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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

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Contributors

Data were gathered by the Kenya Medical Research Institute (KEMRI) field team led by EOO, QA, BA, PO, NKA, BP, VM, HO, FA, and EAO. This included laboratory reading of blood slides, human patient submissions (plus adverse events and serious adverse events tracking), entomology collections, and insecticide resistance assays. ER and SO led national and county level stakeholder engagement at the Ministry of Health and Busia Department of Health, respectively, and supported epidemiological and entomological data collection in coordination with KEMRI field teams. JEG, RL, and WO provided technical support and supervised conduct of all aspects of the study. SAH and AM provided technical support and assisted with coordination between social science, epidemiological, and entomological data collection and analysis. BS and JH developed and provided technical support for the electronic data management system used in this study and data verification before analysis. AH provided programme management support for all aspects of the study including ethical approvals and data reporting. Statistical analyses were done by XZ, RZ, and FL. The first draft of the manuscript was written by EOO, JEG, NLA, FL, and JPG, with revision following comments from all the authors. All authors had full access to the full data in the study and accept responsibility to submit for publication. FL accessed and verified the data reported. JEG, RL, and WO are employees of the US Government. This work was prepared as part of their official duties. Title 17 USC §105 provides that "Copyright protection under this Title is not available for any work of the United States Government". Title 17 USC §101 defines a US Government work as a work prepared by a military service member or employee of the US Government as part of that person's official duties. The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the official position of KEMRI or the US Centers for Disease Control and Prevention. This study was funded by Unitaid to University of Notre Dame (grant number 2018-29-UND).

Declaration of interests

The authors declare no competing interests.

See [Online](#) for appendix

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Summary

Background—Spatial repellent products are used for prevention of insect bites, and a body of evidence exists on spatial repellent entomological efficacy. A new option for vector control, spatial repellent products are designed to release active ingredient into the air for disruption of human–vector contact thereby reducing human exposure to mosquito-borne pathogens. Clinical trials have shown spatial repellent epidemiological efficacy against *Aedes*-borne viruses but inconclusive outcomes against malaria. We aimed to show and quantify the protective efficacy of spatial repellents in reducing malaria infection incidence in Busia County, Kenya.

Methods—A prospective, cluster-randomised, controlled trial in Busia County, western Kenya was done to quantify the efficacy of a transfluthrin-based spatial repellent against human malaria infection following mass distribution of insecticide treated nets. Investigators, staff, and study participants were masked to cluster allocation. Infection incidence was measured by microscopy in children aged 6 months to younger than 10 years during a 4-month baseline (March–July 2021) and 24-month follow-up period with intervention (October, 2021–October, 2023). From 58 clusters (29 intervention, 29 placebo), a total of 1526 and 1546 participants from two

consecutive, 12-month cohorts were assessed for first-time malaria infection (primary endpoint) by survival analysis at interim and end-of-trial timepoints, respectively. This trial is registered with [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04766879), [NCT04766879](https://clinicaltrials.gov/ct2/show/study/NCT04766879) and is complete.

Findings—The outcome of the primary endpoint indicated that spatial repellents significantly reduced the hazard rate of first-time malaria infection by 33·4% (95% CI 11·1–50·1; $p=0\cdot0058$) and the hazard rate of overall new malaria infections by 32·1% (15·9–45·2; $p=0\cdot0004$). No reported adverse events and serious adverse events were deemed to be associated with the spatial repellent.

Interpretation—Our trial provides the first evidence of a demonstrative spatial repellent protective efficacy in reducing risk of malaria infection in an African setting characterised by high malaria transmission, pyrethroid resistant malaria vectors, and high coverage of insecticide treated nets. Results support spatial repellent products as a beneficial component of malaria prevention.

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Introduction

Vector control with insecticide treated nets (ITNs) is estimated to account for 68% of all malaria infections averted between 2000 and 2015, with indoor residual spraying accounting for another 11%,¹ which showed the value of vector control to global malaria control approaches. Despite years of investment and efforts, progress in reducing the malaria burden has stagnated and, in some countries, malaria is on the rise, with 249 million cases reported in 2022.² Potential factors contributing to this stagnation include insecticide resistance in the primary mosquito vectors,³ behavioural adaptation in vector biting,⁴ and stagnation in donor funding, which has remained at the same amount since 2015 despite continuous growth in the population at risk of malaria.

Specific to vector control, the global vector control response 2017–30 targets the reduction of mortality from vector-borne diseases by at least 75% by 2030 relative to 2016 indicators.⁵ To meet this target, the global vector control response acknowledges the need for additional multidisciplinary vector control tools such as spatial repellents.⁵ The role for spatial repellents in malaria public health vector control can be highlighted when considering areas of transmission where traditional interventions have incomplete effectiveness (structures not conducive to ITNs or indoor residual spraying, daytime, early-evening biting anopheline mosquitoes).⁶ Products in the spatial repellent intervention class work by releasing volatile chemicals that disperse in the air and create a non-conductive environment for mosquitoes leading to movement away from a house, inhibition of host attraction or feeding, or both, thereby reducing risk of human–vector contact.^{6–8}

Evidence of an epidemiological effect of spatial repellents against vector-borne disease is limited to a single trial against dengue fever in Peru (protective effect of 34·1%)⁹ and another trial against malaria in China (protective effect of 77% by use of metofluthrin coils alone).¹⁰ A third trial in Indonesia¹¹ indicated a reduction in malaria infection incidence by use of spatial repellents (protective effect of 27·7%), although not significant.

