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Estimating a mosquito repellent's potential to reduce malaria in communities

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Abstract

Background & objective: Probability models for assessing a mosquito repellent's potential to reduce malaria transmission are not readily available to public health researchers. To provide a simple means for estimating the epidemiological efficacy of mosquito repellents in communities, we develop a simple mathematical model.

Study design: A static probability model is presented to simulate malaria infection in a community during a single transmission season. The model includes five parameters—sporozoite rate, human infection rate, biting pressure, repellent efficacy, and product-acceptance rate.

Interventions: The model assumes that a certain percentage of the population uses personal mosquito repellents over the course of a seven-month transmission season and that this repellent maintains a constant rate of protective efficacy against the bites of malaria vectors.

Main outcome measures: This model measures the probability of completely evading infection over a seven-month period at diverse rates of vector biting pressure, repellent efficacy, and product acceptance.

Results & conclusion: Absolute protection using mosquito repellents alone requires high rates of repellent efficacy and product acceptance. Using performance data from a highly effective repellent, the model estimates an 88.9% reduction of infections over a seven-month transmission season. A corresponding and proportional reduction in the incidence of super-infection in community members not completely evading infection can also be presumed. Thus, the model shows that mass distribution of a repellent with >98% efficacy and >98% product acceptance would suppress new malaria infections to levels lower than those achieved with insecticide treated nets (ITNs). A combination of both interventions could create synergies that result in reductions of disease burden significantly greater than with the use of ITNs alone.

Key words Malaria prevention; mathematical model; repellent

Introduction

Mosquito repellent interventions against vector borne diseases are rarely considered in public health programmes. In fact, if they are considered at all, they are recommended as supplementary measures and left to the discretion of individuals with the economic means to acquire them. This institutional tendency to disregard repellents is not supported by scientific evidence, as few large-scale epidemiological studies of the effect of mosquito repellents on disease transmission have been undertaken. Where such field studies are lacking, mathematical modeling can demonstrate how a repellent-only intervention can influence the suppression of malaria. However, the theoretical tools for assessing repellent-based inter-

ventions against malaria are similarly lacking. While some models have been used to evaluate the repellent, irritant, and toxic effects of insecticide residues on anopheline mosquitoes[1], no probability models are available for assessing the disease reduction potential of compounds that function solely as mosquito repellents.

To estimate the epidemiological efficacy of repellents in poor communities, we developed a simple mathematical model. To illustrate the model, we incorporated the performance data of NO MAS (NM), a low-cost repellent lotion made with para-Menthane-3,8-diol (PMD) and lemongrass oil (LGO). Designed to reduce infectious disease in conditions of severe poverty, numerous iterations of this water-based repellent have proved to be superior to deet (N,N-diethyl-3-methylbenzamide) when tested against disease vectors in efficacy studies, both in the field and the laboratory (Barnard, personal communication)[2].

Material & Methods

Using a static probability model, we estimated the mean probability of avoiding malaria infections in populations protected by NM. Assuming that each mosquito-biting attempt in a transmission season is an independent event, the following expression estimates the probability that members of a community, at risk of vector borne infections, can escape infection by using repellent-only interventions:

$$F_e = (1 - \mathrm{sh})^{b(1-rc)}$$

Where, F_e = epidemiological efficacy – the probability that a community member avoids infection during the time period associated with variable (b) biting pressure; s = sporozoite (or vector) infection rate – the proportion of vectors infected and infective; h = human infection rate – the proportion of potentially infective mosquito bites that result in human infections; b = biting pressure – the average number of bites per person per unit of time if no repellent were used; r = repellent efficacy – the proportion of potential mosquito bites that are repelled; and c = product acceptance rate – the proportion of people using repellent regularly and appropriately.

