ratio of

32 incidence or prevalence between study arms minus 1 x 100%.

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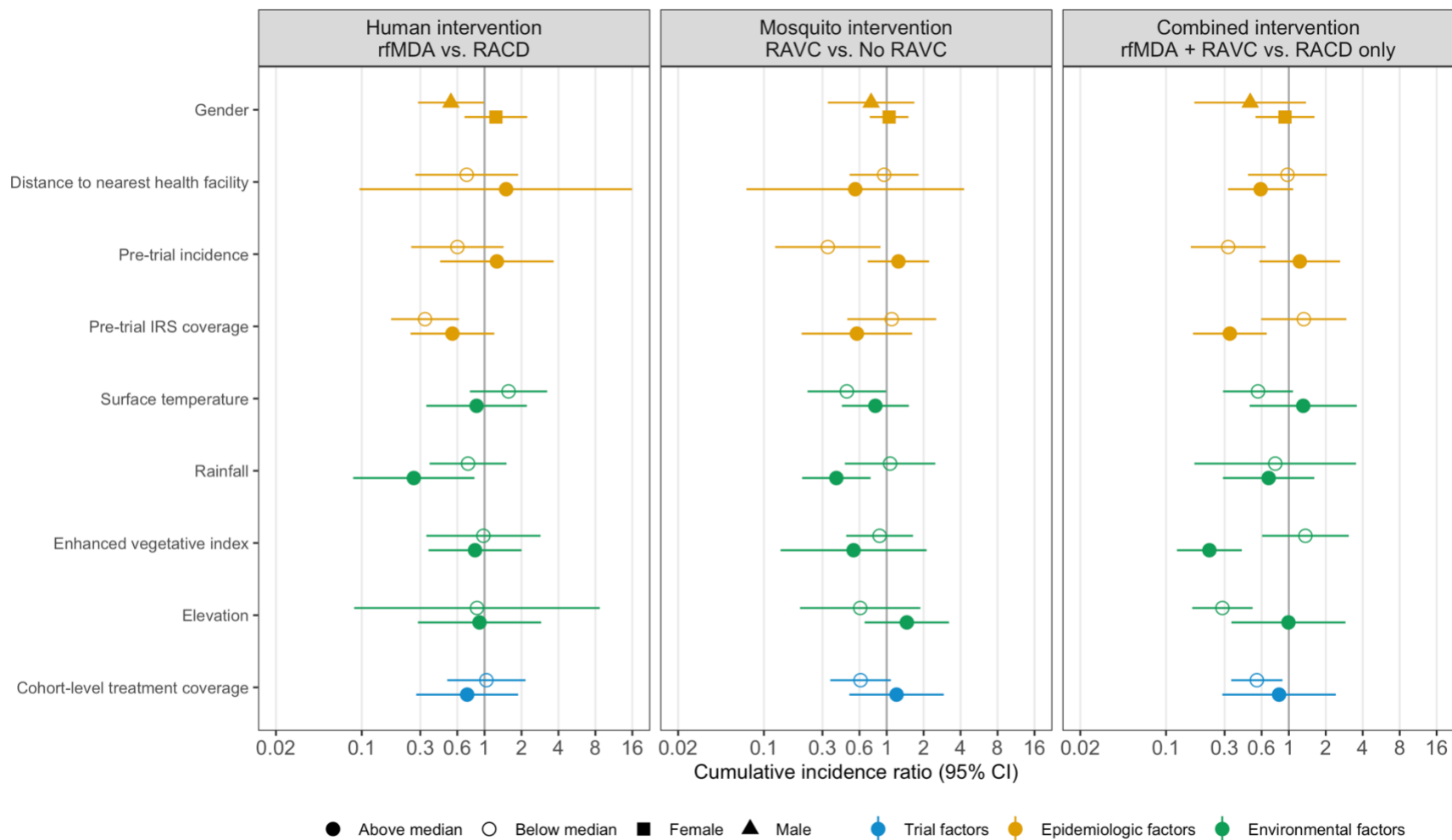


* Some individuals close to cluster boundaries contributed to cohorts in more than one study arm.

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Figure S1. Diagram of study randomization, index cases, and population by arm

RACD: reactive case detection. rfMDA: reactive, focal mass drug administration. RAVC: reactive vector control.



