Community-level impacts of spatial repellents for control of diseases vectored by *Aedes aegypti* mosquitoes

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Abstract

Spatial repellents (SRs) reduce human-mosquito contact by preventing mosquito entrance into human-occupied spaces and interfering with host-seeking and blood-feeding. A new model to synthesize experimental data on the effects of transfluthrin on *Aedes aegypti* explores how SR effects interact to impact the epidemiology of diseases vectored by these mosquitoes. Our results indicate that the greatest impact on force of infection is expected to derive from the chemical's lethal effect but delayed biting and associated negative feedbacks on the vector population could elicit substantial impact in the absence of lethality. The relative contributions of these effects depend on coverage, chemical dose, mechanism of action, and housing density. We also demonstrate potential adverse impacts of increased partial blood-feeding and reduced exiting, which could offset gains achieved by other effects. Our analysis demonstrates how small-scale experimental data can be leveraged to derive expectations of epidemiological impact of SRs deployed at larger scales.

Introduction

Recent decades have seen significant progress in reducing the burden of malaria, in part due to the success of insecticide treated nets (ITNs) (1). Public health successes of vector control have also been achieved for dengue and yellow fever, but none of these successes were sustainable (2). The continued expansion of dengue virus (DENV) and others transmitted by *Aedes aegypti* (2)—combined with setbacks in the development of effective vaccines for dengue and Zika (3)—underscores the growing need for more effective vector-based strategies for controlling these diseases.

Spatial repellents (SRs) are one of many vector control tools currently being evaluated for their potential public health value. SRs consist of products aimed at reducing contact between humans and mosquitoes by preventing mosquito entrance into human-occupied spaces, interfering with the detection of humans, or disrupting the blood-feeding process (4). The effectiveness of SR products has been demonstrated in entomological studies against a range of vector species (5, 6) and has also been indicated in epidemiological studies of malaria (7, 8). Meanwhile, diversion of mosquitoes to untreated houses was found to offset beneficial community-level effects in some studies (9, 10) but this is thought to be outweighed by the beneficial effects in other studies (11, 12).

Spatial repellency constitutes a range of effects distinct from other chemically induced effects, such as contact irritancy and lethality (4). Most compounds exhibit a combination of these modes of action (13): *i.e.*, repellency or deterrency (preventing entry), irritancy or expellency (promoting exit), reduced biting, and lethality (Fig. 1). In addition, excitatory effects can promote adverse behaviors, such as reduced exiting or increased probing, wherein hyper-agitated mosquitoes remain in treated spaces and attempt multiple, partial blood meals prior to full engorgement and oviposition (14). At the same time, these behaviors can also lead to delayed oviposition or increased mortality associated with host contact during blood feeding. Similarly, reduced exiting does not necessarily result in an increased probability of blood feeding at a particular house, as it may be accompanied by reduced blood feeding due to sensory overstimulation (6).

How the balance of these (species-specific) effects influences the public health value of SRs is likely to depend on details of the product's formulation; e.g., the active chemical ingredient and its dosage (13). Furthermore, public health value at the community level may differ substantially across settings with different types of housing structures and densities, outdoor and indoor mosquito predators, and with other ongoing vector control efforts, among other factors. The interplay of these effects complicates projections of the epidemiological impact of SRs and other vector control products that exert multiple effects on mosquito behavior and bionomics.

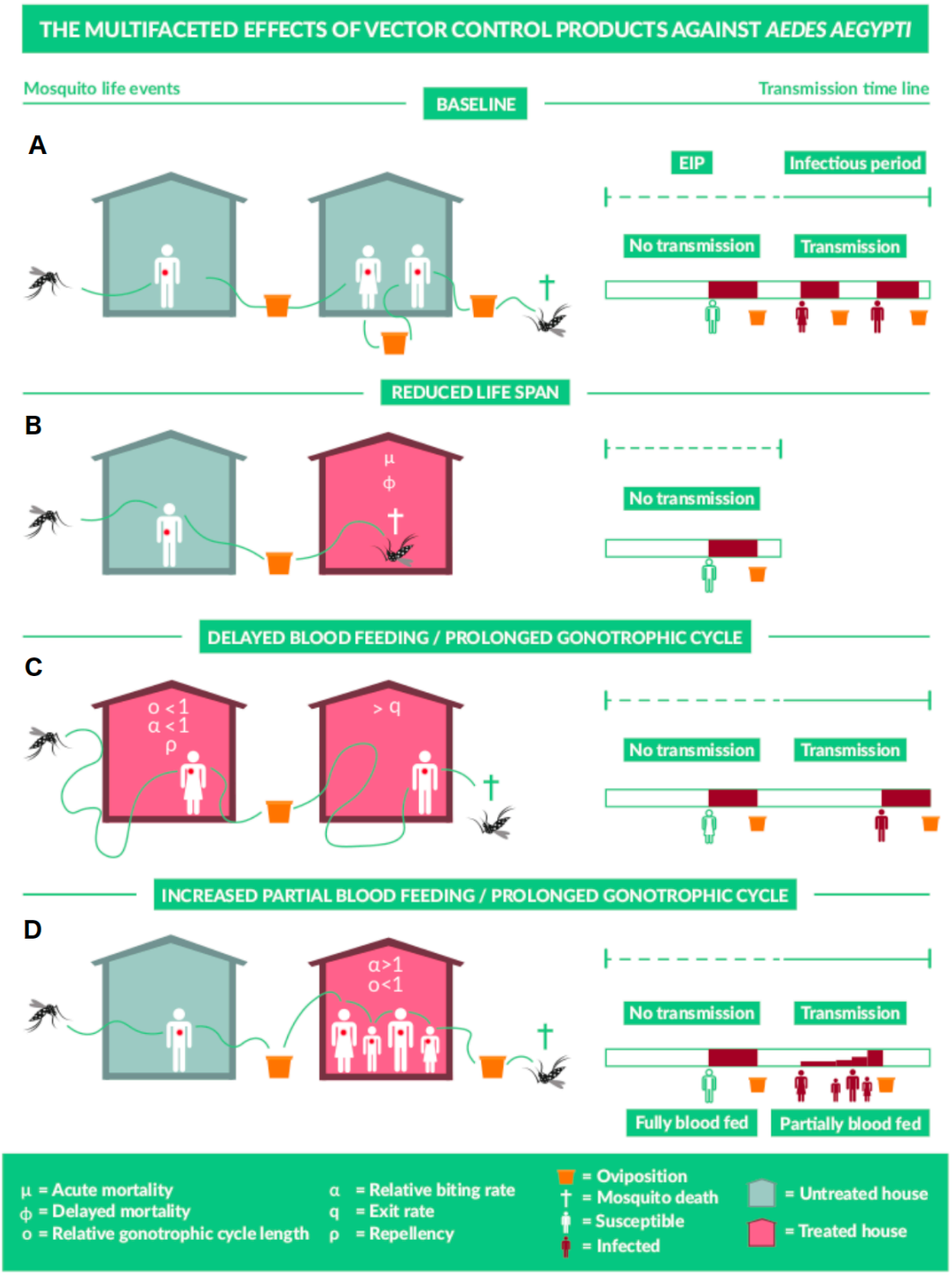

Fig. 1. Multiple effects SR products on mosquito behavioral and bionomic traits and impact on mosquito-borne pathogen transmission. Each row presents a potential scenario of mosquito life events after it has become infected, in the absence (top row) or presence (other rows) of SRs. On the left, flight behavior in search for blood meals or oviposition sites (containers) is depicted in untreated (gray) and treated houses (pink). On the right, the mosquito's life span after human-to-mosquito transmission is shown, with duration of the extrinsic incubation period (EIP) (dashed green line) and infectious period (solid green line). Blood meals (full or partial) may result in mosquito-to-human transmission (red human) following the EIP, but not before (white humans). Once a mosquito is fully blood-fed, it searches an oviposition site, after which the next gonotrophic cycle starts. Scenarios presented from top to bottom: A) baseline in absence of the SR, B) reduced mosquito life span resulting from lethality effects of the SR (μ or ϕ), C) reduced blood feeding and prolonged gonotrophic cycle resulting from repellency (ρ), excitatory effects (α and o), and expellency, and D) increased blood feeding and prolonged gonotrophic cycle due to increased partial blood feeding (α) but prolonged time until fully blood-fed (o).

Examining the many possible combinations of effects that different products have and addressing their context-specificity in epidemiological field trials would be extremely costly, if not altogether unfeasible. Modeling has therefore been used to sharpen understanding of the epidemiological impact of combinations of effects of other vector control tools for malaria, such as insecticide-treated nets (ITNs) (15, 16) and attractive toxic sugar baits (17). Insights have been gained on both the individual- and community-level impact of various products and combinations thereof (18, 19), including explorations of circumstances with adverse diversion effects (15), impacts on insecticide resistance (19-21), and product decay (21).

In contrast to the focus of previous modeling work on malaria, we developed a model of SR product impact specifically for diseases vectored by *Ae. aegypti*. Our model considers a broad range of acute and delayed effects, including repellency (decreased entry) and expellency (increased exit), excitatory effects on biting, distinguishing probing from time until oviposition, and examining the context specificity of epidemiological impact. For consistency, the product effect is hereby referred to as 'lethality' (chemical toxicity) and the bionomic effect as 'mortality' (to include both lethality and hazards due to transit). We informed the model with data from small-scale entomological experiments of transfluthrin on *Ae. aegypti* behavior and bionomics. Because these experiments used differing means of application or delivery of transfluthrin, this work does not constitute a projection of the epidemiological impact of a singular product formulation. However, these data demonstrate how this model can be used to estimate the relative change in DENV force of infection brought about by a product with such properties introduced into a community at a given coverage.