This trial, part of the Advancing Evidence for the Global Implementation of Spatial Repellents consortium,¹² was designed to show and quantify protective efficacy of spatial repellents in reducing malaria infection incidence in Busia County, Kenya. Additionally, the trial sought to investigate whether the spatial repellent intervention induced a diversionary effect (ie, pushing mosquitoes from intervention areas to neighbouring unprotected households), as well as the effect of the spatial repellent intervention on entomological correlates of infection.⁷

Methods

Study design

Detailed descriptions of study design, methods, and statistical analyses have been published previously¹² and are reported following CONSORT guidelines (appendix pp 1–5).¹³

The study protocol (appendix pp 6–49) was reviewed and approved by Kenya Medical Research Institute Scientific and Ethics Review Unit (protocol 3870, reference KEMRI/RES/7/3/1), Institutional Review Boards at Centers for Disease Control and Prevention (protocol number 7252), University of Notre Dame (protocol number 19-08-5506), and the WHO Ethical Review Committee (ERC.0003185). Study staff obtained the written informed consent of parents or legal guardians of study participants for cohort participation, mosquito collectors conducting human landing catch (HLC) collections, and heads of households for product placement.

Our parallel-group, cluster-randomised, controlled trial was done in Teso North and Teso South Districts of Busia County, Kenya (appendix p 53), the county with the highest malaria prevalence in Kenya at 39%, as reported in the Kenya Malaria Indicator Survey 2020.¹⁴ The main vector control strategy implemented in the region is mass ITN distribution every 3 years supplemented with routine distribution to children and pregnant women. The main malaria vectors in this setting are *Anopheles gambiae*, *Anopheles arabiensis* and *Anopheles funestus*, all of which are resistant to multiple pyrethroid insecticides.¹⁵ Clusters were delineated by a central core area, where spatial repellent or placebo products were distributed, and a surrounding buffer area (400 m), consisting of households that received no product but were within a 300–500 m distance from the nearest household in the core area.

The study was not powered to detect a significant reduction by spatial repellents in entomological endpoints compared with placebo, which were secondary study endpoints. As previous studies suggested, entomological endpoints are subject to large variability; detecting a meaningful reduction (eg, human landing rate via HLC) would have required numbers of required clusters and households per cluster that were too large to be accommodated in this study. As such, numbers of clusters and households and sampling schemes for Centers for Disease Control light traps (CDC-LTs) and HLC collections were primarily driven by logistics and resource considerations. This trial is registered with [ClinicalTrials.gov](https://www.clinicaltrials.gov/ct2/show/study?term=NCT04766879), [NCT04766879](https://www.clinicaltrials.gov/ct2/show/study?term=NCT04766879).

Participants

Enrolment was done by the study team. Participation included census, disease surveillance (bi-weekly blood sampling based on fever history), monthly blood draws, entomological surveys, and intervention application in the house. To be eligible for enrolment, participants needed to meet inclusion criteria of age (6 months to <10 years), having slept in the study clusters for more than 90% of nights each month, with no plans for extended travel exceeding 5 weeks outside the cluster, maintaining haemoglobin concentrations at greater than 5 g/dL, not participating in another clinical trial or being on regular malaria prophylaxis, and parents or guardians providing written consent. Participants were classified as male or female on the basis of observation of birth certificates or self-reporting. Sex was not an exclusion criterion. Since artemether–lumefantrine was the first-line treatment used for malaria infection in our study, participants needed to be willing to take artemether–lumefantrine and have no history of hypersensitivity to it. Participants in the intervention period were enrolled after cluster randomisation.

Randomisation and masking

Clusters were selected in November, 2019. The entomology sampling frame was completed in November, 2019. Randomisation and intervention allocation occurred in September, 2021. All randomisation was done by an external statistician using the sample function from RStudio 2021.09.0+351.pro6 (or R version 3.6.3). Investigators, staff, and study participants were masked to cluster allocation.

A total of 60 clusters (30 per group; average 206 resident households per cluster with approximately 32 enrolled households aggregated over cluster core and buffer areas) were included in baseline malaria infection incidence monitoring. Before the intervention period, two clusters (9 and 43; appendix p 53) were removed before randomisation and treatment allocation based on outcomes from a formal, preplanned baseline analysis, which indicated zero (cluster 43) and third-lowest (cluster 9) incidence rates at baseline. Cluster 9 was excluded from the entomology sampling frame during baseline owing to the rapid urbanisation of the village; therefore baseline entomology endpoints are not affected.

In the intervention period, a total of 58 clusters (29 per group; average 205 resident households per cluster with approximately 28 enrolled households per cluster core area) were randomly assigned to ensure allocation of 58 clusters (29 spatial repellent, 29 placebo); allocation of 20 clusters (ten spatial repellent, ten placebo) for monitoring indoor adult mosquito density using CDC-LT; and allocation of 12 clusters (six spatial repellent, six placebo) for monitoring indoor–outdoor adult mosquito diversity, density, and human landing rate by use of HLCs.

Our intervention was a transfluthrin-based passive emanator (Mosquito Shield) designed and produced by SC Johnson & Son (Racine, WI, USA), as described previously.¹² Spatial repellent and placebo products had identical packaging and were deployed by trained study personnel and applied onto interior walls of enrolled houses by use of a masked coding scheme. Intervention application rate (2 units per 9 m²) and replacement schedule (28-day, with +2-day window) followed manufacturer specifications for indoor use conditions. Our

study did not withhold standard of care for clinical management of malaria or vector control interventions (eg, ITNs and indoor residual spraying) in either the spatial repellent or placebo group, but instead, these were monitored and recorded throughout the trial.

Procedures

Before enrolment, all structures were mapped and a census, including house construction characterisation, was administered.

Following consent, participants were screened for inclusion–exclusion criteria and provided with malaria parasite clearance therapy. The first scheduled follow-up visit commenced 2 weeks after clearance. If the malaria smear microscopy done on this visit was positive, participants were administered second-line treatment. During the course of treatment, participants were followed up at home by the community interviewer to monitor adherence.

Follow-up included fever history and blood sampling for microscopy diagnosis (primary endpoint) at scheduled monthly, scheduled bi-weekly, and unscheduled sick visits. Malaria infection incidence within cluster core area households was used to assess spatial repellent efficacy on first-time (primary endpoint) and overall new infections (secondary endpoint). Malaria infection incidence within cluster buffer area households was used to assess for spatial repellent diversionary effect (secondary endpoint).

