DEVELOPING COST-BENEFIT TOOLS FOR MOSQUITO RELEASE INTERVENTIONS

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INTRODUCTION

Globally, vector-borne diseases are responsible for 17% of total infectious disease cases and more than 700,000 deaths annually (World Health Organization, 2020). Malaria is caused by Plasmodium parasites transmitted by *Anopheles* mosquitoes and is annually responsible for 230 million cases and over 400,000 deaths (WHO, 2020). Dengue is the most prevalent viral disease transmitted by *Aedes* mosquitoes with nearly 100 million cases and 10,000 deaths annually (WHO, 2020). Dengue virus is transmitted mainly by *Aedes aegypti and* Aedes *albopictus*, which also transmit chikungunya, yellow fever and Zika viruses.

Despite promising interventions such as the distribution of antimalarial treatment, indoor residual spraying (IRS), and insecticide treated bed nets, we are far from achieving elimination of malaria (Gething et al. 2016). Additionally global dengue burden is expected to continue increasing dramatically due to climate change, urbanization, and population growth, putting nearly 6 billion people at risk for the disease by the end of the 21st century (Messina et al. 2019). Unlike malaria, dengue has no known treatment. A vaccine with limited efficacy and higher risks among seronegative individuals is available, and issues with *Aedes* mosquitoes developing insecticide-resistance limit vector control effectiveness (WHO, 2020; Eisen et al. 2009; Gubler et al. 1989; Oki et al. 2011).

Given the substantial current and future threat of vector-borne diseases, novel biotechnological innovations have been developed in which mosquitoes, biologically modified to alter disease transmission, are released to suppress, or replace existing mosquito species (Yen et al. 2020). Descriptions of each intervention are shown in ***Table 1*** (Ritchie et al. 2017).

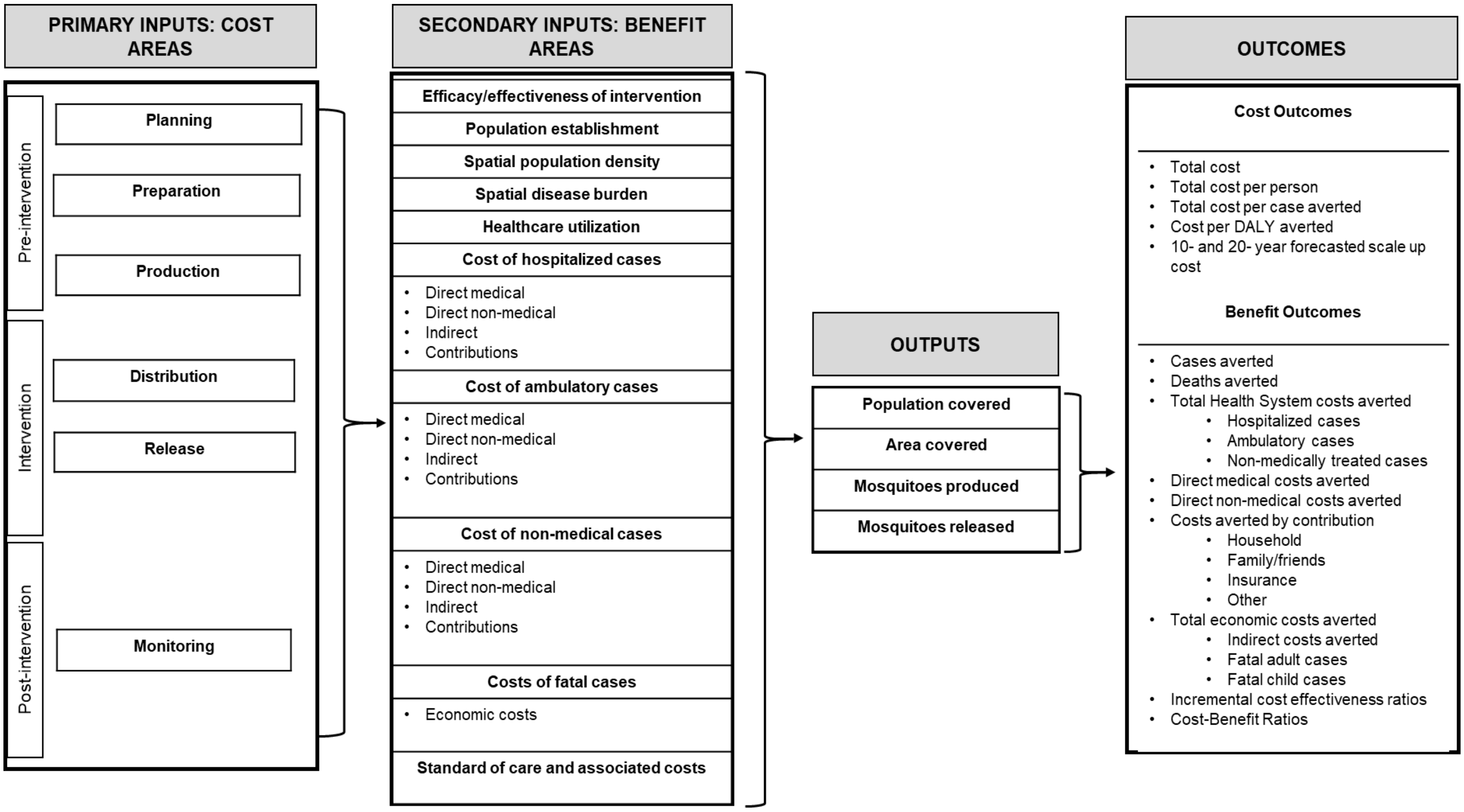
Table 1: Summary of Mosquito Release Interventions