Results

Product effects

Exposure to transfluthrin resulted in increased time until fully blood-fed and an increased propensity for partial blood feeding.

We performed experiments to estimate the effect of exposure to low (8.4×10^{-7} g/L) and high (12.6×10^{-7} g/L) dosages of transfluthrin on the rate at which mosquitoes took blood meals. We distinguished partial and full blood meals. Contrary to a full blood meal, a

single partial blood meal did not lead to full engorgement and thus required further feeding attempts.

Both full and partial biting rates (a) (Table 1) were affected significantly upon exposure to the experimental dosages of transfluthrin in comparison to estimates from the control (full: $P=1.6x10^{-2}$, partial: $P=6.3x10^{-17}$, t-test, df = 24) (Table 2). The average time until blood feeding was increased by 22% (95% highest density interval HDI: 12-30) after exposure at low dosage and by 31% (HDI: 16-46) at high dosage (Fig. 2). This result was largely driven by a reduction in the rate at which full blood meals were taken, with the average time until a full blood meal increasing relative to the control by 45% (HDI: 33-58) (low) and 75% (HDI: 52-97) (high). Part of this reduction in the rate at which full blood meals were taken was offset by an increase in partial blood meals (probing effect), but not enough to result in a net increase in blood-feeding rate. The partial blood-feeding rate increased in response to exposure by 17% (HDI: 4-29) (low) and 24% (HDI: 6-40) (high) relative to the control. The probability of blood feeding over time extrapolated by dosage was derived using eqns. S3 and S5 (Fig. 2). We parameterized the biting rate (a_C) to be a fraction α of 0.82 (HDI: 0.76-0.89) (low) and 0.77 (HDI: 0.68-0.89) (high) and the oviposition rate (o_C) a fraction 0.69 (HDI: 0.63-0.75) (low) and 0.57 (HDI: 0.50-0.66) (high) (Table 2).

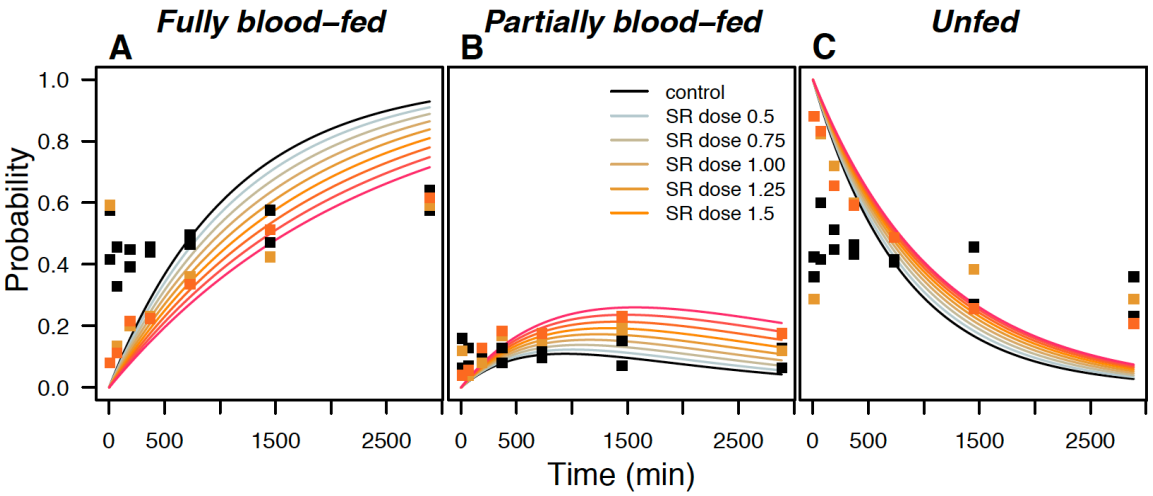

Fig. 2. Dose effect of an experimental SR product containing transfluthrin on the probability of blood feeding over time. (A) fully blood-fed, (B) partially blood-fed, and (C) unfed *Aedes aegypti* mosquitoes. SR dose is relative to the low dosage regimen of 8.4x10-7 g/L.

Exposure to transfluthrin resulted in both acute and delayed mortality.
We performed experiments to estimate the effect of exposure to low ($8.4x10^{-7}$ g/L) and high ($12.6x10^{-7}$g/L) dosages of transfluthrin on mosquito mortality. We distinguished two product effects: 1) acute lethality (μ), which occurs within a relatively short timeframe after exposure, and 2) delayed lethality (ϕ), where lethal product effects have a prolonged effect on mosquitoes and eventually result in shorter life spans compared to unexposed mosquitoes.

Deaths that occurred during the first day of the lethality experiments showed that there was a significant effect of transfluthrin, and its dosage, on the probability of mortality shortly after exposure to the SR (μ) ($P=2.8x10^{-14}$, t-test, df=74) of 8% (HDI: 5-11) (low) and 38% (HDI: 28-49) (high) (Table 2).

Deaths that occurred after the first day showed a significant effect of transfluthrin, and its dosage, on what we regarded in our model as delayed lethality (ϕ) ($P=3x10^{-9}$, LRT, df=1, $\chi^2=35.16$) (Table 2), with mean time until death reduced by 71% (HDI: 64-79) at low dosage and 60% (HDI: 51-70) at high dosage. Although these results are based on an assumption of exponentially distributed time until death, estimates of ϕ based on alternative parametric models with different assumptions about time-varying hazards of mortality were similar (Table S2).

Exposure to transfluthrin resulted in reduced entry to and exit out of treated spaces. We performed experimental hut studies to measure the effect of exposure to low ($0.0025g/m^2$) and high ($0.005g/m^2$) dosages of transfluthrin on rates of entrance into treated spaces (repellency) and exit out of treated spaces (expellency).

Repellency (ρ) was highest at a low dosage of transfluthrin, with a median proportion of 19% (HDI: 3-36%) of mosquitoes being deterred by the product and opting to move away from rather than towards the treated hut. Repellency was lower at the higher dosage of transfluthrin, with a median of 8% repellency (HDI: -9-25%) (Fig. S3A). The mosquitoes that did enter the treated hut were estimated to have exited at a lower rate, suggesting disorienting hyperactivity responses of transfluthrin in the experimental hut study. At low dosage, median exit rates (q_T) were a factor 0.70 (HDI: 0.41-0.1.09) relative to exit rates from an untreated hut (q_U). A similar effect was estimated at high dosage (0.69, HDI: 0.40-1.06).

Model-based projections of community-level epidemiological impacts

Projections of community-level impacts of a SR product indicated substantial reductions in the force of infection, largely driven by lethality.
For an SR product with characteristics similar to those quantified in our experiments, the total estimated community-level impact on relative force of infection (FoI) was projected to be substantial, with a 50% reduction in FoI estimated at 25% coverage (HDI: 18-33) at low dosage and a 50% reduction in FoI estimated at 9% coverage (HDI: 6-12) at high dosage (Fig. 3A). The nonlinear relationship of this effect indicates strong indirect effects of the SR when community-level effects are accounted for. A large portion of this effect was attributable to the lethality of the product (Figures 3A and 4). This is a result of the cubic scaling of reductions in mosquito lifespan on FoI; i.e., reducing mosquito density, reducing the probability that a mosquito becomes infected in its lifetime, and reducing the probability of surviving the incubation period and thus being able to transmit the pathogen (22).

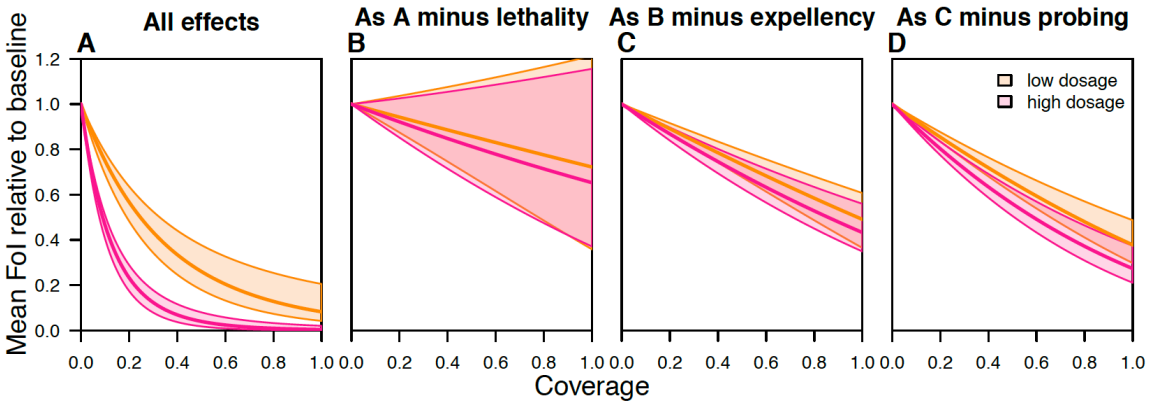

Fig. 3. Composite effects of an experimental SR product containing transfluthrin on relative force of infection (FoI) as a function of coverage across houses in a community. (A) all effects, (B) as A without lethality effects, (C) as B without expellency, and (D) as C without probing effect, with the median default estimates (solid lines) and the 2.5th and 97.5th percentile for the low (orange) and the high (pink) experimental dosage.

Projections of community-level impact of a SR product without lethality indicated modest reduction in force of infection due to increased probing.

