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Target Product Profiles for Mosquito Gene Drives: Incorporating Insights From Mathematical Models

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Mosquito-borne diseases such as malaria continue to pose a major global health burden, and the impact of currently-available interventions is stagnating. Consequently, there is interest in novel tools to control these diseases, including gene drive-modified mosquitoes. As these tools continue to be refined, decisions on whether to implement them in the field depend on their alignment with target product profiles (TPPs) that define product characteristics required to achieve desired entomological and epidemiological outcomes. TPPs are increasingly being used for malaria and vector control interventions, such as attractive targeted sugar baits and long-acting injectable drugs, as they progress through the development pipeline. For mosquito gene drive products, reliable predictions from mathematical models are an essential part of these analyses, as field releases could potentially be irreversible. Here, we review the prior use of mathematical models in developing TPPs for malaria and vector control tools and discuss lessons from these analyses that may apply to mosquito gene drives. We recommend that, as gene drive technology gets closer to field release, discussions regarding target outcomes engage a wide range of stakeholders and account for settings of interest and vector species present. Given the relatively large number of parameters that describe gene drive products, machine learning approaches may be useful to explore parameter space, and an emphasis on conservative fitness estimates is advisable, given the difficulty of accurately measuring these parameters prior to field studies. Modeling may also help to inform the risk, remediation and cost dimensions of mosquito gene drive TPPs.

Keywords: attractive targeted sugar baits, gene drive mosquitoes, long-acting injectable drugs, malaria, odor-baited traps, population modification, population suppression

INTRODUCTION

Mosquito-borne diseases such as malaria, dengue and yellow fever continue to pose a major public health burden throughout much of the world. These diseases primarily impact low and middle-income countries, with over 90% of malaria cases and deaths occurring in sub-Saharan Africa (1). While malaria incidence in Africa has significantly declined since the wide-scale distribution of interventions beginning in 2000 (2), disease transmission is now stagnating at an unacceptably high level (1). In addition to increasing access to long-lasting insecticide-treated nets (LLINs) and other currently-available tools such as artemisinin combination therapy drugs (ACTs), it is clear that new tools will be needed to meet Global Technical Strategy milestones for reductions in malaria incidence and mortality, with two of the most promising novel tools currently being malaria vaccines and gene drive-modified mosquitoes. Gene drive approaches bias inheritance in favor of an introduced allele intended to spread through the mosquito population, and fall into two main categories: i) "population suppression," whereby the introduced allele induces a fitness load or sex bias, reducing mosquito numbers, and ii) "population modification," whereby the introduced allele disrupts pathogen transmission, reducing mosquito vector competence (3).

In order for gene drive mosquito products to advance from laboratory to field studies, their characteristics will be assessed against target product profiles (TPPs) - planning tools that provide a list of preferred characteristics and minimum criteria products must satisfy as they progress through the development pipeline. TPPs for gene drive mosquitoes are becoming increasingly relevant as the technology matures and moves closer to release. A draft TPP for a population modification gene drive product has been proposed (4), and a workshop hosted by the Foundation for the National Institutes of Health (FNIH) discussed TPPs for gene drive products at length (5). A common theme from these publications is that, while TPPs should be based as much as possible on empirical studies, rigorous modeling will be needed where empirical data is not available. Key outcomes for vector control tools are entomological (i.e., effects on mosquito populations) and epidemiological (i.e., effects to human health outcomes) and can only be observed following a release, meaning that the initial decision to release will be based on model predictions.

Fortunately, there has been a growth in malaria modeling over the last 10-15 years, with several detailed models being published that concisely describe malaria transmission dynamics in the mosquito vector and human host. These include *OpenMalaria* (6, 7) and the Imperial College London malaria model (8, 9). Over this same period, other novel malaria control tools have also been developed and advanced through stages of laboratory and field testing - most recently and visibly, attractive targeted sugar baits (ATSBs) (10) and malaria vaccines (11). These provide case studies for the application of mathematical models to TPPs, and we draw from these previous analyses to explore the role that mathematical models should play in informing TPPs for mosquito gene drive products.