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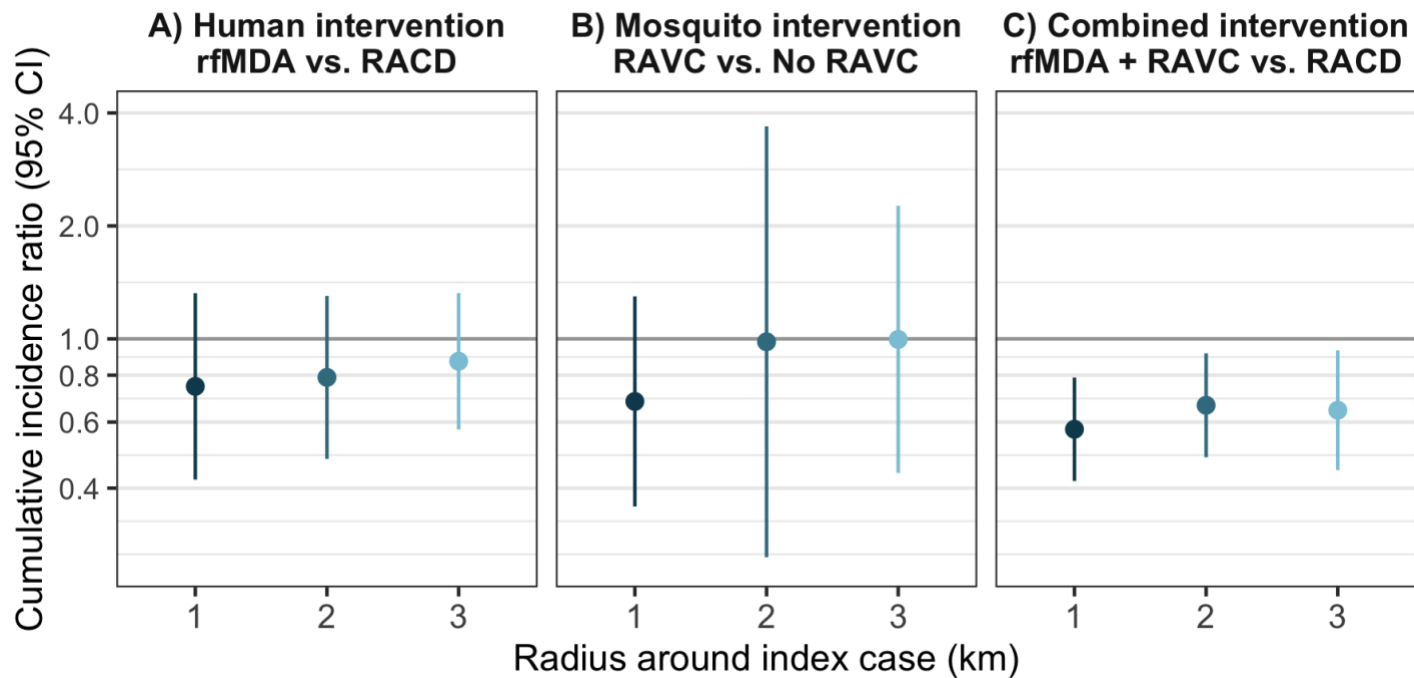
42 **Figure S2. Spillover effect estimates on cumulative incidence within subgroups**

43 Cumulative incidence ratios estimated with hierarchical TMLE; outcome models were fit with cohort-level data. Models were adjusted for
 44 covariates that were screened separately for each model using a likelihood ratio test. Models for rfMDA + RAVC vs. RACD were unadjusted due
 45 to data sparsity. Confidence intervals account for cohort overlap. For rfMDA and RACD arms, the analysis includes the period from 0-35 days
 46 following index case detection for direct effects and 21-56 days for spillover effects. For rfMDA+RAVC and RAVC only arms, the analysis includes

47 the period from 0-6 months following index case detection for direct effects and 17 days to 6 months for spillover effects. Total effects analyses
48 include the person-time for the direct effects and spillover effects analyses. Direct effect includes treated in target zone. Spillover effect includes
49 intervention non-recipients up to 1km from an index case. Total effect includes all individuals (intervention recipients and non-recipients) up to
50 1km from index case. For the human intervention, confidence interval upper bounds were truncated at 16 for above median distance to the
51 nearest health facility (observed value: 23).

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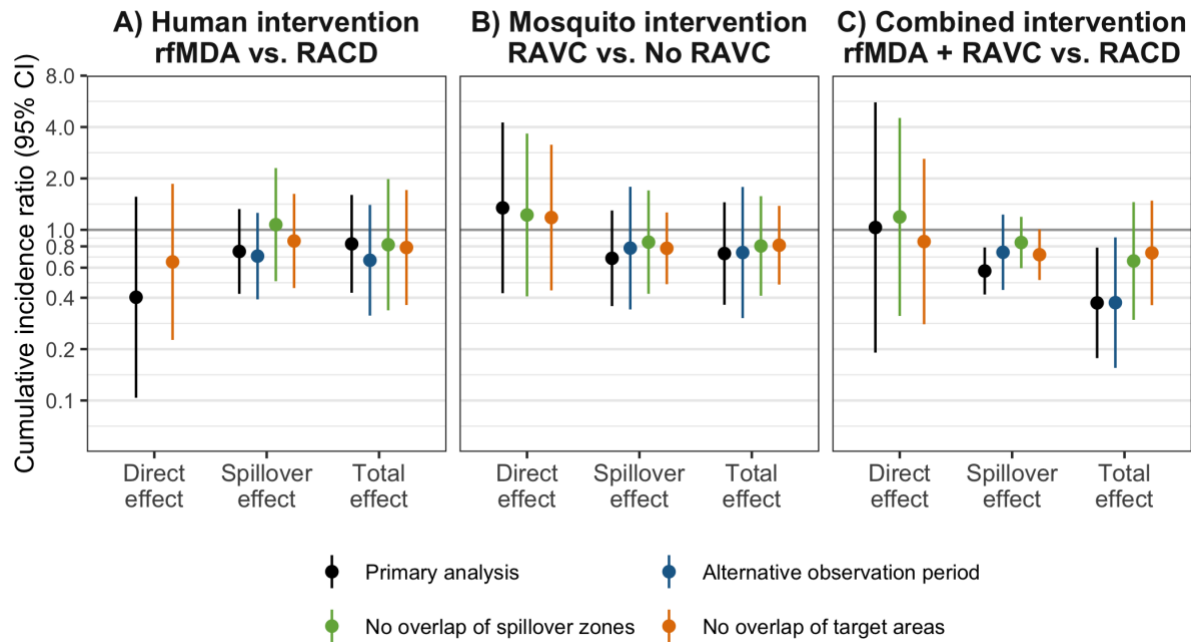
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Figure S3. Sensitivity analyses for spillover effects on cumulative incidence of malaria with different distance radii