CDC-LT and HLC sampling were done to measure entomological endpoints. Further details of the entomology sampling and processing are provided in the appendix (p 54).

Participants were monitored for adverse events or serious adverse events at each bi-weekly (home) and monthly scheduled clinic follow-up. Quarterly summary reports of adverse events and serious adverse events were submitted to the data safety and monitoring board (DSMB) for safety assessment based on events likely to be associated with spatial repellents.

Data collection was designed around CommCare (Dimagi, MA, USA), a tablet-based survey platform linked to a custom-built database and web portal. The data portal was constructed by use of Django+PostgreSQL for the back end and VueJS for the front end. Docker was used for containerisation and deployment. Python scripts were developed for data cleaning and analysis. Data were cleaned according to the protocol and statistical analysis plan. Data were cross-checked, identifying missing, incomplete, or suspect data submissions. Queries were relayed to the site data manager for resolution, after which data were verified, locked, and extracted for analysis.

Outcomes

Our main objective was to show and quantify the protective efficacy of spatial repellents in reducing first-time malaria infection (defined in the appendix pp 78–103), as measured by microscopy, in a cohort of children aged 6 months to younger than 10 years in cluster core areas. Secondary epidemiology endpoints were overall new malaria infections in cluster core areas (number of infections averted) and first-time and overall infections in cluster buffer areas (spatial repellent diversionary effect). Entomology endpoints were adult female anopheline: indoor, outdoor abundance; blood-fed status (proxy for human-

biting rates); parity status (proxy for age structure). Additional endpoints are outlined in [ClinicalTrials.gov](https://www.clinicaltrials.gov/ct2/show/study/NCT04766879) (NCT04766879) with outcomes reported in the appendix (pp 50–77).

Statistical analysis

Details of sample size calculations are provided in the appendix pp 78–103. Sample size and power calculations for the primary endpoint are also published.¹² The study's primary hypothesis is H_0 , spatial repellent does not have a protective effect against the first-time malaria infection compared with placebo versus H_1 , spatial repellent has a protective effect against the first-time malaria infection compared with placebo. In brief, the number of clusters per treatment group and the number of patients per cluster were established to detect a 30% reduction in first-time malaria infection (event) hazard rate by spatial repellent compared with placebo (primary endpoint). With assumptions of a baseline first-time infection HR of 3.0 per person-year and a between-cluster coefficient of variation of 48%, a total of 1056 events would be required to yield 80% power for establishing the primary hypothesis that spatial repellents reduce the first-time malaria HR compared with placebo at a 5% one-sided type-I error rate with a formal interim analysis done after 50% of the required total events were collected. To obtain 1056 events in the 2-year study with two sequential cohorts and a 35% loss to follow-up rate, each cohort during the intervention period was followed up for 1 year with 29 clusters per treatment and 28 households (one patient per household) per cluster. The study design included two sequential cohorts (cohort 1 and cohort 2) during the intervention period to mitigate participant fatigue and loss to follow-up. Regarding the secondary hypothesis H_0 , spatial repellent does not have a protective effect against new malaria infections compared with placebo versus H_1 , spatial repellent has a protective effect against new malaria infections compared with placebo, given there was no planned interim analysis and the endpoint often has a smaller coefficient of variation and larger protective efficacy, it was expected that the sample size requirement for the primary hypothesis would establish the secondary hypothesis with greater than 80% power at a 5% one-sided type-I error rate.

The detailed analytical approach is provided in the appendix (pp 78–103). Data analyses were done with SAS version 9.4 and RStudio 2023.12.0.

The primary hypothesis on protective efficacy of spatial repellents against first-time malaria infection was tested by comparing the event hazard rates in cluster core areas between spatial repellent and placebo in the intention-to-treat population. The complementary-log-log (cloglog) regression was used to model interval-censored time to event data (collected every 2 weeks) and estimate the hazard ratio between spatial repellent and placebo with a proportional hazard assumption.^{16,17} Besides the treatment group (spatial repellent vs placebo) and visit (bi-weekly), the cloglog model also contained individual-level, household-level, and cluster-level covariates as fixed effects (eg, age, sex, number of doors, number of windows, open or closed eaves, roof type, baseline malaria infection incidence rate, and cluster population size, etc), and two independent zero-mean normally distributed random effects of cluster and of patient nested within cluster. The null hypothesis of protective efficacy is 0%, against the alternative hypothesis of protective efficacy is greater than 0%, was tested by the lower one-sided Wald test.

The study adopted a group sequential design with one formal preplanned interim analysis of the primary endpoint when 50% of the required events were collected. Decision boundaries for interim and final looks at data were calculated for non-binding stopping for futility or efficacy by use of the O'Brien–Fleming error spending function.^{18,19}

The secondary hypothesis on protective efficacy against overall new malaria infections was tested by comparing hazard rates of the overall malaria infection in core areas between spatial repellent and placebo in the intention-to-treat population by use of a similar cloglog model as above. When establishing which positive malaria infection in a patient was new or a carry-over case from a preceding malaria infection, we applied rules such as whether and when a patient with positive malaria diagnosis received antimalarial treatment and whether two positive diagnoses were separated by a negative diagnosis, and factored in a 14-day protection (risk-free) period following anti-malarial treatment.

For both the primary and secondary hypotheses above, although prespecified as one-sided, two-sided 95% CIs and p values were provided, per the request of the reviewers, alongside the prespecified one-sided 95% CIs and p values.

In addition, we estimated spatial repellent protective efficacy against first-time and new infections by removing all fixed-effect baseline covariates from cloglog models. We also calculated protective efficacy of spatial repellent against first-time and overall infections by age group (<6 years old vs ≥6 years old at enrolment) via similar cloglog models.

To assess diversion effect of spatial repellent on malaria infections, similar cloglog models were applied to data collected from cluster buffer zones. The study did not have a formal hypothesis on diversion effect. The required household sample size (40 per cluster) in buffer areas was established to provide sufficient statistical precision to compare the hazard rates between spatial repellent and placebo.