An SR without any lethality (i.e, $\mu = 0$, $g_T = g_U$) was estimated to have a more modest impact on FoI (Fig. 3B). When considering the combined effects on blood-feeding and repellency without reduced exiting, the maximum estimated reduction in FoI at low dosage was 51% (HDI: 39-63) at 100% coverage, and similar for high dosage (57%, HDI: 46-68) (Fig. 3C). The increased propensity for partial blood feeding limits the community-level impacts of the SR in our model. In the absence of a partial blood-feeding effect (i.e., $o_C = a_C$), the maximum impact of this product would increase at low dosage to a reduction in FoI of 62% (HDI: 52-71) at 100% coverage and 75% (HDI: 64-80) at high dosage (Fig. 3C).

The role of expellency and repellency on community-level impacts of a SR product depend on the context and product profile.

Exposure to transfluthrin in the hut experiments reduced the rate at which mosquitoes exited the huts. This reduction in the exit rate ($q_U/q_T = 0.70$) prolongs the time to take a blood meal indoors, thereby increasing the probability of transmission at that location. This relative enhancement of FoI (Fig. 4F) is greater if outdoor mortality is higher relative to indoor mortality (Fig. S4J) because the prolonged time spent indoors reduces exposure to outdoor hazards. Conversely, if a SR has strong effects on delayed mortality, reduced exit rates can increase exposure to the product, resulting in substantial reduction in FoI (Fig. 4Df). If a SR with a positive effect on exiting the treated space (e.g., $q_U/q_T = 1.30$) were to be used, the result of more bouts transiting between houses would enhance the maximum community-level impact of the SR from a 28% (HDI: -17- 64) reduction in FoI at low dosage to a 63% (HDI: 54-72) reduction at similar indoor and outdoor death rates ($g_U/g_\tau=1$). If outdoor mortality were three times higher than indoor mortality, this would enhance the maximum population-level impact of the SR to an 83% (HDI: 74-93) reduction in FoI. Similar reasoning holds for the impact of repellency effects.

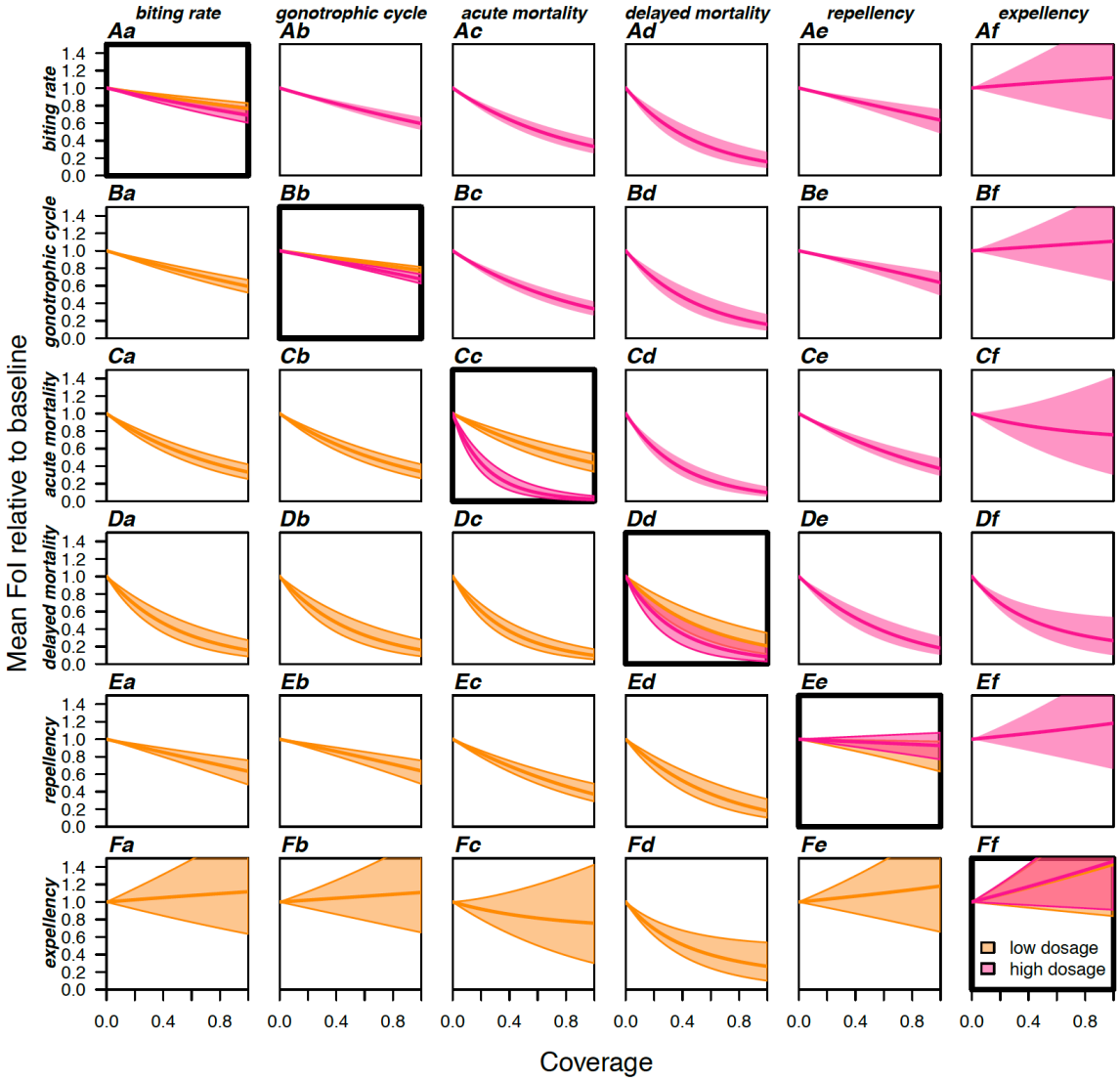

Fig. 4. Composite effects of an experimental SR product containing transfluthrin on relative force of infection (FoI). Effects were assessed as a function of population coverage for different modes of action (Table 2). The diagonal (bold) shows each product effect by itself. Off-diagonal planes show each product effect combined with one other product effect. The mean default estimates (solid lines) and the 2.5th and 97.5th percentile are shown for the low (orange, below diagonal) and the high (pink, above diagonal) experimental dosage.

Sensitivity analysis

We found that the estimated effects of the SR were robust to some but not all free parameters. The results were sensitive to the extrinsic incubation period (EIP, n), the baseline mortality rate (g_U), the ratio between the indoor and outdoor mortality rate (g_U/g_τ), and the ratio between average time indoors versus outdoors (q_U/q_τ) (Fig. S4A,G,H,J). We found that an SR product with characteristics similar to those in our model were less effective if the EIP (n) were longer and baseline mortality rates (g_U) were higher. The risk of not surviving the EIP—and not successfully transmitting DENV—was increased under such assumptions, resulting in relatively smaller impacts

on FoI of SR-induced mortality. When mortality was higher outdoors than indoors, the effect of the SR was also reduced under the scenario of decreased exiting from the treated space. This was due to a lower proportion of time spent outdoors than in the absence of treatment. This pattern was reversed when a product that increases exit rates or elicits stronger repellency was assumed. Lastly, the effect of an SR product with characteristics similar to those in our model was reduced in the event that mosquitoes spend more time in transit to another house relative to their residence time indoors (assuming $g_U=g_\tau$). In such a setting, mosquitoes encountered the SR less often over the course of their lifetimes, thereby diminishing the effect of the SR.

Discussion

We have introduced a model for making projections of community-level impacts of spatial repellent (SR) products on diseases vectored by *Ae. aegypti*. The impacts captured by our model derive not only from individual protection but from a combination of direct and indirect effects at different levels of product coverage within a community. Using a suite of laboratory and experimental-hut experiments, we parameterized six distinct effects of an experimental transfluthrin-based SR product on mosquito behavioral and bionomic traits. This example product was not an optimized, commercially formulated product, but rather served to exemplify the suite of effects a single product may elicit and how these effects can act in concert to reduce transmission. We demonstrated that a product with a profile similar to this one could have a substantial epidemiological impact by way of reducing the force of infection (FoI) of a pathogen transmitted by *Ae. aegypti* in a community with appreciable product coverage. This is largely driven by the product's lethality, but not completely. For instance, when deployed in a mosquito population that has gained partial resistance to lethality (23) a product such as the one in our analysis could still lead to a meaningful reduction in FoI due to multiple forms of delayed blood feeding.

One potential use of our model is as a tool to guide the design of new products and to assess their potential impact when deployed at scale. As a demonstration of this capability, we found that the transfluthrin treatment examined in this study significantly increased mortality and reduced overall biting and hut entry. However, the product was also found to result in increased partial blood feeding and delayed exiting from treated spaces. The relative probability of transmission following partial and full blood feeding is unclear, but increased partial blood feeding could negatively affect the epidemiological impact of the product if the probability of transmission is similar to what it is with full blood feeding (24). Irritancy, inducing effects such as increased partial blood feeding, was common at low, sub-lethal dosages (13) and could compromise the potential net benefit of a SR product. This underscores the importance of understanding how dosage affects multiple behavioral and bionomic traits. How these effects attenuate as chemical actives decay over space and time will also be critical to quantify, to enable better prediction of downstream effects on neighboring premises. Field experiments that allow for measurement of multiple effects in conjunction and across space and time would increase accuracy of effect estimates by allowing environmental and exposure conditions to be matched (25).