Intervention	**Incompatible Insect Technique (IIT)**	**Sterile Insect Technique (SIT)**	**Release of Insects with Dominant Lethality (RIDL)**	***Wolbachia*-infected Mosquitos**	**Gene-drive**
Description	Release of males infected with *Wolbachia* that produce offspring that are unable to hatch. This approach has been used in *Aedes albopictus* in the US and China; *Aedes aegypti* in the US	Release of males sterilized with radiation and infected with *Wolbachia*, eggs fail to hatch	Release of males that have a dominant lethal gene variant (OX513A in *Aedes aegypti*)	Release of males and females infected with *Wolbachia* (wMel in *Aedes aegypti*) which results in offspring infected with Wolbachia	Release of mosquitoes that are genetically modified with a gene drive (CRISPR-Cas9), which results in sterile eggs or reduced vector competence
Desired Outcome	Mosquito population reduction	Mosquito population reduction	Mosquito population reduction	Mosquito population modification	Mosquito population modification
Persistence	Self-limiting	Self-limiting	Self-limiting	Self-sustaining	Self-sustaining, or self-limiting depending on gene drive

Mosquitoes infected with the naturally occurring, vertically transmitted bacterium *Wolbachia* suppress arbovirus replication and have demonstrated significant efficacy and effectiveness across field trials and randomized control trials globally (Nguyen et al. 2019; Dorigatti et al. 2018). These studies have demonstrated that the intervention effectiveness is evidence-based and empirically supported, thus making it ready for widespread implementation. What is not known to date is how to best implement a mosquito-targeted approach at scale across technologies, diseases, and geographies. Specifically, there is a need to better understand the factors that contribute to the cost of implementing mosquito-targeted interventions at scale, and what the benefits would be in terms of disease cases averted and health system and economic costs saved. An approach to determine this is critical for interventions that are already established (e.g., *Wolbachia*-infected mosquitoes) as they expand to new geographies, and for new interventions that are likely to be implemented in the near future (e.g., gene drive technology for malaria control). Without evidence on the estimated costs and benefits of such interventions, there is a risk that mosquito release programs will not be implemented in areas where there is the greatest need and potentially the greatest payoff for the investment. This knowledge gap will be addressed by describing cost drivers associated with mosquito-targeted intervention delivery.

The purpose of this white paper is to describe how several key cost factors for introducing mosquito release interventions may vary between contexts. With these considerations, our team will develop a generalizable cost-estimation tool that can be used for new programs and is flexible across geographic settings, disease contexts, and mosquito release interventions, such as those described above. The characteristics of this tool are described below in ***Figure 1.*** It is intended to be useful for implementers of mosquito release programs who may want to estimate costs of implementation and expected benefits in novel geographic settings.

Figure 1: Flowchart of Inputs, Outputs, and Outcomes for the Cost Estimation Tool



PRIMARY INPUTS: COST AREAS

Pre-Intervention

Cost areas are divided into three key phases: pre-intervention, intervention, and post-intervention. There are three primary categories of pre-intervention activities. These include the Planning, Preparation, and Production phases, all of which are described in this paper from the perspective of a first-in-country operation where infrastructure for local or regional mosquito production is required.

Planning

The planning phase of a mosquito release intervention is critical because adequately characterizing the eventual release area will dictate most future costs. The necessary steps to the planning phase include identifying data sources for geospatial disease burden, population demographics, health systems costing, environmental covariates, and vector bionomics that are all likely to affect the creation of a coordinated release plan. The necessary vector bionomics will include the primary target species and other mosquitoes present in a given area, the main transmitters of human disease, and how these abundance levels are affected by seasonality. If any of these datasets do not exist and need to be created, this will add substantially to the time and cost involved in the planning stage. Identifying and working with in-country partners to use these data in identifying a release area is an activity that will vary between countries but likely not between mosquito interventions. Identifying a target mosquito vector and the technology that will be used to insert the mosquito intervention into the ecosystem will also have important ramifications on total program costs. In the case of scaled releases for public health intervention, all of the following stages would take place following extensive studies including laboratory, cage environment, and small-scale field trials. Data from these studies will inform many of the questions mentioned in the following sections.