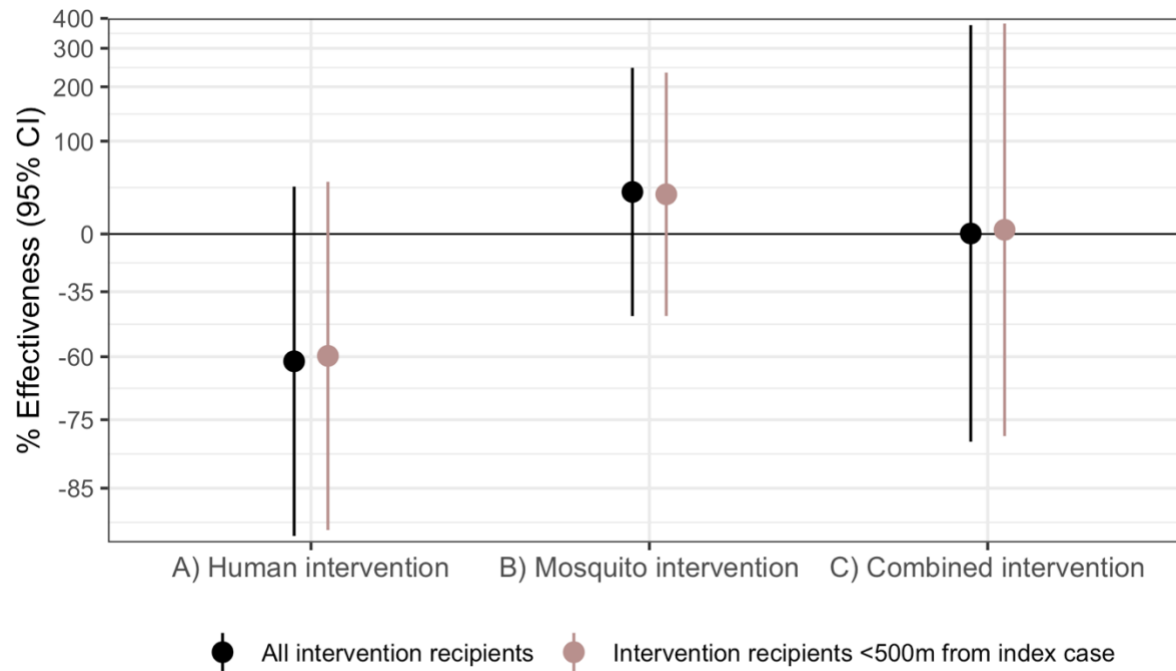
For rfMDA and RACD arms, the primary analysis includes the period from 0-35 days following index case detection for direct effects and 21-56 days for spillover effects; the alternative observation period analysis includes the period from 0-21 days following index case detection for direct effects and 21 to 42 days for spillover effects. For rfMDA+RAVC and RAVC only arms, the primary analysis includes the period from 0-6 months following index case detection for direct effects and 17 days to 6 months for spillover effects; the alternative observation period analysis includes the period from 0-7 days following index case detection for direct effects and 17 to 90 days for spillover effects. Total effects analyses include the person-time for the direct effects and spillover effects analyses. Direct effect includes intervention recipients in target zone. Spillover effect includes intervention non-recipients up to 1km from an index case in the primary analysis and up to 2km or 3km in sensitivity analyses. Total effect includes all individuals (intervention recipients and non-recipients) up to 1km from index case in the primary analysis and up to 2km or 3km in sensitivity analyses. Includes cohort-level analyses for all estimates except spillover effects of the combined intervention. All incidence outcome models were fit with cohort-level data except for models of spillover effects of rfMDA vs. RACD and rfMDA + RAVC vs. RACD only.



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Figure S4. Sensitivity analyses for effects on cumulative incidence of malaria

For rfMDA and RACD arms, the primary analysis includes the period from 0-35 days following index case detection for direct effects and 21-56 days for spillover effects; the alternative observation period analysis includes the period from 0-21 days following index case detection for direct effects and 21 to 42 days for spillover effects. For rfMDA+RAVC and RAVC only arms, the primary analysis includes the period from 0-6 months following index case detection for direct effects and 17 days to 6 months for spillover effects; the alternative observation period analysis includes the period from 0-7 days following index case detection for direct effects and 17 to 90 days for spillover effects. Total effects analyses include the person-time for the direct effects and spillover effects analyses. Direct effect includes intervention recipients in target zone. Spillover effect includes intervention non-recipients up to 1km from an index case. Total effect includes all individuals (intervention recipients and non-recipients) up to 1km from index case. Sensitivity analyses for no overlap of spillover zones excluded any cohorts whose spillover zones overlapped spatially or temporally with other spillover zones. Sensitivity analyses for no overlap of target areas excluded any cohorts whose target areas overlapped spatially or temporally with other target areas. Some direct effects models could not be fit due to data sparsity. All incidence outcome models were fit with cohort-level data except for models of spillover effects of rfMDA vs. RACD and rfMDA + RAVC vs. RACD only.



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Figure S5. Sensitivity analyses for direct effects including all intervention recipients

The observation period was 0-35 days for rfMDA and RACD arms and 0-6 months for rfMDA+RACD and RACD only arms. Black points indicate estimates from analyses including all intervention recipients, regardless of whether they resided within the target zone within 500m of index cases. Mauve points indicate estimates from analyses restricting to intervention recipients within 500m of index cases that triggered interventions. Analyses were performed at the cohort level.