The projected epidemiological impact of SRs and other vector control products depends on both the characteristics of the products (chemical actives, application format) and the context of their deployment. We found the potential impact of the example SR product in this study to be highest in densely populated urban areas where mosquitoes are assumed to spend a relatively large portion of time indoors and transit relatively quickly between houses (14). In these settings, mosquitoes may be more likely to have frequent encounters with the SR and thereby to be affected by the lethal, irritant, and excitatory effects. However, if the SR has stronger repellency and expellency effects (*i.e.*, increased exit rates), such as the metofluthrin formulation used in (6), longer transit times in sparsely populated areas would result in longer biting delays and increased transit-related mortality, resulting in a further reduction of transmission. Notably, high-dosage SRs could have reduced impacts in very densely populated areas at low coverage. In that situation, the repellency effect could protect mosquitoes from entering a house with high SR-associated mortality. A delay in biting as a result of the SR would then be offset by the reduced life span it would have experienced if it had entered the house. At low coverage, densely populated settings could be most prone to the adverse effects of diversion of infected mosquitoes to untreated homes. The potential for diversion is strongly tied to the risks a mosquito experiences both from its exposure to the product and from its transit between houses. In settings where transit is relatively hazardous, SRs that reduce time indoors are expected to have a greater impact. Push-pull strategies, which trap mosquitoes in sentinel traps after they have been repelled or expelled from a house (26), may therefore be a promising candidate in this context.

We made a number of simplifying assumptions that may affect the outcome of SR implementation. First, our model assumes homogeneous mixing such that each house has an equal probability of being visited by a mosquito, irrespective of its proximity to the house where the mosquito was previously. In addition, the model assumes that no biting occurs in transit. This does not, however, exclude the possibility of outdoor biting. The houses in the model should be regarded as the totality of all space affected by the SR and may thus include semi-enclosed and open areas in sufficiently close proximity of the product. Further, we assumed that placement of the product was random. A clustered rollout may be logistically desirable and could, depending on the context and the formulation of the product, result in community-level impacts that differ from our estimates. One possible advantage of clustered rollout could occur if the product has beneficial downstream effects to adjacent, untreated houses. Such effects are currently not included in our framework, but they could enhance the impact of the product unless adverse, irritating effects such as partial blood feeding or reduced expellency occur downstream.

Downstream effects (*i.e.*, in adjacent, untreated spaces) of the experimental transfluthrin treatment were observed in the experimental hut study (25). These include reduced expellency (for both dosages) and lethality (only for the high dosage) effects. Downstream effects on blood-feeding rates are currently unknown but may well occur in tandem with other irritating effects such as reduced expellency (6). In addition, dosage decay over time may alter the product profile by increasing irritating effects and

decreasing effects on mortality as the product expires. Although our framework does not allow for temporal changes in treatment effects, it does allow for the exploration of a suite of different profiles. Given appropriate experimental data on effects following the decay of the product, our framework could be used to estimate the cross-sectional effects of an SR at different stages of the product's lifetime as a way to inform best practices for replacement timing. Coupling more detailed models with additional laboratory and hut experiments would aid in capturing the full effects of heterogeneity in exposure and protection, both on treated and untreated spaces. The model presented here provides a general way to gain insights on the projected interplay of different behavioral and bionomic effects of an SR in a variety of settings.

The sustained burden of dengue and the emergence of other pathogens transmitted by *Ae. aegypti* mosquitoes highlight the need for novel vector control paradigms (2). Spatial repellents are one promising tool for settings where other vector control products are insufficient, such as the control of day- and outdoor-biting mosquitoes, in settings with high potential for resistance against lethality, or as an additional tool in outbreak response. Our model could likewise be extended to other vector control tools with multifaceted effects on mosquito behavioral and bionomic traits, including push-pull regimens and window screening, similar to how alternative modeling frameworks for malaria have been used to address effects of multiple interventions (15, 16). In general, our model offers a way of synthesizing the results of feasible experiments at small scales to meet public health challenges at large scales.

Materials and Methods

Our study involved 1) the development of a new model to project the epidemiological impact of vector control products that elicit multifaceted effects on *Ae. aegypti* behavioral and bionomic traits; 2) the collection and analysis of experimental data to quantify those effects; and 3) sensitivity analyses of the model-based estimates of community-level impact informed by experimental results. The experiments comprising the second component of our study all involved transfluthrin but did so with differing means of application or delivery of that chemical. Consequently, the third component of our study should be regarded as a hypothetical, but empirically grounded, analysis rather than a specific analysis of a singular product formulation.

Model

To estimate the community-level impact of vector control products that potentially affect transmission through multiple behavioral and bionomic traits, we built on existing frameworks for modeling mosquito-borne pathogen transmission (27). We assumed a well-mixed community in which each house has a probability C of being protected by the product at any given time. Consequently, upon searching for a blood meal, mosquitoes encounter a treated house with probability C, assuming the possibility of repellency or attraction of the product can only occur once the mosquito has "encountered" the house (*i.e.*, chemical cue) at close proximity. Below, we describe the effects that the product

may have on a mosquito once it makes such an encounter, how those effects scale with coverage C, and how those scaled effects impact the force of infection of a mosquito-borne pathogen transmitted in a community in which these interventions are deployed (Fig. 1).

Entomological effects – blood-feeding

We assume that blood-seeking mosquitoes encounter an SR product with probability C, upon which they are repelled with probability ρ. After this occurs, mosquitoes move at rate $1/\tau$ to another house. Due to various excitatory/agitation behavioral responses associated with the product, a mosquito that does enter a treated house delays its feeding by a proportion α of the entire feeding cycle, which has an average length $1/a$ in the absence of the SR. In addition, the expellency caused by the intervention alters the time a mosquito spends in the house from $1/q_U$ to $1/q_T$, on average.

To arrive at an estimate of the overall delay in blood feeding that results from the combination of these effects, we first calculated the average delay associated with each of these events weighted by the probability of each such event. In the event that a mosquito encounters a treated house but does not enter it, which occurs with probability $C\rho$, the delay before the next house is visited is simply the transit time τ. In an untreated house, which mosquitoes enter with probability 1-C, a mosquito fails to blood-feed before leaving the house with probability $e^{\frac{-a}{q_U}}$ .The average delay associated with this is $1/q_U+\tau$. In a treated house, which mosquitoes enter with probability $C(1-\rho)$, a mosquito fails to blood-feed before leaving the house with probability $e^{\frac{-a\alpha}{q_T}}$. The average delay associated with this is $1/q_T+\tau$. Together, the probability of one of these three events occurring is $D = C\rho + C(1-\rho)e^{-\frac{a\alpha}{q_T}} + (1-C)e^{-\frac{a}{q_U}}$, and the expected delay conditional on one of these events occurring is

$$\delta = \frac{\tau C\rho + (q_T^{-1}+\tau)\left(C(1-\rho)e^{\frac{-a\alpha}{q_T}}\right) + (q_U^{-1}+\tau)((1-C)e^{\frac{-a}{q_U}})}{D}. \quad (1)$$

We next considered that multiple such delays could occur consecutively. If experiencing one of these delays from one blood-feeding attempt to the next are independent events, then the expected number of delays before successful blood feeding is $D / (1 - D)$. To capture these effects within a single modified biting rate a_C, we can equate the reciprocal of that biting rate with the average time until a successful blood meal, which is

$$\frac{1}{a_C} = \delta\frac{D}{1-D} + \frac{1}{a}. \quad (2)$$

Entomological effects – mortality

In the event that a mosquito is undeterred by the repellent effect of the product, it becomes exposed to the lethal effects of the product and is assumed to die with probability μ within a relatively short timeframe after entering the house. In addition, exposure to the product may have delayed lethal effects that increase the baseline death

rate of the mosquito (g_T). Lastly, a mosquito that is successfully repelled by the product may experience additional mortality later—e.g., due to predation—while it is transitioning to another house, experiencing a mortality rate g_τ during transit. The interplay of these lethal effects augments the background mortality rate g in the absence of vector control to result in a new overall mortality rate g_C in the presence of an SR product at coverage C. The new overall mortality rate follows from the sum of rates associated with each of three states (in transit: Δ; present in a treated house: T; present in an untreated house: U), weighted by the proportion of time spent in each state.

To derive the proportion of time spent in each state, we use a continuous-time Markov chain model of the whereabouts of a mosquito in one of three states {Δ, U, T} over time and use that model to derive an expectation for the long-term average of time allocation across those three states. That model is driven by the infinitesimal matrix (28)

$$\mathbf{A} = \begin{bmatrix} \tau^{-1}(\rho C - 1) & \tau^{-1}(1-C) & \tau^{-1}(1-\rho)C \\ q_U & -q_U & 0 \\ q_T & 0 & -q_T \end{bmatrix}, \tag{3}$$

where the rates in each element of the matrix determine the instantaneous probability of a mosquito moving from one state to another and are consistent with parameter definitions and assumptions in the previous section on delayed blood-feeding.