MODEL-INFORMED TARGET PRODUCT PROFILES FOR OTHER MALARIA CONTROL TOOLS

As the goals of TPPs are product-focused, much of the modeling work in this area does not feature in academic journals. We therefore focus on a handful of published modeling analyses, each conducted by a different research group, that have supported TPP specification for ATSBs (12), odor-baited traps (13), and long-acting injectable drugs (LAIs) for seasonal malaria prevention (14). We summarize these analyses, and additional TPP modeling analyses for malaria vaccines (15) and vector control pesticides (16, 17), in **Table 1**.

Lessons From Attractive Targeted Sugar Baits

ATSBs were proposed as an outdoor vector control strategy to complement existing indoor tools such as LLINs and indoor residual spraying with insecticides (IRS), and work by attracting mosquitoes to the fruity or flowery scent of a bait laced with a combination of sugar and an oral toxin (18). In 2008, a field study demonstrated that ATSBs were capable of reducing *Anopheles gambiae* mosquito populations by 90% in Bandiagara, a semi-arid area of Mali (19). Then in 2017, a randomized controlled trial (RCT) involving 14 villages in Mali demonstrated that ATSBs were capable of significantly reducing *An. gambiae* populations, including sporozoite-infected females, when LLINs were already present (10). Both studies had focused on entomological outcomes (i.e., mosquito density and sporozoite infection), and a mathematical model was used to estimate the expected epidemiological impact based on the RCT results (12) prior to planning epidemiological RCTs.

Predicting outcomes, especially epidemiological ones, based on product parameters embodies the primary role that mathematical models play in informing TPPs. For ATSBs, the key product parameter is the excess daily mosquito mortality rate caused by the intervention, which was estimated to be 0.09 per mosquito per day from the Mali RCT (12). In this study, the Imperial College London malaria model (8, 9) was used to predict all-ages malaria prevalence and clinical incidence following intervention with ATSBs in a range of transmission settings (baseline malaria prevalence ranging from 10-50% with varying degrees of seasonal transmission). This malaria model includes acquired and maternal human immunity, symptomatic and asymptomatic infection, human age structure, mosquito biting heterogeneity, and antimalarial drug therapy and prophylaxis (8). A detailed mosquito life history model is also included, incorporating vector control tools such as LLINs and IRS (20, 21). Predictions from this model suggest that the RCT-inferred excess mosquito mortality rate due to ATSBs should result in reductions in malaria prevalence exceeding 30% and reductions in clinical incidence exceeding 50% for the range of transmission settings considered (12).

This analysis addressed questions directly informative of a TPP for ATSBs. An excess mortality rate due to ATSBs of ~0.05

TABLE 1 | Model-informed target product profiles for malaria and vector control tools.

Product	Attractive targeted sugar baits	Odor-baited traps	Vector control pesticides	Long-acting injectable drugs	Malaria vaccines
Product parameters	Excess mosquito mortality rate due to ATSBs (ATSB feeding rate, mortality rate upon feeding)	Attractiveness of traps to mosquitoes, cost per trap	Excess probability of mosquito diversion &/or death before feeding	Initial LAI protective efficacy, shape & half-life of decay in protective efficacy	Initial vaccine efficacy, duration of protection, dose regime (timing & titre/efficacy of 4th dose)
Intervention parameters	N/A (although ATSB coverage determines feeding date)	Trap coverage (number of traps per 1000 people)	Pesticide coverage (treated LLINs & outdoor products)	LAI coverage	Vaccine coverage (first 3 doses, 4th dose)
Target outcomes	>30% reduction in all-ages clinical malaria incidence or prevalence	Reduction in EIR equivalent to that achieved by 50% coverage with LLINs	Highest reduction in EIR for user/household & community	Clinical malaria cases averted (children 0-5 years) equivalent to that achieved by SMC	Most clinical malaria cases averted (children 0-5 years) for 10 years following introduction
Models used	Imperial College London malaria model	Deterministic model of mosquito host-seeking & ovipositing	Deterministic model of mosquito host-seeking & ovipositing	*OpenMalaria*	Imperial College London malaria model
Settings considered	Baseline malaria prevalence of 10-50%, varying degrees of seasonal transmission	Baseline EIR of 200 infective bites per person per year (high transmission settings)	Baseline EIR of 200 infective bites per person per year, equal numbers of humans & cattle	Settings that resemble Mali & Senegal (seasonality, mosquito species, interventions)	4 distinct transmission settings (initial malaria prevalence of 5%, 15%, 30%, 45%)
Minimally acceptable criteria	Excess mosquito mortality rate >0.05 or >0.1 per mosquito per day	Traps more attractive than humans, >20-130 traps per 1000 people, cost per trap < $4-$27	High coverage with mosquito-toxic profiles is optimal, deterrence provides personal protection	Sigmoidal protective efficacy profile, half-life > duration of transmission season	High initial vaccine efficacy, high titre of 4th dose, long interval between 3rd & 4th doses
References	Fraser et al. (12)	Okumu et al. (13)	Killeen et al. (16) Killeen and Moore (17)	Burgert et al. (14)	Hogan et al. (15)