There were minimal missing values in the covariates used in the cloglog models, except for household characteristics related to the number of windows, occurring in approximately 1·4% of households in the core zones and approximately 0·14% in the buffer zones. Given this low missing fraction and the missingness was probably completely random,²⁰ cases with complete household covariate information were used in the models.

Summary statistics were provided for all the prespecified entomological endpoints, including CDC-LT anopheline density, anopheline human landing rate, sporozoite positivity rate, entomological inoculation rate, anopheline female parity rate, and blood-fed rate. Model-based analysis that accommodates the longitudinal nature of the collected data was also done, as applicable, to examine the entomological effects of spatial repellent compared with placebo. Detailed description of the statistical methods can be found in the appendix (pp 78–103).

Total numbers of adverse events and serious adverse events by symptom, frequency, and percentage of patients who had at least one episode of adverse event or serious adverse event, were summarised for both baseline and intervention periods, by treatment (spatial repellent, placebo), and cluster area (core, buffer), respectively.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or submission of paper.

Results

A total of 5716 participants were enrolled (figure 1; 6120 sample size target). A total of 1935 participants were enrolled across 60 clusters for follow-up during baseline (2040 sample size target; 20 per cluster core; and 14 per cluster buffer area). During the intervention period, a total of 3781 patients were enrolled for follow-up across 58 clusters (2040 sample size target; 14 per cluster core; and 20 per buffer area, for each cohort 1 and cohort 2). Each cluster included a baseline cohort, cohort 1, and cohort 2. Participants enrolled at baseline were eligible to participate in cohort 1 or cohort 2, but those who participated in cohort 1 were ineligible for cohort 2.

Baseline patient recruitment, screening, and enrolment commenced on March 1, 2021 (figure 2). The 4-month baseline occurred between April and July, 2021, followed by two, 1-year intervention periods from October, 2021 to October, 2022 (cohort 1), and from October, 2022 to October, 2023 (cohort 2). Before the start of baseline, Busia County received pyrethroid-only ITNs (Permanet 2.0, Vestergaard Sarl, Lausanne, Switzerland) in 2018. A mass campaign with pyrethroid plus piperonyl butoxide ITNs (Olyset Plus, A to Z, Arusha, Tanzania) was done in July–August, 2021 achieving coverage of up to 98% in the study area. During the course of the study, there was no indoor residual spraying campaign in Busia County. Intervention deployment commenced on October, 2021, 2 weeks before clearance.

Patient retention rate was 94·7% in the spatial repellent group and 94·1% in the placebo group. Baseline participant characteristics from the intention-to-treat population (cluster core, primary endpoint) were balanced between the spatial repellent and placebo groups at individual, household, and cluster levels (table 1). ITN usage was balanced between groups.

Cluster-level product coverage rate per cluster (percentage of household structures in a cluster that received at least one product during the intervention) was approximately 77·0% on average for both the spatial repellent and placebo groups on the basis of interim data (range 58·4–92·0% in the spatial repellent group; 64·6–90·7% in the placebo group) and was approximately 84% on the basis of the final data (range 73·4–92·6% in the spatial repellent group; 76·9–90·4% in the placebo group). The average household-level product application rate fluctuated from approximately 82·0% to 100% in the spatial repellent group and approximately 76·0% to 100% in the placebo group (appendix p 60).

The estimated protective efficacy of spatial repellents against first-time malaria infection relative to placebo from the intention-to-treat cohort population (cluster core areas) at the interim timepoint (table 2) was 33·4% (95% two-sided CI 11·1–50·1; one-sided $p=0·0029$ and two-sided $p=0·0058$). The one-sided p value was smaller than the prespecified cutoff one-sided p value 0·0088 at the interim, providing confirmatory evidence that spatial repellents reduce first-time malaria infection hazard rates compared with placebo in Kenya.

Despite these positive results at the interim, the study continued epidemiological and entomological data collection on endpoints per study protocol without inflation of the type-I error rate as efficacy was already established at the interim.

The estimated protective efficacy of spatial repellents against first-time malaria infection from the intention-to-treat cohort population based on final data (table 2) to the trial's end was 32.7% (95% CI 12.6–48.2; one-sided $p=0.0015$ and two-sided $p=0.0030$). The one-sided p value was smaller than the prespecified cutoff of 0.047 for the final look per the O'Brien–Fleming error spending function,^{18,19} further confirming the conclusion regarding the significant protective efficacy of spatial repellents compared with placebo established at interim. The time profiles of the incidence rate during the intervention also show the protective efficacy of spatial repellents against first-time malaria infection through the study (figure 3).

The protective efficacy of spatial repellents against overall new malaria infections relative to placebo was 32.1% (95% CI 15.9–45.2; $p=0.0004$) based on interim data and 29.5% (12.0–43.5; $p=0.0020$) based on final data. Protective efficacy estimates from the models without the baseline covariates ranged from 33.2 to 36.3%, depending on datasets (interim *vs* final) and the endpoint type (first-time *vs* new infections; appendix p 55). We estimate that about 60 malaria overall new infections can be averted for every 100 people per year by use of the product.

Regarding diversion effect, spatial repellents reduced first-time malaria infection in treatment cluster buffer zones by 27.7% (95% CI 9.9 to 41.9) compared with placebo and cumulative infections by 23.0% (4.8 to 37.6) at interim. In the final analysis, the malaria hazard rate as measured by first-time infection was reduced by 26.8% (9.9 to 40.6) in intervention cluster buffer zones. Overall infections were reduced by 16.5% (–1.5 to 31.4%; appendix p 55).

The results suggest spatial repellents had a numerically stronger protective efficacy in older children (≥ 6 years) versus younger (< 6 years) with considerable overlaps between 95% CIs of protective efficacy between the two groups, regardless of data type (interim or final) and infection type (first-time or new infections). We added the age-by-treatment interaction term to the primary cloglog models that evaluate protective efficacy of spatial repellents against first-time and overall infections, and no significant interaction was detected between age group and treatment at the 5% significance level (appendix pp 61–62).