The transition probabilities $P_{ij}(t)$ satisfy a system of differential equations with rates $\mathbf{A}$ known as the backward Kolmogorov differential equations (28)

$$\frac{dP}{dt} = \mathbf{A}\mathbf{P}(t), \tag{4}$$

where $\frac{dP}{dt}$ follows from the rates of change in each state

$$\begin{aligned} \frac{d\Delta}{dt} &= \tau^{-1}(\rho C - 1)\Delta + q_U U + q_T T \\ \frac{dU}{dt} &= -q_U U + \tau^{-1}(1-C)\Delta \\ \frac{dT}{dt} &= -q_T T + \tau^{-1}(1-\rho)C\Delta. \end{aligned} \tag{5}$$

At equilibrium, $\frac{dP}{dt}$ =0 and so the stationary distribution $\lim_{t\to\infty} \boldsymbol{P}(t) = \pi = (\pi_\tau, \pi_U, \pi_T)$ follows from eqn. (4) and the notion that the probabilities must sum to one. Solving $0 = \mathbf{A}\mathbf{P}(t)$ under that condition gives the probabilities

$$\begin{aligned} \pi_\tau &= -\frac{\tau q_U q_T}{q_U C(\rho-1) + q_T(C - \tau q_U - 1)} \\ \pi_U = \frac{(1-C)\pi_\Delta}{\tau q_U} &= \frac{(C-1)q_T}{q_T(C - \tau q_U - 1) + C(\rho-1)q_U} \end{aligned} \tag{6}$$

$$\pi_T = \frac{(1-\rho)C\pi_\Delta}{\tau q_T} = \frac{C(\rho-1)q_T}{q_T(C-\tau q_U-1)+C(\rho-1)q_U}$$

that a mosquito is in a given state at any given time. The average mortality rate g_C under coverage C then follows by taking the probabilities from eqn.(6) and using them to weight the state-specific probabilities μ, g_T, and g_U according to

$$g_C = \pi_T(\mu q_T + g_T) + \pi_U g_U + \pi_\tau g_\tau. \quad (7)$$

Entomological effects – mosquito density

We assume that effects of the SR product on mosquito density act through effects on demographic processes; *i.e.*, birth and death. A general form for equilibrium mosquito density is $m = \varepsilon / g$, where ε is the rate of emergence of new adult mosquitoes and g is death rate. One formulation of the emergence rate ε is that it is the product of the expected number of blood meals that each mosquito takes over the course of its lifetime and a combination of immature-stage mortality and development rates (27). We treat the latter as an unspecified constant and the former as the product of the rate of oviposition o and the expected lifetime $1/g$, implying that $m_C \propto o_C / g_C^2$.

Epidemiological impact

We use the force of infection (FoI) as our focal metric for quantifying the epidemiological impact of an SR product. FoI is defined as the rate at which susceptible individuals become infected. In Ross-Macdonald models of mosquito-borne pathogen (MBP) transmission, FoI = $bmaY$, where b is the probability that a human becomes infected after being bitten by an infectious mosquito, m is the ratio of mosquitoes to humans, a is the rate at which a mosquito engages in blood feeding (either partial or full blood feeding), and Y is the prevalence of infection among mosquitoes (22). The latter depends further on the daily mosquito mortality rate g, the incubation period n in the mosquito, the probability c that a mosquito becomes infected upon biting an infectious human, and the prevalence of infection in humans X according to

$$\text{FoI} = bmaY = \frac{bma^2cXe^{-gn}}{g+acX}. \quad (8)$$

Under equilibrium assumptions in an SIS-SI malaria model, X can in turn be solved for as a function of model parameters (27). Under non-equilibrium assumptions, however, the formulation in eqn. (8) is equally valid for other types of compartmental models (e.g., SEIR-SEI) provided that X is regarded as a free parameter, which is appropriate given its highly dynamic and uncertain nature for strongly immunizing MBPs such as DENV.

To derive an expectation for how FoI will change in response to a SR, we can take the ratio of the expression in eqn. (8) evaluated with parameter values reflecting the intervention at a given coverage C against the expression evaluated with parameter values reflecting conditions in the absence of the SR. We allow for the possibility that any or all of m, a, o, and g may change in response to the SR. This results in a ratio of FoIs of

$$\mathrm{FoI}_{rel} = \frac{\mathrm{FoI}_C}{\mathrm{FoI}} = \frac{m_C {a_C}^2}{ma^2} \frac{g + acX}{g_C + a_C X} e^{-(g_C - g)n} . \quad (9)$$

Substituting the result $m_C \propto o_C / g_C^2$ into eqn. (9), we obtain

$$\mathrm{FoI}_{rel} = \frac{o_C a_C^2 g^2}{o a^2 g_C^2} \frac{g + acX}{g_C + a_C X} e^{-(g_C - g)n} , \quad (10)$$

which effectively depends on the effects of the intervention on rates of blood feeding and mortality, as well as three free parameters, *C*, *X*, and *n*.

Collection of experimental data

Mosquito populations

Laboratory experiments to measure effects on blood feeding and mortality were performed using colonized, pyrethroid-resistant adult *Ae. aegypti* (F_5) from the Department of Entomology, Katsetsart University, Thailand. Field experiments to measure effects of repellency and expellency were performed using $F_{1\text{-}4}$, pyrethroid-susceptible adult *Ae. aegypti* maintained from field-collected immatures in Iquitos, Peru.

SR effect on blood feeding

Ae. aegypti of age 5-7 days (*N*=125 for each arm), starved for 24 hrs pre-test, were exposed to transfluthrin or solvent alone (control) for 10 minutes using a high-throughput screening mechanism following previously described protocols (29). An hour after exposure, mosquitoes were allowed to feed on human blood using a membrane feeding system. After a predefined follow up time, mosquitoes were dissected and recorded as fully blood-fed, partially blood-fed, or unfed. The experiment was repeated for seven follow-up times (0, 1, 3, 6, 12, 24, and 48 hours) for each of three different dosages (control, low: 8.4×10^{-7} g/L, and high: 1.5 times low dosage). Each experiment was performed at 80°F and 75% humidity.

SR lethality

Ae. aegypti of age 5-7 days (*N*=120 for each arm) were exposed to transfluthrin or control as described above, after which cohorts were maintained at 80°F and 75% humidity with access to 10% sugar solution. Adult survival was monitored daily for 25 days. The experiment was repeated for five different treatment dosages relative to the 8.4×10^{-7} g/L (0: control, 0.5, 0.75, 1, 1.25, 1.5). Dosages 1 and 1.5 are hereafter referred to as low and high dosage, respectively.

SR effect on entry and exit rates

To quantify rate of entry and exit of *Ae. aegypti* exposed to transfluthrin under field conditions, an experimental hut study was performed in Iquitos, Peru (25). A unique hut design was employed in which five experimental structures were aligned in a single row with adjoining walls containing open eave gaps to create a continuum of indoor space. This design mimicked a housing structure common to Iquitos, Peru, as well as other

dengue-endemic areas. Each 4m x 6m x 2m hut was equipped with exit traps. The center hut contained transfluthrin-treated material or solvent alone (control) during baseline experiments. In each of the huts, a human was present under an untreated bed net to generate host-seeking cues and monitor mosquito knockdown (inability to fly). For each experiment, 5-7 day old, sugar-fed mosquitoes (n=25, $F_{2\text{-}3}$), uniquely marked according to individual huts, were released inside all but the center hut at 5:30 AM. Exit traps were checked every 30 minutes from 6:00 AM until 6:00 PM, and knockdown was monitored hourly within this same time frame. At 6:00 PM, remaining mosquitoes were recaptured from inside each hut using aspirators, and their release and recapture locations were recorded based on marking color scheme. The experiment was repeated five times for three different treatments (control, low: 0.0025g/m^2, high: 0.005g/m^2).

Analysis of experimental data

SR effect on blood feeding

We used data collected in the blood-feeding experiments to estimate partial (a_p) and full blood feeding (a_f) rates as a function of the dose of transfluthrin. Details of this analysis are described in Supplementary Materials. Briefly, we assumed that blood feeding follows a Poisson process with dose-dependent rates $a_p(x_{dose}) = e^{-(\beta_{p,0}+\beta_{p,1}x_{dose})}$ and $a_f(x_{dose}) = e^{-(\beta_{f,0}+\beta_{f,1}x_{dose})}$. For each of the three possible outcomes (partially blood-fed, fully blood-fed, unfed) the probability of observing the outcome was derived, while taking note that the number of fully blood-fed mosquitoes observed in the experiment includes both mosquitoes that were fully engorged after one meal and those that became fully engorged after multiple partial blood meals (Supplementary Materials). Using these probabilities, we maximized the multinomial likelihood of the model parameters given the observed number of mosquitoes in each feeding category using the *bbmle* package (30) in R (31) and in doing so obtained best-fit estimates of the coefficients $\beta_{p,0}$, $\beta_{p,1}$, $\beta_{f,0}$, and $\beta_{f,1}$ describing the dosage effects of the SR on the biting rates a_p and a_f.

SR lethality

We used data collected during the lethality experiments to estimate two distinct lethal product effects on acute (μ) and delayed (ϕ) lethality. To separate these effects, we consider observed death and survival over the course of day one to be informative of μ and any death and survival thereafter to be informative of ϕ.

Over the course of day one, we assumed that the number of mosquito deaths was a binomial random variable with probability μ with relationship to transfluthrin dose x_{dose} defined by

$$\mu(x_{dose}) = e^{-\beta_0+\beta_1 x_{dose}}\,. \tag{11}$$

We obtained maximum-likelihood estimates of β_0 and β_1 using the *bbmle* package (30) in R (31).

To estimate the delayed lethality effect of the SR (*i.e.*, conditional on survival beyond day one), we fitted different parametric survival models to the interval- and right-

censored time-to-event data collected in the laboratory experiments (32). The methods for this analysis are detailed in Supplementary Materials. Briefly, we sought to estimate the effect of chemical dosage on the hazard over time. The hazard λ is the instantaneous rate at which death occurs and is described as the probability that death occurs between time t and time $t+dt$, given that dt is small and death has not occurred before t. The specific form of the hazard model that we sought to estimate was a function of the transfluthrin dose x_{dose}, expressed at time t as

$$\lambda_i(t|x_{dose}) = \lambda_0(t)e^{\beta_1 x_{dose}}, \quad (12)$$

where λ_0(t) is the baseline hazard for individuals with x_{dose} equal to zero (*i.e.*, the control group) and $e^{\beta_1 x_{dose}}$ is the relative risk associated with a specific dosage, which was assumed to be stable over time (*i.e.*, proportional hazards) (see Fig. S2 and Supplementary Materials for further details and validation of this assumption). Under the assumption that the distribution of survival times results from a continuous-time stochastic process, we used parametric survival models to describe $\lambda_0(t)$ (32), each with different assumptions on how $\lambda_0(t)$ changes over time (Table S2). We used the Akaike Information Criterion (33) to select the best model while penalizing for more parameters in more complex models. The models were fitted and assessed using the *survival* package 2.27-7 (34) and the *flexsurv* package (35) in R (31).