ATSB, attractive targeted sugar bait; EIR, entomological inoculation rate; LAI, long-acting injectable drug; SMC, seasonal malaria chemoprevention.

per mosquito per day or higher was predicted to result in a >30% reduction in clinical incidence in a range of settings, and an excess mortality rate of ~0.1 per mosquito per day or higher was found to result in a >30% reduction in malaria prevalence (12). Depending on the target outcome, either of these excess mortality rates could be considered a minimum criterion that would enable approval of an epidemiological field trial. An important caveat to note is that the excess mortality rate is expected to vary by environmental setting. For instance, in lush settings with an abundance of alternative sugar sources, the excess mortality rate due to ATSBs is expected to be lower. The key product parameter is therefore location-specific, and an environmental assay, such as the feeding rate on attractive sugar baits marked with dyes, would be needed to assess TPP alignment in a new location. That said; the analysis clearly demonstrates the strength of mathematical models in predicting target epidemiological outcomes for a given product parameter in a range of transmission settings.

Lessons From Odor-Baited Traps

Odor-baited traps have long been discussed as a form of vector control (22), although their use to date has been limited to mosquito monitoring (23). In 2010, a series of papers were published detailing odor-baited traps that are more attractive to mosquitoes than humans (24, 25), and a deterministic model describing mosquito host-seeking and ovipositing behavior (26) was adapted to model vector control with odor-baited traps in addition to LLINs (13). One of the motivations for this mathematical analysis was to inform a TPP for odor-baited traps, as a prototype version (25), while potentially effective, was considered too expensive for a community-scale trial. The modeling analysis considered the entomological inoculation rate (EIR) - the rate at which people are exposed to infectious mosquito bites - as the outcome of interest, and calibrated the model to a baseline EIR greater than 200 infective bites per person per year, representing locations in Africa where transmission is consistently high.

To produce a TPP for odor-baited traps, key intervention parameters were explored - the attractiveness of traps to mosquitoes, and the number of traps per 1000 people that would produce a reduction in EIR equivalent to that achieved by 50% coverage with LLINs (a level of coverage considered generally attainable throughout Africa). Given the number of traps required, a corresponding maximum cost per trap was calculated in order for the traps to be at least as cost-effective as LLINs. The analysis concluded that the traps should be more attractive than humans, and that 20-130 traps per 1000 people would be needed to produce the target EIR reduction. This equated to a maximum cost per trap of $4 to $27, which includes costs of production, transport, installation, operation and maintenance (13). An interesting point raised by this and many TPP analyses is that target product characteristics can be traded off against each other - i.e., a more attractive trap can afford to be more expensive as less traps are required. The analysis also emphasized the importance of a comparative cost analysis, and this was influential in preventing these odor-baited traps from being adopted at scale.

Lessons From Long-Acting Injectable Drugs for Seasonal Malaria Prevention

LAIs have been proposed as an alternative to monthly seasonal malaria chemoprevention (SMC) with oral anti-malarials in the

hope that longer-lasting injectable drugs can remedy the spread of drug-resistance and the low adherence rates and high deployment costs of SMC (27). In order for LAIs to be implemented, they must be shown to be non-inferior to existing interventions, and in lieu of clinical studies, a preliminary modeling analysis was conducted (14). In this study, the *OpenMalaria* model (6, 7) was used to predict clinical malaria cases averted by LAIs compared to SMC in the intervention age group (children 0-5 years of age). Simulations were conducted for settings that resemble Mali and Senegal in terms of seasonality, mosquito species and interventions, with these two countries being chosen because they are locations where SMC is implemented and clinical trials are frequently conducted (14). The *OpenMalaria* model is an individual-based simulation of malaria in humans, including heterogeneity in mosquito biting, human immunity and disease susceptibility, and is linked to a deterministic model of mosquito life history (6, 7).