		Human intervention	
		Reactive case detection only (28 clusters)	Reactive focal mass drug administration (28 clusters)
Mosquito intervention	No reactive focal vector control (28 clusters)	Reactive case detection only (14 clusters)	Reactive focal mass drug administration only (14 clusters)
	Reactive focal vector control (28 clusters)	Reactive case detection plus reactive focal vector control (14 clusters)	Reactive focal mass drug administration plus reactive focal vector control (14 clusters)

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92 **Table S1. Two-by-two factorial study design of reactive focal interventions**

93 Reactive case detection (RACD) involved administering rapid diagnostic tests for malaria to individuals living within a 500-m radius of an index case and treating
 94 individuals who tested positive with artemether-lumefantrine and single-dose primaquine. Reactive focal mass drug administration (rfMDA) involved
 95 presumptively treating individuals living within a 500-m radius of an index case with artemether-lumefantrine, without testing for malaria beforehand. Reactive
 96 focal vector control (RAVC) involved spraying the long-lasting insecticide, pirimiphos-methyl, to the interior walls of households located within a seven-
 97 household radius of an index case. The effectiveness of three interventions were compared to three respective controls: (1) rfMDA versus RACD (B and D vs A
 98 and C); (2) RAVC versus no RAVC (C and D vs A and B); and (3) rfMDA plus RAVC versus a RACD only (D vs A). Reproduced from Hsiang et al. 2020 *Lancet* with
 99 permission.

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	Human intervention		Mosquito intervention		Human & mosquito intervention	
	RACD	rfMDA	No RAVC	RAVC	RACD only	rfMDA + RAVC
Population characteristics						
Number of cohorts	161	149	152	158	73	70
Mean cohort population size (SE)	26 (1)	27 (1)	26 (1)	27 (1)	26 (1)	29 (1)
Mean cluster population size (SE)	389.6 (1.94)	346.4 (1.96)	358.9 (2.01)	376.9 (1.94)	353.0 (2.05)	328.0 (1.89)
Malaria incidence per 1,000 in 2016 (SE)	27.0 (0.37)	55.8 (1.26)	31.9 (0.60)	50.0 (1.15)	26.6 (0.56)	75.4 (2.25)
Pre-season indoor residual spray coverage 2016 (SE)	76.3 (0.32)	77.1 (0.36)	77.9 (0.37)	75.6 (0.31)	83.6 (0.43)	81.5 (0.42)
Distance to nearest healthcare facility (km) (SE)	5.2 (0.06)	6.7 (0.08)	5.0 (0.06)	6.7 (0.07)	3.5 (0.06)	6.9 (0.12)
Ecological factors (range)						
Median monthly rainfall November 2016-April 2017 (mm)	23.7 (18.4, 26.7)	23.5 (18.4, 26.7)	23.5 (18.4, 26.7)	23.7 (18.4, 26.7)	23.7 (18.4, 26.7)	23.7 (18.4, 26.7)
Median enhanced vegetative index January 2017-July 2017	0.15 (0.09, 0.31)	0.15 (0.09, 0.27)	0.15 (0.09, 0.22)	0.15 (0.09, 0.31)	0.15 (0.10, 0.21)	0.15 (0.09, 0.27)
Median elevation (m)	522 (387, 1021)	541 (412, 1124)	527 (398, 1124)	547 (387, 1021)	522 (398, 921)	576 (412, 984)
Median daytime land surface temperature (C)	30.5 (28.9, 33.4)	31.1 (28.6, 32.5)	30.7 (28.6, 33.4)	30.8 (28.7, 32.5)	30.7 (28.9, 33.4)	31.1 (28.7, 32.5)

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Table S2. Baseline characteristics among intervention recipients

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Includes data from intervention recipients in target areas located within 500m of an index case.

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	Human intervention		Mosquito intervention		Human & mosquito intervention	
	RACD	rfMDA	No RAVC	RAVC	RACD only	rfMDA + RAVC
Population characteristics						
Number of cohorts	161	149	152	158	73	70
Mean cohort population size (SE)	238 (9)	232 (12)	223 (9)	247 (11)	256 (13)	276 (19)
Mean cluster population size (SE)	379.4 (0.63)	355.8 (0.59)	354.0 (0.58)	380.5 (0.63)	349.5 (0.61)	352.8 (0.63)
Malaria incidence per 1,000 in 2016 (SE)	29.2 (0.12)	41.0 (0.35)	28.3 (0.17)	40.4 (0.29)	27.3 (0.16)	50.0 (0.55)
Pre-season indoor residual spray coverage 2016 (SE)	77.1 (0.10)	81.0 (0.12)	78.6 (0.12)	79.2 (0.10)	82.8 (0.14)	86.9 (0.12)
Distance to nearest healthcare facility (km) (SE)	4.9 (0.02)	6.7 (0.03)	4.4 (0.02)	6.9 (0.02)	3.2 (0.02)	7.3 (0.04)
Ecological factors (range)						
Median monthly rainfall November 2016-April 2017 (mm)	23.7 (18.4, 26.7)	23.5 (18.4, 26.7)	23.7 (18.4, 26.7)	23.7 (18.4, 26.7)	23.7 (18.4, 26.7)	23.7 (18.4, 26.7)
Median enhanced vegetative index January 2017-July 2017	0.15 (0.09, 0.31)	0.15 (0.09, 0.27)	0.15 (0.09, 0.22)	0.15 (0.09, 0.31)	0.15 (0.10, 0.21)	0.15 (0.09, 0.27)
Median elevation (m)	522 (387, 1021)	535 (412, 1124)	527 (398, 1124)	547 (387, 1021)	522 (398, 921)	677 (412, 984)
Median daytime land surface temperature (C)	30.5 (28.9, 33.4)	31.1 (28.6, 32.5)	30.7 (28.6, 33.4)	30.8 (28.7, 32.5)	30.6 (28.9, 33.4)	31.1 (28.7, 32.5)

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Table S3. Baseline characteristics among non-intervention recipients up to 1km away from index cases

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Includes data from intervention non-recipients up to 1km from an index case that triggered interventions.