SR effect on entry and exit rates

Data from the hut experiments included competing interval-censored data on exit (30-minute intervals) and knockdown (hourly intervals) by event hut and release hut. In addition, mosquitoes recaptured at the end of the experiment represent right-censored data. Mosquitoes not recaptured at any point during the experiment were considered to have been lost to follow-up at some unknown time before the end of the experiment.

In brief, ten Bosch et al. (25) used a continuous-time Markov Chain (CTMC) model to describe the probability at a given time for a mosquito, given its release location, to be present in a given hut or to have experienced a given outcome. At any time, a mosquito can be in one of five huts (transient states: H_{2L}, H_{1L}, H_0, H_{1R}, or H_{2R}), or have already experienced one of 15 terminal events: exit, knockdown, or loss to follow-up in any of the five huts (absorbing states: X_i, K_i, and U_i $\forall i \epsilon [2L, 1L, 1R, 2R]$). The rates at which mosquitoes transition either to adjacent huts or to an absorbing state are assumed to be independent of time or previous trajectories, and thus the time spent in each transient state is exponentially distributed. The parameters of the CTMC model were fitted to the data using a Bayesian Markov chain Monte Carlo (MCMC) approach coded in the R language (31) and using the *coda* package (36) for processing of the results.

Modeling analysis

Baseline model parameterization

Six distinct entomological effects of the transfluthrin treatment evaluated are defined by the probability of death upon encountering the SR (μ), increases in mortality rates (ϕ), the probability of repellency (ρ), the rate of change in exit rates (q_U/q_T), delayed blood

feeding (α) expressed as a proportion of the mean rate of blood feeding in the absence of SR, and delayed oviposition (o) (Table 2). Estimates of these parameters were derived from the lethality, blood-feeding, and entry and exit rate experiments described above.

The probability of death shortly after entering a treated hut (μ) follows directly from eqn. (11). From the second part of the analysis of the mortality experiment, we estimated the reduction in time until death in response to the SR relative to the control group (ϕ) from the accelerated failure time survival models. The treatment-adjusted mortality rate is

$$g_T = g_U / \phi. \tag{13}$$

From the blood-feeding experiment, we estimated the blood feeding rate (a_T) in a treated house as the fraction α of this quantity relative to the biting rate (a_U) in an untreated house, where we assume that the ratio of biting rates in treated and untreated houses is the same as the ratio of the biting rates in the treatment and control arms of the laboratory blood-feeding experiment. The oviposition rate (o) is estimated similarly, but solely relies on the rate at which mosquitoes become fully blood fed.

Repellency (ρ) is informed by the proportion of mosquitoes leaving an adjacent hut (H_{1L} or $_{1R}$) that move away from rather than towards the treated hut. Assuming that in an untreated environment mosquitoes move to either neighboring hut with an equal probability (*i.e.*, p_1=0.5), the repellency effect relative to the untreated scenario is $\rho = 1 - (1 - p_{1_T}/0.5)$. The rate at which a mosquito exits a treated house relative to an untreated house follows from the fitted exit rates in (25). The relative exit rate out of the treated house is a fraction q_U/q_T of the default rate q_U (Table 1).

Sensitivity and scenario analysis

For the baseline parameterization of the model, we assumed that exposures across experiments map to similar dosages in the population setting. This assumption is necessary for illustrative purposes, but it should be kept in mind that the level of exposure in real-life settings will differ from any experimental setting, in particular for the laboratory experiments. We examined a range of different combinations of bionomic effects to assess the sensitivity of our estimates to different product profiles and to quantify uncertainty associated with our estimates. Further, we examined the impact of different assumptions on the free parameters (Table 1). We investigated the sensitivity of our relative FoI estimates across a range of plausible values. In addition, the population-level effects of SRs may vary across settings. For instance, whereas densely populated areas could result in shorter travel times between houses (τ), this duration and associated hazards could be elevated in less densely populated settings due to increased distance and more abundant predators. The impacts of different transit times (τ), transit hazards (g_τ), and residence times ($1/q$) on our estimates of relative FoI by coverage were assessed in a similar fashion as the other free parameters.

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Acknowledgments: We thank Theeraphap Chareonviriyaphap for materials and support for experiments conducted in Thailand and Amy Morrison, Roxanne Burus, and Victor Lopez for materials and support for experiments conducted in Peru. We thank Angela Carranci and Suppaluck Polsomboon for assistance with experimental data collection. We thank Edwin Requena, Hugo Jaba and the field team for their support during the experiments in Peru. We thank Neil Lobo, Tom Scott, David Smith, and Steve Stoddard for useful discussions about spatial repellents as vector control tools. We thank Dyon van Essel and Infograaf for artwork.

Funding: This work was supported and funded by the Bill & Melinda Gates Foundation (Grant #48513): "A push-pull strategy for *Aedes aegypti* control." The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript. QAtB was supported by a graduate student fellowship from the Eck Institute for Global Health at the University of Notre Dame. JMW was supported by a grant from the Uniformed Services University.

Author contributions: JMW, FCL, JPG, and NLA designed experiments. FCL and JMW performed the experiments. QAtB and TAP developed the modeling framework. QAtB performed the analyses. QAtB, JPG, NLA, and TAP interpreted the results. QAtB, NLA, and TAP wrote the manuscript. All authors read and approved the final manuscript.

Competing interests: The authors declare that they have no competing interests.

Disclaimer: The views expressed in this work are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, or U.S. Government.

Data and materials availability: At the time of publication, code used to perform the statistical and mathematical analyses will be made available on GitHub and experimental data will be made available on Open Science Framework.

Tables

Table 1. Baseline parameters for force of infection framework.

Symbol	Description	Units	Default	Reference
a	Biting rate	$days^{-1}$	0.76	(14)
$1/o$	Duration of gonotrophic cycle	days	4	(37)
g_U	Daily mortality rate (indoors)	$days^{-1}$	0.18	(38)
g_τ	Daily mortality rate (outdoors)	$days^{-1}$	0.18	
τ	Time spent per transit event	days	0.3 q_U	(39)
n	Duration of the extrinsic incubation period	days	14	(40)
b	Probability of mosquito to human infection		0.5	
c	Probability of human to mosquito infection		0.5	
X	Human infection prevalence		12.5	

Table 2. Fitted model parameters depicting effects of transfluthrin under experimental laboratory and field conditions.

Experiment	Model framework parameter description	Model framework parameter symbol	Fitted equation	Fitted parameters (95% confidence interval: lower bound, higher bound)	Model framework default (HDI)
Blood feeding	Fraction of baseline blood feeding rate	$\alpha(x_{dose})=\frac{a(x_{dose=0})}{a(x_{dose})}-1$	$a=\frac{1}{e^{(\beta_{p,0}+\beta_{p,1}x_{dose})}}+\frac{1}{e^{(\beta_{f,0}+\beta_{f,1}x_{dose})}}$	$\beta_{p,0}$=8.05 (7.91, 8.20) $\beta_{p,1}$=-0.18(-0.33, -0.03) $\beta_{f,0}$=7.00 (6.93, 7.07) $\beta_{f,1}$= 0.37(0.28, 0.46)	0.82 (0.76, 0.89)
	Fraction of baseline oviposition rate	$o(x_{dose})=\frac{a_f(x_{dose=0})}{a_f(x_{dose})}-1$	$a_f=\frac{1}{e^{(\beta_{f,0}+\beta_{f,1}x_{dose})}}$		0.69 (0.63, 0.75)
Lethality	Probability of first day mortality	$\mu(x_{dose})$	$\mu=e^{(\beta_0+\beta_1 x_{dose})}$	β_0=-5.68 (-6.84, -4.67) β_1= 3.14(2.38, 4.00)	0.08 (0.05, 0.11)
	Fraction time until death relative to baseline	$\phi(x_{dose})$	See Table S2	See Table S2	0.71 (0.64, 0.79)
Entry and exit rates	Probability of being repelled	$\rho(x_{dose})$	(25)	ρ	0.19 (0.03, 0.36)
	Fraction of baseline exit rate	$q_U/q_T(x_{dose})$	(25)	q_U/q_T	0.71 (0.40, 1.06)

Supplementary Materials

Materials and Methods

Analysis of blood feeding experiments

Mosquitoes in the blood-feeding experiment could have experienced three different outcomes: partially blood-fed, fully blood-fed, or not blood-fed. We consider the biting rate a referred to previously as the sum of the rates of partial and full blood feeding, a_p and a_f, respectively. We modeled these rates as functions of the dose of transfluthrin, x_{dose}, as

$$a_p(x_{dose}) = \frac{1}{e^{\beta_{p,0}+\beta_{p,1}x_{dose}}} \quad \text{(S1)}$$

and

$$a_f(x_{dose}) = \frac{1}{e^{\beta_{f,0}+\beta_{f,1}x_{dose}}}. \quad \text{(S2)}$$

We assumed that a mosquito can potentially take multiple partial blood meals, with a single partial blood meal having no impact on the probability of taking another partial blood meal or a full blood meal. However, we assume that full blood meals are absorbing states, in the sense that a full blood meal prevents any further blood feeding thereafter within the timeframe of the experiment.