Key product parameters that were varied in this analysis describe initial LAI protective efficacy (i.e., the chance that a malaria case is prevented upon treatment with a LAI) and the shape and half-life of decay in protective efficacy. LAI coverage (i.e., the proportion of the intervention age group receiving the LAI at the beginning of a transmission season) was also varied. Results suggest that the shape of decay in protective efficacy is key, with protective efficacy profiles that remain high for an extended period (e.g. sigmoidal efficacy profiles) being essential to establish non-inferiority of LAIs. The required half-life of protective efficacy mirrored the duration of seasonal transmission in each setting, and a trade-off was observed between protective efficacy and coverage. Given the importance of decay in LAI protective efficacy, it was recommended that studying this phenomenon be prioritized in potential clinical studies (14). Another interesting aspect of this analysis was the use of machine learning to infer non-inferior tool profiles and parameter sensitivities based on a database of TPP malaria model simulations (28).

SPECIAL CONSIDERATIONS FOR MOSQUITO GENE DRIVE PRODUCTS

For mosquito gene drive products, reliable predictions from mathematical models will be required to inform TPPs prior to the first field release, as any release could potentially be irreversible. This elevates the need for rigorous modeling analyses, as accurate predictions of safety and efficacy will be required in the absence of field testing. Here, we describe some of the special considerations that apply to mosquito gene drive products when developing model-informed TPPs, in particular concerning product parameters, target outcomes, biosafety and cost (**Figure 1**).

Product Parameters

Gene drive mosquito products can be described by a large number of parameters. The FNIH workshop on TPPs, for instance, listed homing rate, rate of functional resistance allele generation, male mating competitiveness, female fecundity, and the development and mortality rates of each life stage all as important product parameters (5). Additionally, intervention parameters such as the number and size of releases require specification. In order to provide meaningful criteria for each parameter, consultation with molecular biologists and field ecologists will be essential to narrow the space of parameter exploration, and a machine learning approach will likely assist in exploring the refined parameter space, as it did for LAIs (28). Prior modeling studies can also

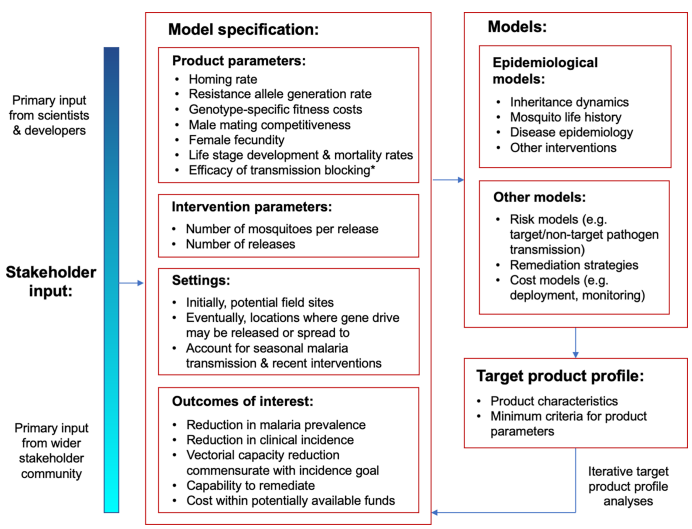

FIGURE 1 | Schematic representation of the role of mathematical models in informing target product profiles (TPPs) for gene drive mosquitoes. Stakeholder input follows a gradient with scientists and developers providing primary input on product parameters and the wider stakeholder community providing primary input on outcomes of interest. The flowchart applies to both population modification and population suppression gene drive systems, although the product parameter for efficacy of transmission blocking* only applies to population modification systems.

help to refine parameter space (29). For example, the EMOD individual-based model of mosquito population dynamics (30) was used to determine the homing rate, resistance allele generation rate and female fecundity parameters required for persistent reduction of disease-competent mosquitoes in sub-Saharan African settings (31). Fitness parameters consistently emerge as highly influential on gene drive model outcomes, and given the inaccuracy of estimating these prior to a field release, a conservative approach would be to focus on their lower bounds when generating criteria for other parameters.