There was no significant intervention effect on entomological endpoints on the basis of aggregated anopheline species abundance, blood-fed rate, sporozoite infectivity rate, or parity rate, in either interim or final datasets, although some numerical effects were observed (appendix pp 62–75). On the basis of WHO susceptibility thresholds ($> 98\%$ mortality), resistance to permethrin was observed in all assessed anopheline samples, as expected (appendix pp 104–08). Resistance to transfluthrin was observed from assays done with *A. gambiae* sensu lato from sampled clusters, but no greater than that seen during baseline.

Among observed adverse event symptoms, cough and running nose were the top two symptoms in both occurrences and percentage of patients who had at least one episode of the

symptoms during both baseline and intervention periods, for both treatment groups, and for both core and buffer areas. Other observed symptoms include headache, skin irritation–rash, abdominal discomfort, nausea–vomiting, diarrhoea, eye irritation, and others (eg, dental cavity). Difficulty breathing and severe malaria related symptoms (eg, unconsciousness–drowsiness, convulsions–seizures, dark urine) were regarded as serious adverse event symptoms and occurred rarely (<0.5% of observed adverse event symptoms). A total of three patient deaths occurred (two during the intervention period: one complicated malaria, one unknown cause). There were no unexpected, implausible, or extreme adverse events or serious adverse events reported during the trial; patterns were consistent with disease frequency expected in study communities. No reported adverse events or serious adverse events were deemed associated with spatial repellents (appendix pp 109–36), and the DSMB found no significant safety concerns for spatial repellents.

A total of 58 unused (from on-site storage) and 78 used products (taken from a subsample of study households from both groups at time of replacement) were analysed in 2024. All unused placebo products (n=29) tested negative for transfluthrin, whereas average transfluthrin quantity from all unused spatial repellent products (n=29) was 103.0 mg (SD 2.1), within the specification range (93.5–126.5 mg). All 78 used products had residual transfluthrin.

Discussion

Despite scale-up of control efforts, malaria continues to be a global burden.² There is, therefore, a growing unmet need for additional, complementary, and effective malaria prevention strategies.⁵ Although the mass piperonyl butoxide ITN campaign done by the National Malaria Control Program in study clusters (before intervention implementation) contributed to a reduction in malaria infection incidence observed during the intervention period, our trial showed that a transfluthrin-based spatial repellent product further reduced malaria infection incidence in an area of western Kenya characterised by high malaria transmission, efficient vectors, insecticide resistance, and universal coverage of ITNs. Outcomes from this trial satisfy one of two trials required by WHO for assessing spatial repellent public health value and developing global health policy for the spatial repellent intervention class.

Although not significant, the numerical protective efficacy against overall new infection was higher in the older participant group. Older children may have different behavioural practices than younger children in relation to malaria risk that could help to explain differences in protective efficacy. Analysis of data from social science research will provide complementary information on night-time activities and net use which, in addition to baseline findings,^{21,22} might further refine our understanding of trial results. Data generated in this study will also be used to inform the cost-effectiveness of spatial repellent deployment.²³

There are several considerations regarding the lack of significant differences between spatial repellent and placebo for entomology endpoints. First, the study was not powered to detect significant effects of entomological endpoints due to the large number of clusters required,

which was restrictive for study implementation. For example, assuming 60% inter-cluster coefficient of variation, and average baseline density of 15 mosquitoes per collection, to detect a 30% decrease by spatial repellent compared with placebo, we would have had to assign 49 clusters and sampled 20 households per cluster. There were observed numerical decreases by spatial repellent compared with placebo in indoor anopheline density in the HLC (15% and 29% based on interim and final data, respectively) with 95% CIs (−66 to 115) based on interim data and (−70 to 66) based on final data, suggesting large uncertainty around direction and magnitude of the effect of spatial repellent on indoor anopheline density. Similar trends were observed for other entomological endpoints such as CDC-LT anopheline density, parity rate, and abdominal status. Although the lack of a quantifiable effect on entomological indices is also probably due to the complex mode of action of spatial repellents, the efficacy of transfluthrin-based spatial repellents in this area of high pyrethroid resistance points to their potency and potential contribution to insecticide resistance management. Entomological methods employed in our trial were based on approaches to spatial repellent evaluation in semi-field studies (HLC)⁷, and programmatic use (CDC-LT) but CDC-LT might be unsuitable for the evaluation of spatial repellent given the phototoxic effect induced by spatial repellent.²⁴

Based on patient responses (yes or no) to the question “did you sleep under the bednet last night” at each follow-up during the intervention period, the ITN coverage rate during the intervention period was 99.62% and 99.75% based on interim data for the placebo and spatial repellent groups, respectively, and was 99.53% and 99.69% based on final data for the placebo and spatial repellent groups, respectively.

Therefore, the established significant protective efficacy of spatial repellent indicates that it provides additional reduction in malaria hazard rate beyond the protection offered by ITN. In addition, reductions in hazard rate of first-time and overall infections in households neighbouring those receiving spatial repellent products compared with those receiving placebos indicate a lack of diversionary effect. The reduction in incidence observed in neighbouring villages indicates that at high coverage, spatial repellents might offer benefit, as has been observed previously in trials of ITNs.²⁵

Results from this trial will contribute evidence of spatial repellent public health value for consideration of spatial repellent inclusion in National Malaria Control Programs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing

De-identified analytical datasets, including de-identified participant data, data dictionaries, and analytical codes, will be made available with publication on request to FL (at fang.liu.131@nd.edu).