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	N cohorts	N	Incidence proportion		Incidence ratio (95% CI)		
			Intervention arm	Reference arm	Unadjusted	Adjusted	Adjusted, CI adjusted for cohort overlap
Human intervention (rfMDA vs. RACD)							
Direct effect	310	8,252	3.4	6.5	0.53 (0.25, 1.11)	0.40 (0.11, 1.48)	0.40 (0.10, 1.56)
Spillover effect	310	72,830	9.0	9.9	0.91 (0.60, 1.37)	0.82 (0.52, 1.29)	0.82 (0.44, 1.51)
Total effect	310	81,082	8.4	9.6	0.88 (0.59, 1.31)	0.83 (0.51, 1.35)	0.83 (0.43, 1.60)
Mosquito intervention (RAVC vs. no RAVC)							
Direct effect	310	8,252	8.9	7.6	1.17 (0.62, 2.23)	1.35 (0.54, 3.34)	1.35 (0.43, 4.25)
Spillover effect	310	72,830	12.9	18.5	0.69 (0.47, 1.03)	0.68 (0.46, 1.00)	0.68 (0.36, 1.30)
Total effect	310	81,082	12.5	17.4	0.72 (0.49, 1.06)	0.73 (0.49, 1.08)	0.73 (0.36, 1.45)
Combined intervention (rfMDA + RAVC vs. RACD only)							
Direct effect	143	3,914	6.4	7.4	0.87 (0.32, 2.41)	1.03 (0.22, 4.81)	1.03 (0.19, 5.58)
Spillover effect	143	38,048	11.2	18.1	0.62 (0.34, 1.13)	0.57 (0.41, 0.80)	0.57 (0.42, 0.79)
Total effect	143	41,962	10.8	17.1	0.63 (0.35, 1.12)	0.37 (0.22, 0.63)	0.37 (0.18, 0.79)

112 **Table S4. Direct effect, spillover effect, and total effect estimates on cumulative incidence of malaria infection**

113 For rfMDA and RACD arms, the analysis includes the period from 0-35 days following index case detection for direct effects and 21-56 days for
114 spillover effects. For rfMDA+RAVC and RAVC only arms, the analysis includes the period from 0-6 months following index case detection for
115 direct effects and 17 days to 6 months for spillover effects. Total effects analyses include the person-time for the direct effects and spillover
116 effects analyses. Direct effect includes intervention recipients in the target zone. Spillover effect analyses includes intervention non-recipients up
117 to 1km from an index case. Total effect includes all individuals (intervention recipients and non-recipients) up to 1km from index case. Models
118 were fit with hierarchical targeted maximum likelihood. All outcome models were fit with cohort-level data except for models of spillover effects
119 of rfMDA + RAVC vs. RACD only. Adjusted models were fit if there were fewer than 10 malaria cases per variable. Covariates were screened
120 separately for each model using a likelihood ratio test. We separately fit individual- and cohort-level outcome models and report the model with
121 the smaller cross-validated mean squared error. All models except spillover effects of the human and combined interventions were fit on cohort-
122 level data.

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	Below median		Above median	
	Minimum	Maximum	Minimum	Maximum
Malaria incidence per 1,000 in 2016	0.0	13.9	14.9	293.3
Pre-season indoor residual spray coverage 2016 (%)	27.2	77.3	77.9	100
Median daytime land surface temperature (C)	28.6	31.1	31.1	33.4
Median monthly rainfall November 2016-April 2017 (mm)	18.4	23.7	23.7	26.7
Median enhanced vegetative index January 2017-July 2017	0.09	0.15	0.15	0.31
Median elevation (m)	387	541	544	1124
Cohort-level treatment coverage (%)	0.0	8.3	8.3	97.4

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Table S5. Range above and below median value in each enumeration area for subgroup variables

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	Primary analysis		Sensitivity analysis with shorter observation period	
	Target areas	Spillover zone	Target areas	Spillover zone
Human intervention (rfMDA vs. RACD)	32.0	28.9	21.2	18.4
Mosquito intervention (RAVC vs. no RAVC)	59.2	47.5	53.8	41.8
Combined intervention (rfMDA + RAVC vs. RACD only)	60.5	28.1	60.2	24.1

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Table S6. Percentage of cohorts overlapping with other cohorts

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Overlap in target area was defined as index cases that triggered interventions located within <1km of each other and observation periods that temporally overlapped with another cohort's. Overlap in spillover zones was defined as index cases that triggered interventions located within 1-2km of each other and observation periods that temporally overlapped with another cohort's. The denominator was the total cohorts included in each analysis.

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	N		Prevalence		Prevalence ratio (95% CI)	
	Intervention arm	Reference arm	Intervention arm	Reference arm	Unadjusted	Adjusted
Human intervention (rfMDA vs. RACD)						
Direct effect	1537	1835	0.029	0.033	0.90 (0.61, 1.31)	0.84 (0.53, 1.32)
Spillover effect	244	229	0.025	0.087	0.28 (0.12, 0.69)	--
Total effect	1781	2064	0.029	0.039	0.74 (0.52, 1.04)	0.79 (0.51, 1.19)
Mosquito intervention (RAVC vs. no RAVC)						
Direct effect	1710	1662	0.026	0.037	0.70 (0.48, 1.03)	0.78 (0.51, 1.21)
Spillover effect	195	278	0.051	0.058	0.89 (0.41, 1.92)	--
Total effect	1905	1940	0.028	0.040	0.71 (0.51, 1.01)	0.64 (0.43, 0.96)
Combined intervention (rfMDA + RAVC vs. RACD only)						
Direct effect	758	883	0.017	0.033	0.52 (0.27, 1.00)	--
Spillover effect	118	152	0.017	0.079	0.21 (0.05, 0.94)	--
Total effect	876	1035	0.017	0.040	0.43 (0.24, 0.78)	--