Target Outcomes

Ongoing discussions will likely be needed to define target outcomes for gene drive mosquito products. Epidemiological outcomes, such as reductions in clinical incidence and prevalence, are likely to be required by stakeholders such as the World Health Organization, with questions remaining over exactly what the target reduction should be. TPPs are blunt instruments, and any target reduction decided upon will likely represent a compromise between demonstrating significant public health benefit, and having an achievable goal that will enable the technology to progress along the product development pipeline. The precedent from the ATSB analysis is a 30% reduction in clinical malaria incidence or prevalence (12), while at the FNIH workshop on TPPs, a 20-50% reduction in clinical malaria incidence was discussed (5). Such target decisions should involve a wider range of stakeholders as the technology gets closer to field release, and should include consideration of national malaria control targets, and recent and current interventions used.

Key decisions also need to be made regarding the modeled transmission settings, as these will have a significant influence on TPP specification. The LAI analysis presents an interesting case study by selecting two locations where comparable interventions and field studies have been conducted (14). For gene drive mosquito projects, similar reasoning would support modeling population suppression products in Mali, Burkina Faso, Kenya or Uganda (field sites of the Target Malaria project), and population modification products in São Tomé and Príncipe or the Union of the Comoros (field sites of the UC Irvine Malaria Initiative). Models in these settings should take into account seasonal malaria transmission profiles alongside current interventions being implemented. If the scale of gene drive interventions grows, then TPPs should consider a representative range of settings, spanning a diversity of local vector ecologies, and malaria transmission and intervention profiles.

For settings with more than one malaria vector present, entomological outcomes may be more suitable than epidemiological ones. To illustrate this, an alternative malaria vector could hypothetically prevent elimination of a target vector species from resulting in a 20-50% reduction in clinical malaria incidence due to the nonlinear relationship between the EIR and malaria incidence (32). To remedy this, the target outcome could be specified as an inferred 20-50% reduction in malaria incidence due to the target species, calculated in terms of a reduction in species-specific vectorial capacity commensurate with the epidemiological goal. Other target outcomes are also important, and may include a rate of spread expected to produce the desired epidemiological impact within the time frame of a field trial (perhaps two years), and a minimum duration of effect of perhaps three years (5).

Biosafety and Cost Considerations

Finally, modeling may play a role in assessing some of the biosafety and cost dimensions of gene drive mosquito TPPs. One aspect of biosafety is the availability of products and strategies to remediate gene drive-modified organisms from the environment in the event of unwanted consequences or a shift in public opinion. The need and capability to remediate gene drive organisms is still being discussed (33, 34); however, in the absence of extensive field data, modeling can provide insights to determine minimum criteria and capabilities for insecticide-based campaigns or genetic systems such as ERACR (element reversing the autocatalytic chain reaction) (35, 36) in order to achieve a defined level of transgene confinement or removal.

Some aspects of a model-informed TPP may overlap with risk assessment. For instance, whether there is a tolerable mosquito biting rate that would not be expected to enhance transmission of target and non-target pathogens (37). Lastly, as demonstrated by case studies of odor-baited traps and LAIs, costing is another important dimension of TPPs that modeling may help to inform. Analyses focusing on deployment costs suggest that, due to their self-propagating nature, highly effective gene drives are expected to be more cost-effective than currently-available tools (38); however, similarly detailed analyses have yet to be conducted for monitoring requirements, which are expected to be a cost driver for the technology (39). That said; gene drives occupy a distinct niche in the malaria control toolkit due to their ability to spread and be effective despite compliance rates; therefore, costs may be best assessed against potentially available funds rather than the costs of other interventions.

DISCUSSION

As gene drive mosquito products mature, TPPs will guide their advancement from lab to field, and mathematical models will necessarily inform TPP criteria. The potential irreversibility of gene drive releases heightens the need for rigorous modeling to assess their safety and efficacy. Recent advances in malaria modeling will facilitate prediction of epidemiological outcomes, data from ecological studies will facilitate predictions of safety, and input from a wide range of stakeholders will facilitate refinement of the target outcomes that modeling seeks to predict.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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