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Research in context

Evidence before this study

We searched the National Library of Medicine PubMed database on June 12, 2024 using the search term “malaria” in combination with: “Spatial Repellents” (93 publications), “clinical trial” AND Kenya (408 publications), “vector control” (4,070 publications) and “vector control” AND Kenya (319 publications) as well as the search term “spatial repellent” in combination with “vector control” and Kenya (15 publications) with no restrictions on date or language. Of the resulting 4905 identified publications, the majority (4389) represent studies of vaccines, drugs, modelling, mosquito diversity and identification, insecticide resistance, and vector control interventions other than spatial repellents (bednets, indoor residual spraying, transgenic mosquitoes), of which 319 were done in Kenya. A total of 93 publications were associated with spatial repellents and malaria, of which 14 were done in Kenya. These publications predominantly focus on semi-field or small-scale, open-field experiments assessing the effect of spatial repellents on reducing mosquito–human contact based on entomology endpoints. One study assessed entomology indicators to evaluate the efficacy of a spatial repellent as a so-called push–pull intervention (in combination with an outdoor trap) to reduce mosquito–human contact. There were two reviews on mosquito repellents for malaria prevention. There were three published protocols of ongoing or upcoming clinical trials evaluating the effect of spatial repellents on human mosquito-borne disease infection. This includes one protocol of the current Kenya study and one trial done in Mali against malaria, which is yet to publish outcomes. The third protocol is associated with a study evaluating spatial repellent efficacy against *Aedes*-borne virus human infection in Sri Lanka, that is ongoing. There was only one rigorously designed cluster-randomised controlled trial from China evaluating a spatial repellent against malaria associated with published epidemiology outcomes. Six studies evaluated community participation or mobilisation strategies for malaria vector control specific to Kenya (of 140 globally). Thus, our search revealed no existing outcomes from a cluster-RCT study design evaluating spatial repellent efficacy against human malaria infection in Africa, specifically Kenya.

Added value of this study

Our trial provides the first evidence of the protective efficacy of a spatial repellent, in this case a transfluthrin-based product, to reduce risk of malaria infection in an African setting characterised by high malaria transmission, pyrethroid resistant malaria vectors, and high coverage of long-lasting insecticidal nets. Results support spatial repellents as a beneficial component to malaria disease prevention.

Implications of all the available evidence

Despite the years of investment and efforts, progress in reducing the burden of malaria has stagnated. There is, therefore, a growing unmet need for additional, complementary, effective malaria prevention strategies. Spatial repellents, a new option for efficient deployment, are products designed to decrease human exposure to malaria by releasing active ingredients into the air that disrupt mosquito–human contact. Spatial repellents have been used for prevention of insect bites, and there exists a body of evidence of

spatial repellents efficacy in reducing human–vector contact. Clinical trials have shown significant epidemiological efficacy against *Aedes*-borne viruses in Peru but inconclusive outcomes against malaria in Indonesia. For the first time, we show protective efficacy of a spatial repellent product to reduce the risk of malaria infections in Africa, which has infrequent mild adverse effects, and no serious adverse events. Considering the continued malaria public health threat, our trial results are, we believe, a public health milestone that will benefit malaria prevention programmes and encourage additional vector control intervention assessments, including spatial repellents.

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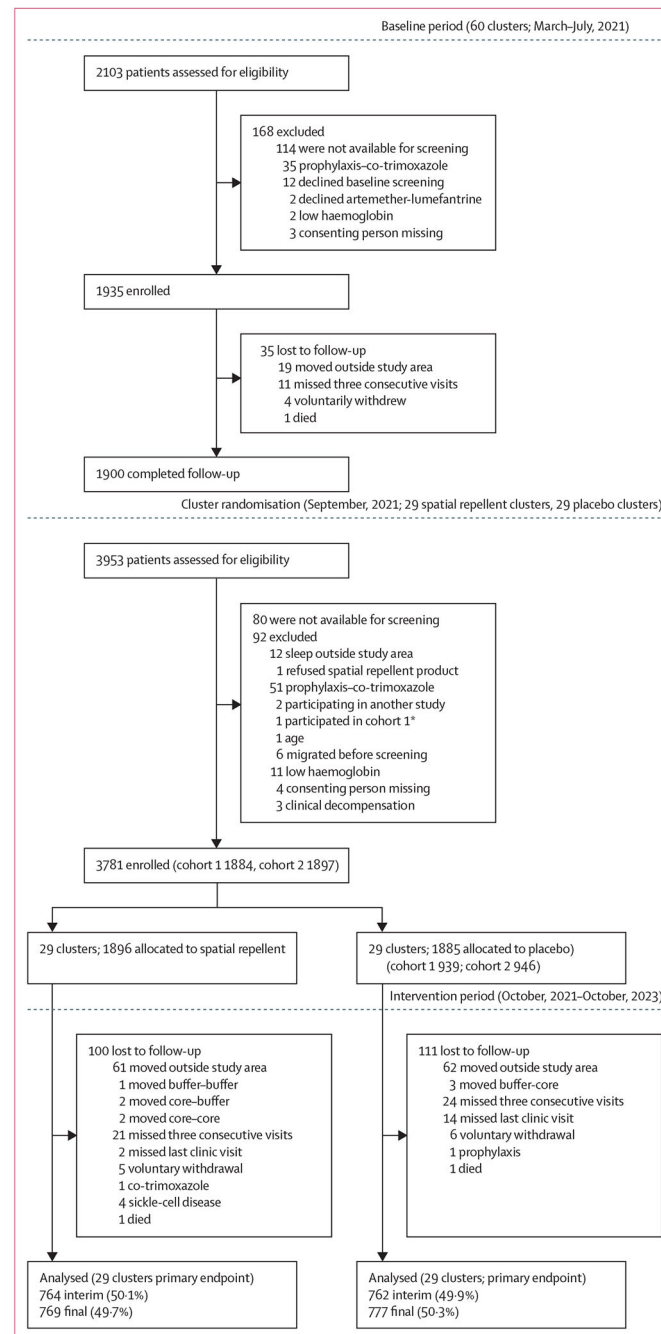


Figure 1: Trial profile

Enrolment and follow-up of the baseline cohort (aggregated participant populations from cluster and buffer area), and allocation and follow-up of the intervention cohort (aggregated cohort 1 and cohort 2 participant populations).