Under these assumptions, the expected number of partial blood meals after time t given $a_p(x_{dose})$ is $a_p(x_{dose})t$, provided that blood feeding follows a Poisson process. This results in the probability of k partial blood meals after time t being described by a Poisson distribution with rate parameter $a_p(x_{dose})t$. Similarly, the probability of a full blood meal to have occurred by time t is the complement of the probability that no full blood meal has occurred by that time; *i.e.*, $1 - e^{-a_f(x_{dose})t}$.

The number of fully blood-fed mosquitoes observed in the experiment includes both mosquitoes that were fully engorged after one meal and those that became fully engorged after multiple partial blood meals. Therefore, the probability for a mosquito to be partially blood-fed is the probability of the intersection of $k_p > 0$ and $k_f = 0$, which is

$$Pr(B_p) = \big(1 - Pr(k_p = 0)\big)Pr(k_f = 0). \quad \text{(S3)}$$

The probability of observing a mosquito that is not blood-fed equals

$$Pr(B_0) = Pr(k_p = 0)\, Pr(k_f = 0), \quad \text{(S4)}$$

and the probability of observing a fully blood-fed mosquito is

$$Pr(B_f) = 1 = 1 - Pr(B_p) - Pr(B_0). \quad \text{(S5)}$$

Using the probabilities in eqns. S4-6 and the observed number of mosquitoes (N) in each feeding category, we calculated the likelihood of the model parameters given the observed data as

$$L = P_{multinom}(\beta_{p,0}\beta_{p,1}\beta_{f,0}\beta_{f,1}|N_p, N_f, N_0). \quad \text{(S6)}$$

We maximized this likelihood using the *bbmle* package (30) in R to obtain best-fit estimates of the coefficients $\beta_{p,0}$, $\beta_{p,1}$, $\beta_{,0}$, and $\beta_{f,1}$ in eqns. S1 and S2 that describe the dosage effects of the SR on the biting rates a_p and a_f.

Analysis of longevity experiments

Conditional on surviving day one, the data consist of a set of interval- and right-censored time-to-event data (32). Let Ψ be a random variable representing the time until death, $f(\Psi=t)$ its probability density function (pdf), and $F(\Psi=t)$ its cumulative distribution function (cdf). The complement of the cdf is the survival function $S(t)$, defined mathematically as

$$S(t) = \Pr\{\Psi \geq t\} = 1 - F(t) = \int_t^{\infty} f(x)dx\,, \quad \text{(S7)}$$

which describes the probability that death has not yet occurred by time t. A related characterization of the distribution of Ψ, and fundamental to survival analysis, is the hazard function, $\lambda(t)$ (32). The hazard denotes the instantaneous rate at which death occurs and is described as the probability that death occurs between time t and time $t+dt$, given that dt is small and death has not occurred before t, taking the form

$$\lambda(t) = \lim_{dt\to\infty} \frac{\Pr\{t \leq \Psi < t + dt|\Psi \geq \mathrm{t}\}}{dt}. \quad \text{(S8)}$$

The hazard can be written as the ratio of the joint probability that Ψ is in the interval [t, $t+dt$] and that $\Psi > t$

$$\lambda(t) = \frac{f(t)}{S(t)}. \quad \text{(S9)}$$

To estimate the effect of chemical dosage on the hazard over time, we fitted different survival models to the time-to-event data collected in the laboratory experiments. A specific feature of these data is censoring; for some mosquitoes, death has not yet occurred by the end of the study and thus we only know that Ψ exceeds the observation time. An important assumption here is that this censoring is independent of the probability of an event to occur.

For uncensored mosquito i, we can express the likelihood of a given hazard model conditional on an observed event time $\Psi = t_i$ as the product of $S(t)$ and $\lambda(t)$ as

$$L_i = f(t_i) = S(t_i)\lambda(t_i). \tag{S10}$$

For censored observations, the likelihood function only reflects that Ψ exceeds t_i

$$L_i = S(t_i). \tag{S11}$$

We can write this into a single expression

$$L = \prod_{i=1}^{n} L_i = \prod_{i} \lambda(t_i)^{d_i} S(t_i), \tag{S12}$$

where d_i is the event indicator and takes a value of 1 if the event has occurred before the end of the observation time and 0 otherwise.

The specific form of the hazard model that we seek to estimate is a function of the transfluthrin dose x_{dose}, expressed at time t as

$$\lambda_i(t|x_{dose}) = \lambda_0(t)e^{\beta_1 x_{dose}}, \tag{S13}$$

where $\lambda_0(t)$ is the baseline hazard for individuals with x_{dose} equal to zero (*i.e.*, the control group) and $e^{\beta_1 x_{dose}}$ is the relative risk associated with a specific dosage, which is assumed to be stable over time. Such proportional hazard (PH) models allow for a distinct separation of the effect of time from the effect of the covariate. This becomes clearer when we express the model in terms of the log of the hazards, finding a simple additive model $\ln\left(\lambda_i(t|x_{dose})\right) = \alpha_0(t) + \beta x_{dose}$. We will assume that PH holds in this analysis; *i.e.*, that the relative effects of the products do not change over time. We verified this assumption by performing a log transformation on the survival data (Fig. S2) and assessed whether, under this transformation, the curves fitted to observations were parallel across dosages. Doing so tests our assumption that the effect of dosage on survival is additive.

The shape of the baseline hazard $\lambda_0(t)$ affects the results of the final proportional hazards model. Under the assumption that the distribution of survival times is the result of a continuous-time stochastic process, one can use parametric survival models to describe $\lambda_0(t)$ (32). We examined the performance of five candidate models with different assumptions about $\lambda_0(t)$ (Table S2). The exponential model assumes a stable baseline hazard $\lambda(t) = \lambda$. Alternatively, the Weibull model allows $\lambda(t)$ to monotonically increase or decrease over time: $\lambda(t) = v\lambda(\lambda t)^{v-1}$. The gamma distribution too allows for $\lambda(t)$ to

monotonically increase or decrease. There is no closed form expression for the hazard function of the gamma distribution. Whereas the exponential model describes the waiting time until the first event occurs in a Poisson process, the gamma describes the waiting time until *k* events occur. For comparable rate parameters *k* or *v* (Table S2), the hazard described by the Weibull distribution decreases more rapidly than in a gamma distribution. The lognormal model allows for an initial increase in λ(t) to be followed by a decrease as time progresses. Lastly, the generalized gamma distribution is an extension of the gamma distribution with an added scale parameter that allows for increased flexibility in $\lambda(t)$. The gamma (v =1), Weibull (κ=1), lognormal ($\kappa \to inf$), and exponential (κ=1 and v =1) models are all special, nested cases of the generalized gamma distribution. We used the Akaike Information Criterion (33) to select the best model, thereby accounting for different numbers of parameters across models. The models were fitted and assessed using the *survival* package 2.27-7 (34) and the *flexsurv* package (35) in R 3.2.3 (31).

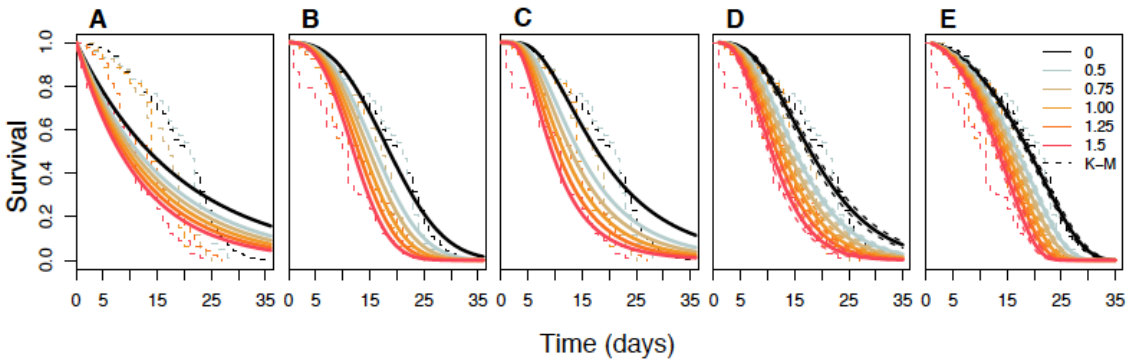

Fig. S1. Estimated dose effects of an experimental SR product containing transfluthrin on mosquito longevity. (A) exponential, (B) Weibull, (C) lognormal, (D) gamma, and (E) generalized gamma models. The dashed lines depict the Kaplan-Meier curves at associated dosages relative to the low dosage used (8.4x10-7 g/L).