136 **Table S7. Direct effect, spillover effect, and total effect estimates on malaria prevalence measured by qPCR**

137 Prevalence was measured in a cross-sectional survey in a random sample of households at the end of the malaria season. Analyses were
 138 restricted to individuals located within 3 km of at least one intervention recipient. Direct effects include individuals with any intervention
 139 recipients within 500m, spillover effects include individuals with no intervention recipients < 500m and any intervention recipients 500m-3km,
 140 and total effects include individuals with any intervention recipients <3km during the study. Prevalence ratios were estimated using TMLE with
 141 individual-level data, and standard errors were adjusted for clustering at the enumeration area level. Adjusted analyses were not fit there were
 142 fewer than 30 observations within strata of the intervention and outcome. Adjusted models were not fit if the number of cases within treatment
 143 arm strata was <30.

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	N households		Prevalence		Unadjusted Prevalence Ratio (95% CI)
	Intervention arm	Reference arm	Intervention arm	Reference arm	
Human intervention (rfMDA vs. RACD)					
Direct effect	456	506	0.018	0.018	0.99 (0.38, 2.54)
Spillover effect	72	69	0.000	0.043	0.00 (0.00, 0.00)
Total effect	528	575	0.015	0.021	0.73 (0.30, 1.76)
Mosquito intervention (RAVC vs. no RAVC)					
Direct effect	481	481	0.012	0.023	0.55 (0.20, 1.46)
Spillover effect	65	76	0.015	0.026	0.58 (0.05, 6.35)
Total effect	546	557	0.013	0.023	0.55 (0.22, 1.37)
Combined intervention (rfMDA + RAVC vs. RACD only)					
Direct effect	219	244	0.005	0.016	0.28 (0.03, 2.48)
Spillover effect	36	40	0.000	0.050	0.00 (0.00, 0.00)
Total effect	255	284	0.004	0.021	0.19 (0.02, 1.53)

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147 **Table S8. Direct effect, spillover effect, and total effect estimates on household-level malaria prevalence of measured by qPCR**

148 Prevalence was measured in a cross-sectional survey in a random sample of households at the end of the malaria season. Analyses were run at
149 the household level. Household-level malaria prevalence was the percentage of households with more than one malaria case detected in the
150 prevalence survey by qPCR. Direct effects include households with any intervention recipients within 500m, spillover effects include households
151 with no intervention recipients < 500m and any intervention recipients 500m-3km, and total effects include households with any intervention
152 recipients <3km during the study. Prevalence ratios were estimated using TMLE with household-level data. Adjusted analyses were not fit there
153 were fewer than 30 observations within strata of the intervention and outcome. Adjusted models were not fit if the number of cases within
154 treatment arm strata was <30.

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	N		Prevalence		Prevalence ratio (95% CI)	
	Intervention arm	Reference arm	Intervention arm	Reference arm	Unadjusted	Adjusted
Human intervention (rfMDA vs. RACD)						
Direct effect	1316	1611	0.215	0.285	0.75 (0.66, 0.86)	0.84 (0.71, 1.00)
Spillover effect	198	182	0.227	0.225	1.01 (0.69, 1.46)	1.32 (0.73, 2.41)
Total effect	1514	1793	0.217	0.279	0.78 (0.69, 0.88)	0.85 (0.73, 0.99)
Mosquito intervention (RAVC vs. no RAVC)						
Direct effect	1475	1452	0.241	0.267	0.90 (0.80, 1.02)	0.90 (0.79, 1.04)
Spillover effect	133	247	0.188	0.247	0.76 (0.50, 1.15)	--
Total effect	1608	1699	0.236	0.264	0.90 (0.80, 1.01)	0.88 (0.76, 1.01)
Combined intervention (rfMDA + RAVC vs. RACD only)						
Direct effect	634	770	0.194	0.295	0.66 (0.54, 0.80)	--
Spillover effect	81	130	0.136	0.208	0.66 (0.55, 0.80)	--
Total effect	715	900	0.187	0.282	0.65 (0.34, 1.25)	--

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Table S9. Direct effect, spillover effect, and total effect estimates on Etramp5.Ag1 seroprevalence

Prevalence was measured in a cross-sectional survey in a random sample of households at the end of the malaria season. Analyses were restricted to individuals located within 3 km of at least one intervention recipient. Direct effects include individuals with any intervention recipients within 500m, spillover effects include individuals with no intervention recipients < 500m and any intervention recipients 500m-3km, and total effects include individuals with any intervention recipients <3km during the study. Prevalence ratios were estimated using TMLE with individual-level data, and standard errors were adjusted for clustering at the enumeration area level. Adjusted analyses were not fit there were fewer than 30 observations within strata of the intervention and outcome. Adjusted models were not fit if the number of cases within treatment arm strata was <30.