*For cohort 2 eligibility.

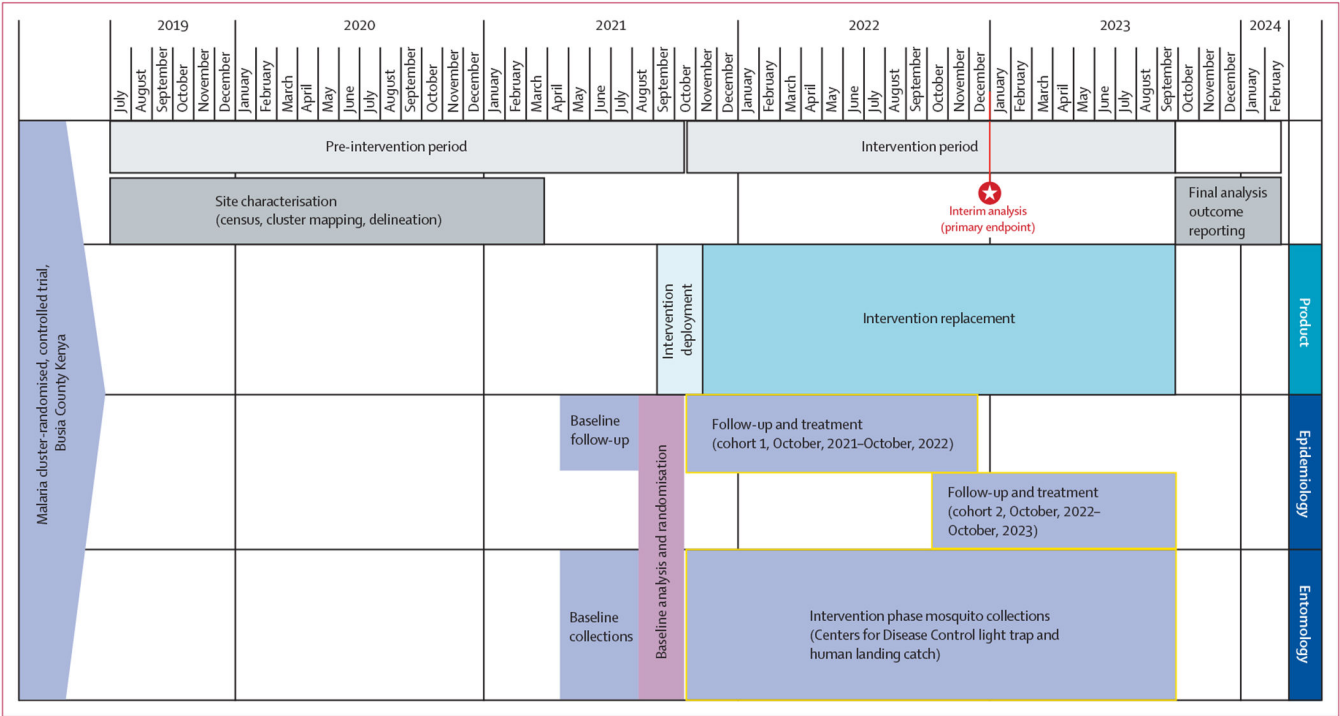


Figure 2:
Study activity timeline

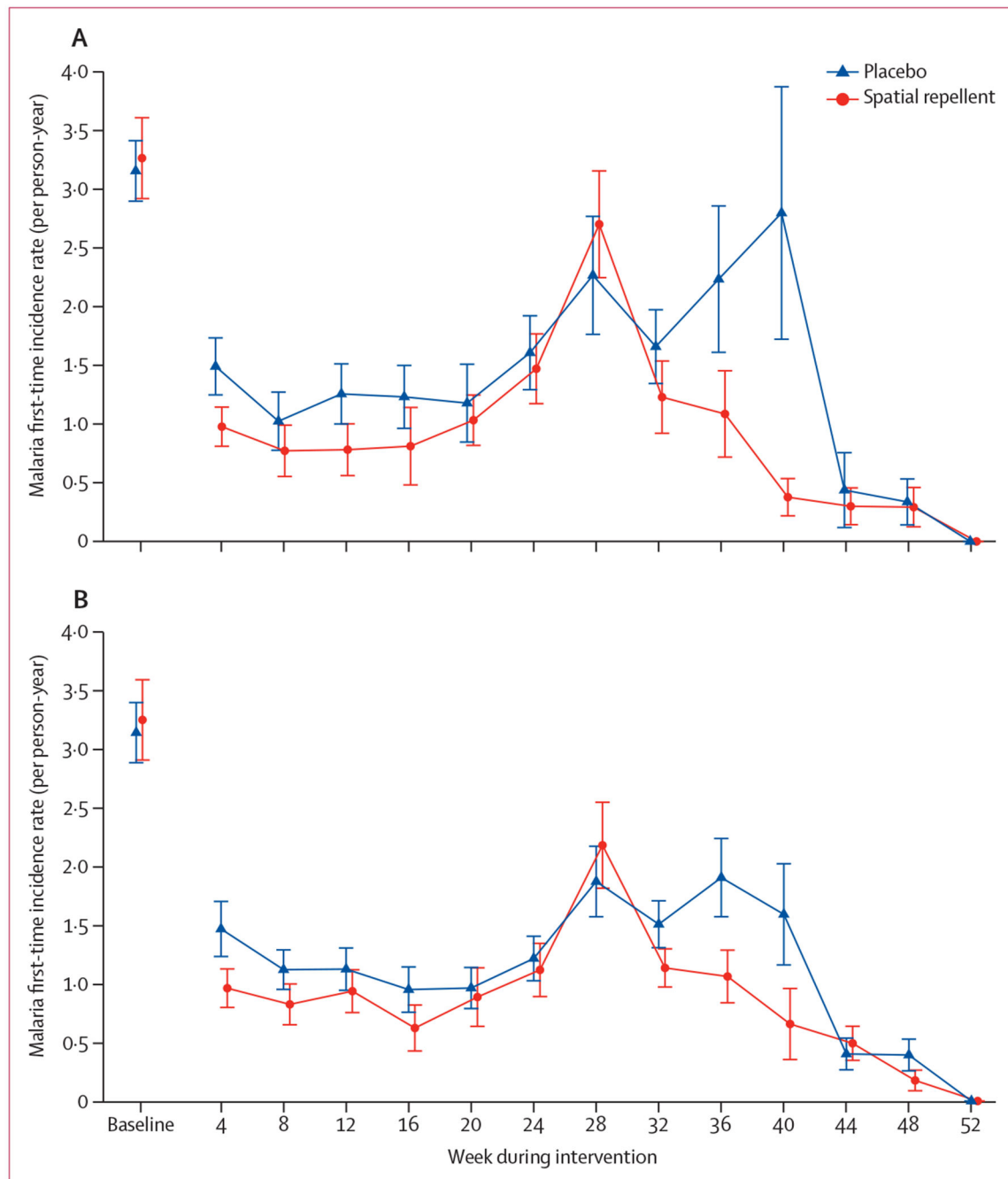


Figure 3: Malaria incidence rates

(A) Interim data. (B) Final data. Mean (SE) of the incidence rate of the first-time malaria infection (primary endpoint) for 29 spatial repellents and 29 placebo clusters in participants from cluster core areas at interim and at the end of the intervention period. The numbers of patients at risk for the first-time infection at each timepoint are presented in the appendix (p 61) for the spatial repellent and placebo groups.

Table 1:

Baseline characteristics

	Interim timepoint		Final data	
	Spatial repellent	Placebo	Spatial repellent	Placebo
Patient level [*]				
Age, years at enrolment, mean (SD); (min, max)	5·5 (2·6); (1·1, 10·9)	5·8 (2·6); (1·2, 10·9)	5·5 (2·6); (1·1, 10·9)	5·8 (2·6); (1·2, 10·9)
Sex				
Male	47·1%	47·6%	47·1%	47·1%
Female	52·9%	52·4%	52·9%	52·9%
Household level				
House wall type, mud, %	78·9%	82·4%	78·9%	82·4%
House wall type, bricks and cement, %	20·4%	16·4%	20·4%	16·5%
House roof type, corrugated iron, %	81·9%	84·0%	81·5%	83·9%
House roof type, grass thatch, %	17·8%	15·6%	18·2%	15·7%
Open eaves, yes, %	69·5%	68·8%	69·6%	69·0%
Number of doors, mean (SD); (min, max)	1·07 (0·27); (1, 4)	1·06 (0·24); (1, 3)	1·07 (0·27); (1, 4)	1·06 (0·24); (1, 3)
Number of windows, mean (SD); (min, max)	2·32 (1·72); (0, 14)	2·32 (1·63); (0, 20)	2·32 (1·72); (0, 14)	2·33 (1·64); (0, 20)
Number of glass windows, mean (SD); (min, max)	1·02 ± 1·84 (0, 13)	0·81 ± 1·63 (0, 9)	1·03 ± 1·85 (0, 13)	0·82 ± 1·65 (0, 9)
Number of screen windows, mean (SD); (min, max)	0·42 (1·36) (0, 13)	0·38 (1·13) (0, 8)	0·42 (1·36) (0, 13)	0·39 (1·17) (0, 9)
Number of wooden windows, mean (SD); (min, max)	1·84 (1·88); (0, 14)	1·64 (1·66); (0, 9)	1·85 (1·89); (0, 14)	1·65 (1·68); (0, 9)
Cluster level [†]				
Cluster population mean (SD); (min, max)	777·3 (55·9); (694, 918)	770·1 (60·3); (657, 865)	777·3 (55·9); (694, 918)	770·1 (60·3); (657, 865)
Baseline first-time 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)	3·266 (1·846); (0·9, 7·7)	3·138 (1·381); (1·1, 6·9)