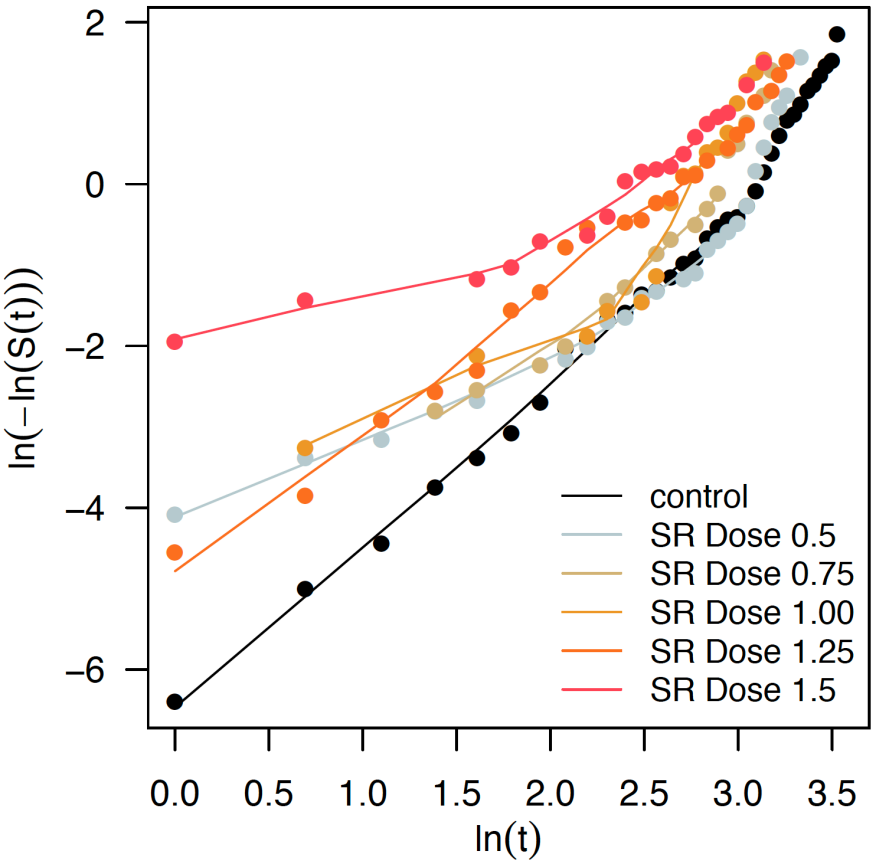

Fig. S2. Proportional hazard test for longevity data conditioned on first day survival. The proportional hazards assumption holds for dosage regimen that are parallel to each other when plotted with these transformations.

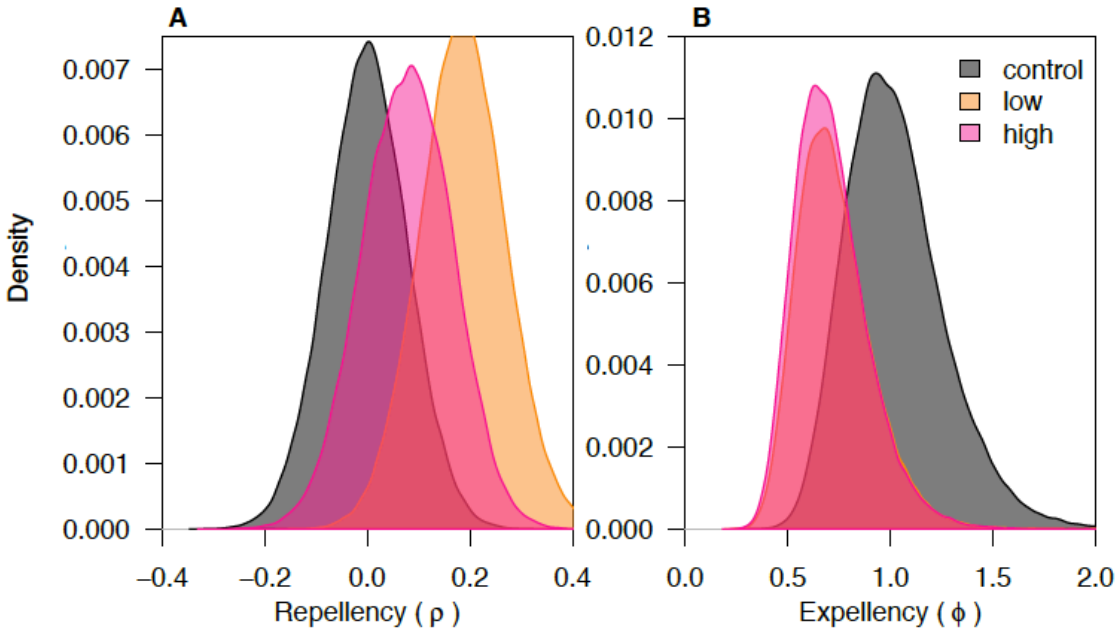

Fig. S3. Posterior estimates of effects of an experimental SR product containing transfluthrin. (A) repellency (decreased entry) and (B) expellency (increased exit) during exposure to control, low (0.0025 g/m2), and high (0.005g/m2) dose regimen.

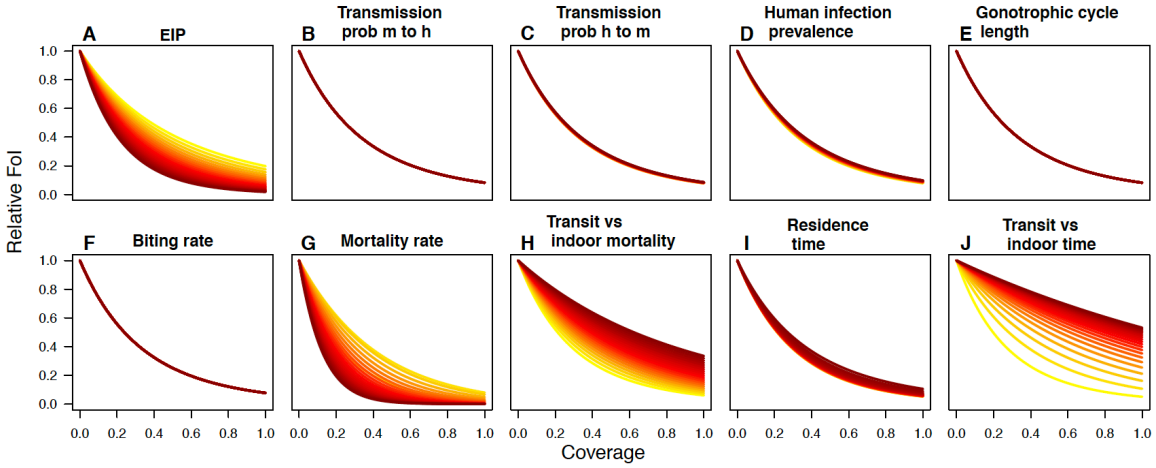

Fig. S4. Sensitivity of relative force of infection (FoI) estimates to the baseline parameters as a function of population coverage. (A) extrinsic incubation period from 3 to 33 days, (B) transmission probability from mosquito to human from 0.01 to 1, (C) as B but from human to mosquito, (D) human infection prevalence from 1 to 99%, (E) the duration of the gonotrophic cycle from 1 to 14 days, (F) the baseline biting rate from 0.2 to 10, (G) the baseline mosquito mortality rate from 0.025 to 2.5, (H) mortality rate during transit relative to indoor mortality rate from 0.1 to 10, (I) average time spent in an untreated house from 0.05 to 5 days, and (J) the proportion of time a transit event takes relative to the baseline residence time, from 0.01 to 10. Across all panels, yellow depicts low values and dark red signifies high values.

Table S1. Transfluthrin effects on mortality by survival model (low dosage, 8.4×10^{-7} g/L)

Model	ϕ	95% confidence interval
exponential	0.71	(0.63, 0.79)
Weibull	0.75	(0.72, 0.78)
log-normal	0.65	(0.61, 0.70)
gamma	0.71	(0.67, 0.75)
generalized gamma	0.79	(0.77, 0.81)

Table S2. Survival functions.

Model	Probability density function (f(t))	Survival function	Parameters	With covariates	Mean (95% Confidence interval: lower bound, higher bound)	AIC	ΔAIC
Exponential	$\lambda e^{-\lambda t}$	$e^{-\lambda t}$	λ =rate	$\lambda = \lambda(x)$ $\lambda(x) = \frac{1}{e^{\beta_0+\beta_i x_i}}$	β_0=2.97 (2.89, 3.05) β_1= -0.34(-0.45, -0.23)	8623	1201
Weibull	$v\lambda t^{v-1} e^{-\lambda t^v}$	$e^{-\lambda t^v}$	λ=rate v = shape	$\lambda = \lambda(x)$ $\lambda(x) = e^{\beta_0+\beta_i x_i}$	v = 0.07 (0.06, 0.08) β_0=3.06 (3.02, 3.08) β_1=-0.29(-0.33, 00.25)	7564	143
Log-normal	$\frac{1}{x\sigma\sqrt{2\pi}} e^{-\frac{(\ln(t-\mu)^2}{2\sigma^2}}$	$\frac{1}{2}+\frac{1}{2}erf\left[\frac{\ln(x-\mu)}{\sqrt{2\sigma}}\right]$	μ = location σ = scale	$\mu = \mu(x)$ $\mu(x) = e^{\beta_0+\beta_i x_i}$	σ =0.59(0.56, 0.61) β_0=2.88 (2.83, 2.93) β_1=-0.43(-0.49, -0.36)	8078	656
Gamma	$\frac{\lambda(\lambda t)^{\kappa-1} e^{-\lambda t}}{\Gamma(\kappa)}$	No closed form	λ=rate κ = shape	$\lambda = \lambda(x)$ $\lambda(x) = v / e^{\beta_0+\beta_i x_i}$	κ = 4.08 (3.77, 4.42) β_0= 0.21(0.19, 0.23) β_1=0.34(0.29, 0.40)	7786	364
Generalized Gamma	$\frac{\lambda v(\lambda t)^{v\kappa-1} e^{-(\lambda t)^v}}{\Gamma(\kappa)}$	$1-(\gamma\{\kappa,(\lambda t)^v\}/\Gamma(\kappa))$ $\gamma(s,x) = \int_0^x t^{s-1} e^{-t}\, dt$	λ =rate v = shape 1 κ = shape 2	$\lambda = \lambda(x)$ $\lambda(x) = e^{\beta_0+\beta_i x_i}$	κ = 0.23 (0.18, 0.28) v = 7.99 (6.76, 9.43) β_0= 29.20(28.42, 30.00) β_1=-0.24(-0.26, -0.21)	7421	0