	Intervention cost	N individuals		Prevalence		Prevalent cases		Total prevalent cases averted (95% CI)	Incremental cost-effectiveness ratio (95% CI)	% change from original estimate
		Target area	Spillover zone	Target area	Spillover zone	Target area	Spillover zone			
Human intervention										
RACD	\$354,750	8,187	996	0.033	0.087	268	87	(ref)	(ref)	
rfMDA	\$368,321	8,060	1,301	0.029	0.025	236	32	87 (77, 96)	\$156 (\$141, \$177)	-3%
Mosquito intervention										
No RAVC	\$261,409	7,845	1,290	0.037	0.058	288	74	(ref)	(ref)	
RAVC	\$461,661	8,426	980	0.026	0.051	217	50	95 (82, 108)	\$2,105 (\$1,859, \$2,430)	-21%
Combined intervention										
RACD only	\$127,312	3,697	626	0.033	0.079	121	49	(ref)	(ref)	
rfMDA+RAVC	\$234,223	3,878	635	0.017	0.017	66	11	94 (74, 113)	\$1,142 (\$944, \$1,446)	-37%

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170 **Table S10. Cost-effectiveness analysis**

171 Prevalent cases averted were estimated using hierarchical TMLE models for prevalence measured by qPCR. The number of prevalent cases
172 averted equaled the produce of the difference in prevalence between arms among intervention recipients and non-recipients by the estimated
173 population size within target areas vs. spillover zones. The incremental cost effectiveness ratio is the ratio of the difference in cost between arms
174 by the difference in prevalent cases averted in both target area and spillover zones within 3 km of index cases for rfMDA + RAVC vs. RACD.
175 Original estimates were reported in Ntuku et al., 2022 10.1136/bmjopen-2021-049050.

Supporting Information

Study population

This study analyzed data from a cluster-randomized trial of focal malaria interventions conducted in Zambezi region of Namibia from January 1 to December 31, 2017 (NCT02610400) (1, 2). The region has seasonal malaria transmission that peaks between January and June. *Plasmodium falciparum* is the dominant species, and annual *Pf* incidence was less than 15 per 1,000 from 2010-2015. In 2016, the incidence was 32.5 per 1,000 following an outbreak (3). In 2015, prevalence measured by loop-mediated isothermal amplification was 2.2% (4). In the study site, the Namibia Ministry of Health and Social Services routinely delivered case management and annual pre-season household IRS with dichlorodiphenyltrichloroethane, with the exception of a small number of structures that were sprayed with deltamethrin. In addition, they offered reactive case detection (RACD) within 500 m of confirmed malaria cases, which included testing with rapid diagnostic tests and treatment with artemether-lumefantrine and single-dose primaquine for those who tested positive.

Cluster-randomized trial design

The trial included 56 clusters defined based on census enumeration areas that were within the catchment area of study health care facilities. Enumeration areas were eligible for inclusion in the trial if they 1) were located in the catchment areas of 11 health facilities, 2) had complete incidence data from 2012-13, and 3) had at least one incident case during the trial. Using a two-by-two factorial design, the trial randomized 56 clusters to four arms: 1) RACD only, 2) reactive focal mass drug administration (rfMDA) only, 3) reactive vector control (RAVC) + RACD, 4) RAVC + rfMDA. rfMDA included presumptive treatment with artemether-lumefantrine to individuals in target areas (Extended Data Table 1). The trial used restricted randomization with the following criteria: mean annual incidence in 2013 and 2014, population size, population density, and mean distance from the household to a health-care facility. It was not practical to blind study participants or field staff to intervention assignment, but laboratory analyses and primary statistical analyses were blinded.

Interventions

Field staff delivered interventions in response to passively detected malaria index cases that were confirmed by rapid diagnostic tests or microscopy if the case had resided in the study cluster at least one night in the prior 4 weeks. The trial delivered interventions in “target areas” within approximately 500 m of confirmed malaria cases detected through passive surveillance. In the RACD arms, individuals were eligible to receive rapid diagnostic tests, and individuals who tested positive were eligible for treatment with artemether-lumefantrine and single-dose primaquine (Coartem, Novartis Pharmaceuticals, Kempton Park, South Africa; or Komefan 140, Mylan Laboratories, Sinnar, India). In the rfMDA arms, individuals were eligible for presumptive treatment with artemether-lumefantrine. In the RAVC arms, households were eligible for IRS with pirimiphosmethyl (Actellic 300CS, Syngenta, Basel, Switzerland). In all arms, study teams aimed to deliver interventions within 500 m of a clinical malaria case and within 7 days to 5 weeks of the case report. RACD and rfMDA interventions were delivered to at least 25 people within target areas and RAVC was delivered to at least seven households within target areas.

Over 80% of eligible confirmed malaria cases received interventions, and over 85% of eligible intervention recipients were covered by interventions (2). Since compliance was high, for intervention recipients, we analyzed treatment as randomly assigned. Field staff did not offer repeat interventions in response to subsequent index cases within 5 weeks for rfMDA and RACD and within the same malaria season for RAVC. Field staff recorded the household geocoordinates of the index case and intervention recipients. Additional details about the interventions were previously published (1, 2).

Procedures

Prior to randomization, field staff conducted a geographic census and recorded the latitude and longitude of all households in the study area. During the trial, trial staff extracted data on confirmed incident malaria cases and travel history from the rapid reporting system. At the end of malaria season between May and August 2017, the study team collected an endline cross-sectional survey to measure infection prevalence. Field staff collected dried blood spots on filter paper (Whatman 3 Corporation, Florham Park, NJ, USA) by finger prick from consenting individuals, and qPCR was performed targeting the acidic terminal sequence of the *var* gene.(5) Field staff also collected 250 ml of whole blood in BD Microtainer tubes with EDTA additive (Becton, Dickinson and Corporation, Franklin Lakes, NJ, USA) for serological analyses. Using human plasma, Luminex assays were performed to detect malaria antigens using previously described procedures (6, 7). Field staff recorded the geocoordinates of all sampled households.

Informed consent

In the original trial, written informed consent was obtained from individual participants for rfMDA or RACD, and from heads of households (≥ 18 years of age) for RAVC. A parent or guardian was required to provide written informed consent for children younger than 18 years receiving rfMDA or RACD, and written assent for receiving these interventions was also obtained from children aged 12–17 years.