In effect, this equation predicts the probability that the average person in this population exposed to infected vectors will avoid infection. The base probability of becoming infected by a mosquito bite is represented as a product of the proportion of mosquitoes infected (s) and the probability that a single infectious bite leads to a human infection (h). Each mosquito bite is then considered as an independent event, hence its representation as an exponential term. The biting pressure (b) is modified by the repellent efficacy (r) and the proportion of the community (c) that accepts regular use of a repellent. Subtracting from the integer one (1) delivers the proportion of host-seeking mosquitoes that evade the effects of repellent and are able to bite members of the community to which this estimator model is applied. Human infection rate (h) per infectious bite can vary greatly by age and transmission intensity. The parameter estimate used here (0.022) is derived from a robust data set originally published by Pull and Grab[3] and further evaluated by Nedelman[4]. Recent investigations[5] indicate this value provides a reasonable intermediate estimate of h for partially immune populations living in areas of moderate to intense malaria transmission.

Alternatively, (h) can be estimated from specific localities by exploiting the relationship between entomological inoculation rate (E_{ir}) and prevalence. The proportion of people escaping malaria infection over a given period (P_n) is a function of their probability of escaping infection from one infective mosquito bite (1-h) iterated over the number of infective bites (E_{ir}) they receive over a period of the same length preceding incubation.

$$Pn = (1-h)^{1/E_{ir}}$$

Since, h is the parameter of interest in our estimator, solving for h yields:

$$h = 1 - Pn^{1/E_{ir}}$$

This provides a means of estimating *h* from two parameters obtained from field-based blood surveys and entomological assessments. Ideally, (*h*) should be estimated separately for distinct age classes (infants < six months old, children > six months, < five yr, six to fifteen-year olds and adults) to account for differences in protective immunity and converted into a weighted average for each community.

Sporozoite rates (*s*) can also vary over a wide range, both temporally and spatially. We have chosen an illustrative value (0.015) to represent situations where the vector infection rate and malaria transmission are relatively intense, but not extreme. This value corresponds roughly to median sporozoite rates estimated from several mesoendemic areas in Ethiopia[6,7].

Using the above values as constants, we explored how diverse levels of user compliance and efficacy could influence malaria infections under a wide range of biting pressures. However, to establish the scale of protection that is possible with this repellent intervention, these values were applied to a large-scale hypothetical population scenario: a portion of Equatorial West Africa where 10 million people are at high risk of contracting malaria.

Applying the above parameters for vector and human infection rates, we hypothesized that significant transmission occurs over a seven-month season, with a mean biting pressure (for people not protected from malaria vectors by other measures) of 40 bites per night. Again, we chose a value representative of many situations around the world without going to extremes. This biting pressure corresponds roughly to the median biting levels measured at nine sites in a rice-growing region of lowland Kenya[8].

Efficacy data for NM from a California field study (Carroll, personal communication) indicated a >6 h 100% complete protection time (CPT). Numerous cage tests in Florida (Barnard, personal communication) have indicated a >9 hour 100% CPT. Data from a 120-day product acceptance study in Loreto, Peru (Kiszewski *et al*, in preparation) show that 99.5% of 369 NM-using households elected to continue repellent use at the end of the study. We assumed a repellent efficacy of 98% in our theoretical West African scenario.

Results

To protect vulnerable populations from malaria infection during prolonged transmission seasons, it is necessary for mosquito repellents to achieve both high product acceptance and high efficacy rates. Indeed, the probability of avoiding infections is highly sensitive to small changes in these exponential parameters, especially where biting rates are most intense (Fig. 1).

In the absence of other preventive interventions, and under the conditions described in the previous scenario ($s = 0.015$, $h = 0.022$, $b = 40$) at least 9,375,000 malaria infections would be expected during a seven-month malaria transmission season. However, with mass distribution of a highly effective mosquito re-