Baseline characteristics for participants from the intention-to-treat cohort population (cluster core areas) in the spatial repellent and placebo groups. One patient per household was recruited; the numbers of patients and households are the same.

^{*} Interim timepoint: spatial repellent, n=764; placebo, n=762; final data: spatial repellent, n=769; placebo, n=777.

[†] Interim timepoint: spatial repellent, n=29; placebo, n=29; final data: spatial repellent, n=29; placebo, n=29.

Table 2:

Summary of protective efficacy estimates

	Number of patients	Number of first-time infections	Person-years	Incidence rate per person-year (SE)	Hazard ratio* (95% one-sided CI) (95% two-sided CI) [†]	Protective efficacy [‡] , % (95% one-sided CI) (95% two-sided CI) [†]	One-sided and two-sided p values
Interim data							
Spatial repellent	764	233	234	1.00 (0.088)	0.67 (0–0.85)	33.4% (15.2–100)	0.0029
Placebo	762	297	216	1.38 (0.130)	(0.50–0.89)	(11.1–50.1)	0.0058
Final data							
Spatial repellent	769	392	456	0.86 (0.071)	0.67 (0–0.84)	32.7% (16.2–100)	0.0015
Placebo	777	482	413	1.17 (0.108)	(0.52–0.87)	(12.6–48.2)	0.0030

Summary of protective efficacy estimates from patient data for intention-to-treat analyses (cluster core areas) for the spatial repellent intervention against first-time malaria infection measured by microscopy (primary endpoint) including covariate effects.

* Obtained from the complementary-log-log (grouped proportional hazard) model.

[†]The primary hypothesis on the protective efficacy of spatial repellent against the first-time infection is one-sided per the study protocol and the prespecified statistical analysis plan (the rationale for using the one-sided is provided in the appendix pp 137–38). The reviewers suggested presenting two-sided 95% CI and two-sided p value as the primary results in the main text. Whether one-sided or two-sided, there is confirmatory evidence on the protective efficacy of spatial repellent against the first-time malaria infection.

[‡]Protective efficacy=(1 – hazard ratio) × 100%.