Construction of analytic cohorts for incidence analysis

To construct cohorts, we matched index cases and intervention recipients to individuals recorded in the baseline census using household geocoordinates, age, and sex. We required that geocoordinates be $< 100\text{m}$ apart to allow for small deviations in the location of geocoordinate recordings. We excluded 32 cohorts from the analysis for which it was not possible to merge intervention recipient geocoordinates with index data geocoordinates. Because clusters were contiguous with no buffer zones between them, to capture potential dependencies across study clusters, we allowed cohorts to include individuals assigned to an adjacent cluster with a different treatment assignment from the triggering index case if it was within 1 km of an index case.

Follow-up periods for analytic cohorts

We pre-specified cohort follow-up length based on the period in which we expected each intervention to reduce malaria among intervention recipients (direct effects) and non-recipients (spillover effects). Day 0 for each cohort was the date of index case detection. For comparisons of rfMDA and RACD interventions, the direct effect follow-up period was 0 to 35 days, the

length of intrinsic incubation period for *Pf* malaria (8). This is the period of time in which we would expect the intervention to interrupt the parasite life cycle in treated, infected individuals, and in turn, prevent symptoms and/or infectiousness. The spillover effect follow-up period was 21 to 56 days; the 3-week lag period allowed for gametocyte clearance in the treated individual, sporozoite development in mosquitos, and development of detectable merozoites in humans. For RAVC interventions, the direct effects follow-up period was 6 months since IRS can remain effective for an entire transmission season (9). The spillover effects follow-up period was from day 17 to 6 months. A mosquito bite could hypothetically be prevented on the day of intervention, so the earliest secondary case could occur after sporozoite development in mosquitos (minimum 10 days), and development of detectable merozoites in humans (minimum 7 days). We conducted a sensitivity analysis with alternative follow-up lengths (rfMDA and RACD direct effects: day 0-21; spillover effects: day 21-42; RAVC direct effects day 0-7; spillover effects day 17-90).

Hierarchical TMLE

We compared incidence between arms using hierarchical targeted maximum likelihood estimation (TMLE) (10). We fit propensity score models at the cohort-level since interventions were delivered to cohorts. Within study clusters and cohorts, we expected individuals' outcomes to be correlated due to interventions, social interactions, and local environmental factors. We fit two types of outcome models that accounted for statistical dependence in different ways (11). Cohort-level models allowed for statistical dependence between individuals in the same cohort without making any assumptions about the nature of the dependency. Individual-level models assumed that cluster-level and individual-level covariates removed any dependence between outcomes of individuals in nearby geographic areas (11). We separately fit individual- and cohort-level models and then chose the outcome model with the smaller cross-validated mean squared error.

We fit outcome and propensity score models using an ensemble machine learning algorithm (the Superlearner) (12). For propensity score models, learners included generalized linear models, least absolute shrinkage and selection operator (LASSO) (13), and elastic net regression (14). For outcome models, we used the same learners as well as extreme gradient boosting (15). We performed 10-fold cross-validation using a loss function at either the individual- or cohort-level (11). Validation samples were constructed from randomly sampled individuals or cohorts. Because comparisons of rfMDA + RAVC vs. RACD had rare outcomes and a smaller sample size, we used 30-fold cross-validation.

Adjusting standard errors for cohort overlap

We adjusted standard errors to account for potential correlation due to overlap between some cohorts using a model of cohort-level influence curves analogous to variance-covariance models used in cross-random effects models (16, 17). Specifically, we fit the model:

$$D_i \times D_j \sim d(i,j) + t(i,j) + C \quad (1)$$

where $D_i \times D_j$ is the product of influence curves of cohorts i and j , $d(i,j)$ is the distance between the location of the index case that triggered the intervention in each cohort, $t(i,j)$ is the start date of the intervention in each cohort, and C is the cluster-level intervention assignment (18). Adjustment for intervention assignment accounted for correlation due to shared exposure to or receipt of the intervention. For cohorts with no overlap, we set $D_i \times D_j$ to zero. The regression was implemented with a simplified SuperLearner library including the generalized linear models and LASSO (13). We calculated the variance accounting for outcome dependence as follows:

$$\text{var}(\hat{\psi} - \psi) = \text{var}\left(\frac{1}{N} \sum_{i=1}^N D_i\right) = \frac{1}{N^2} \left(\sum_{i=1}^N \text{var}(D_i) + 2 \sum_{i < j} \text{cov}(D_i, D_j) \right)$$

where $\hat{\psi}$ is the estimator, ψ is the estimand, and N is the number of cohorts.

In both incidence and prevalence analyses, we excluded any categorical covariates with less than 5% prevalence to avoid positivity violations. To minimize empirical positivity violations (19), we only fit models if the number of outcome events per variable was ≥ 10 and only fit adjusted models if the number of observations per strata was ≥ 30 (20).

Deviations from pre-analysis plan

The analysis plan for this study was pre-specified at <https://osf.io/s8ay4/>. We note the following deviations from the plan:

1. We originally planned to conduct an individual participant data meta-analysis including data from three trials in Namibia, Eswatini, and Zambia. However, after reviewing the data for the Eswatini and Zambia trials, we determined that the geocoding of participants was not sufficient to allow for the planned spillover analyses. Thus, we proceeded with an analysis using data only from the Namibia trial.
2. In primary analyses using incidence data, we did not impose bounds on the mean outcome conditional on treatment and covariates because in initial models using bounds, estimates were very unstable.
3. In secondary analyses using prevalence data, we corrected standard errors at the cluster-level instead of at the household-level as specified in the pre-analysis plan. This better reflected the clustered sampling in the original trial.

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