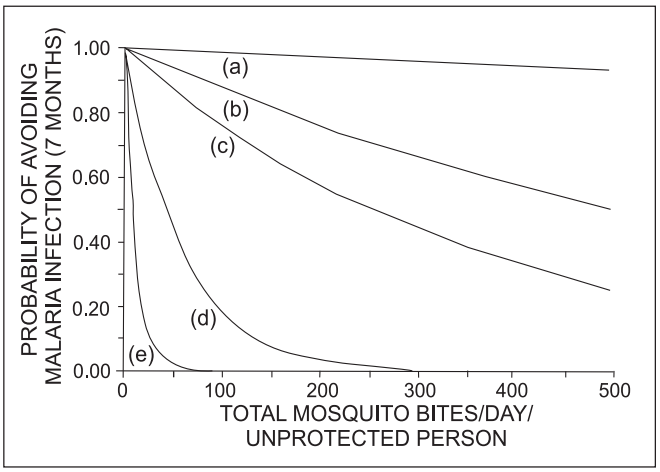

Fig. 1: Probability of avoiding malaria infection. The probability that a repellent-using population can avoid malaria infection during a seven month transmission season, assuming a sporozoite rate of 1.5% and a human infection rate of 2.2%. Scenarios of repellent efficacy and user compliance include: (a) 99.9% efficacy and compliance, (b) 99% efficacy and compliance, (c) 98% efficacy and compliance (corresponding to estimates of compliance in a 2007 Peruvian field study), (d) 95% efficacy and 80% compliance and (e) Zero protection or compliance.

pellent (r = 0.98, c = 0.98), only about 1,040,000 malaria infections would be expected in the same period. This represents an 88.9% reduction in infections derived solely from the use of an efficacious, well-tolerated repellent. Substituting lower efficacy (95%) and product acceptance (80%) still results in 48.2% fewer new infections than the unprotected population, approaching the burden reductions expected in communities where at least 80% of people at risk possess and use ITNs[9].

Discussion & Conclusion

The estimator calculates the probability of avoiding all infective bites. It does not distinguish between single, serial or multiple infections among those not escaping infection. It also disregards the diversion of infective bites toward unprotected people, an event that could increase the likelihood of infection among them, especially in areas where vectors are highly focused on human biting. However, where user acceptance rates reached levels observed in the Peruvian study (> 98%), the epidemiological significance of diversion becomes negligible.

The output generated in Fig. 1 depicts the probability of completely avoiding a patent infection of *falciparum* malaria. Absolute prevention is particularly critical for vulnerable subpopulations such as pregnant women and children less than five years old where every clinical infection has the potential to cause severe illness or death. However, not depicted explicitly in our simple model is the effect of reduced exposure to infectious bites on the clonal diversity and multiplicity of infections. Fewer and less diverse super-infections would be expected in communities using repellents. Certain studies suggest that reduced super-infection can lead to more favorable outcomes in people afflicted with malaria[10,11] although in some cases, protective immunity may also be affected. Thus, repellents may benefit not only those who completely evade transmission but those who reduce their overall incidence of infection across a transmission season.

This model was conceived during a time of extraordinary disruptions in the world's economy and climate. It is a time when funding for clinical studies to measure the impact of repellents on malaria is scarce, and finding dependable weather conditions to stage such costly studies is less certain. In these circumstances, the model could provide public health researchers in malaria-endemic countries with a low-cost means to estimate the epidemiological impact of repellents in their communities. Importantly, this "snapshot" of parasitemic conditions is one that could be employed without significant moneys from donors, or technical assistance from abroad. While it is clearly not intended to replace full clinical studies, the estimator could help demonstrate the need for such further studies and the desirability of funding them in the future. It can also be used to determine the range of impacts possible across a range of likely parameters.

Our model suggests that a highly efficacious repellent, one that is also acceptable to users, could surpass the disease reduction potential of ITNs when distributed en masse. When deployed together with ITNs, such repellents could offer powerful synergies, compensating for incomplete coverage by bed nets, while enhancing their mass killing effects by repelling mosquitoes toward the net's treated surfaces. Consequently, we believe that both the model and the repellent it demonstrates deserve serious consideration as tools in the war against vector borne disease.

Competing Interests

This study was funded and directed by S.T. Darling. A patent in Darling's name is pending on the repellent mentioned in this manuscript, and all royalties from licensing this product have been pledged by him to support its not-for-profit distribution to poor communities with vector borne diseases. A.E. Kiszewski, the co-author, gave his services freely to this effort and is, therefore, independent from the funder.

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