Preparation

The preparation phase of a mosquito release intervention includes the regulatory and stakeholder engagement logistics that are critical for programmatic success. Determining and meeting regulatory requirements from country to country is an unfortunately opaque process, and one that would likely benefit from cooperation and sharing of experiences between mosquito rearing organizations. One potential driver of cost in this phase is the completion of an Environmental Impact Assessment, the cost of which may vary depending on the regulatory standards of the country of interest. These costs will also vary with the mosquito target and intervention in question. For malaria control targets in rural areas, the release area and the area over which an impact assessment must be conducted will be larger and therefore more expensive than diseases such as Dengue that have primarily urban transmission. It is also quite likely that public uncertainty around certain interventions like gene drive’s ability to spread in the environment will result in higher cost and time barriers to approval than likely to arise from more “natural” interventions such as Wolbachia.

Stakeholder and community engagement costs vary heavily by geography, as well as on the strategies chosen for their completion. For instance, social mobilization and community sensitization can comprise large proportions of a program budget, including up to 23% of total deployment costs in a scaled up Aedes aegypti release by the World Mosquito Program in Northern Australia (O'Neill et al, 2019). Individual program costs are likely to be variable and highly dependent on the methods used for implementation. For instance, mass media outreach will entail a different range of costs than on-the-ground visits to many affected towns or villages spread across a wide geographic area. Prior malaria control community engagement efforts have shown that the population density of these areas will also be a driver of cost in most instances (Worrall and Fillinger, 2011). Another primary driver of cost variation will be the stage of implementation that the program is in. Programs that are first-in-country will bear significant infrastructure costs that will not be incurred in subsequent stages as experience with the intervention is built.

One question that will affect the costs of these efforts will be the measurement of success. If surveys are undertaken to show the impact of community engagement on public opinion, and if there are target levels of community approval that must be achieved to make the intervention acceptable to program staff or local government officials, these are likely to increase program costs for community engagement in comparison to purely educational efforts. Additionally, if an intervention intends to leverage community in-program distribution or implementation, through egg distribution or insect collection teams, this may reduce cost in the release and monitoring phases but will also require larger up-front investments in community engagement and training. It is possible that some programs will be able to reduce costs by integrating their community engagement and training efforts with existing programs for malaria control or public health campaigns such as mass drug administration, the likelihood of which will depend on the public health infrastructure and existing health interventions in the geographic area in question.

Production

The production phase of a mosquito intervention is typically dominated by fixed costs for mosquito rearing and mass production that are reliant on an established manufacturing facility. Building or leasing an appropriate facility will represent the largest proportion of costs in this phase, as well as recruiting and training the requisite staff for mosquito rearing. Whether a release program uses one central rearing facility and several smaller adult emergence centers, or sends centrally produced eggs internationally will impact costs in this phase by determining the number of facilities to be built and workers to be trained. These considerations are discussed at length in the distribution section. The creation of a mosquito breeding line will generally represent a fixed cost category across intervention sites but may vary depending on the technology being used in a particular program. For instance, the backcrossing to a native population of mosquitoes is a critical component for Wolbachia interventions that may be significantly more or less complex for applications of future Gene Drive mosquitoes.

Tests for vector competence, including insecticide resistance and health checks of lab-produced mosquitoes, should be fixed from site-to-site, as should activities that ensure line stability and amplification of the original breeding colony. These may include PCR checks of brood stock genetic stability, outcrossing with wild males, the sourcing of human, animal, or synthetic blood, the cost of which will vary depending on the source, as human blood would need to be screened for pathogens, and may present additional ethical, regulatory and community engagement considerations. Synthetic sources for blood meals such as SkitoSnak are slightly more expensive to produce but present fewer costs for pathogen testing (Gonzalez et al, 2018) and less concerns for community misunderstanding.

Intervention

The proportion of costs dedicated to the distribution and release of lab-augmented mosquitoes will be driven by several factors. Interventions that involve the release of adult mosquitoes must consider survival factors that are independent of those important for egg distribution. Major differences in mosquito genera requirements will drive the cost of distribution and release, in particular the ability to sex-sort pupae which is feasible at scale for Aedes, but not for Anopheles. Several experimental techniques are being studied to overcome this difference (Lutrat et al, 2019), but the current state of sexing for Anopheles entails manual sorting by a trained specialist that can achieve a maximum rate of only 500 pupae per hour with an error rate approaching 1% (Papathanos et al, 2018). If pupae are not sex-sorted prior to their development into adults, extra time and funding considerations must be made at their emergence or rearing facilities to ensure that disease-viable female adults are not taken to release sites.

Distribution

Once they have been sex-sorted, adult mosquitoes can be chilled and compacted for smooth transport to their release location (Zhang et al, 2020). This lowers the metabolism of the adult mosquitoes to a point where large numbers can be compacted into small tubes for transport with a reduced risk of death or injury and eventual competitiveness. Culbert et al, 2017 have demonstrated ideal storage conditions for *Anopheles arabiensis* mosquitoes, finding that temperatures between 4 and 10°C and compaction in transport tubes did not significantly affect mosquito survival, provided that some ventilation was provided, and that such conditions lasted no more than 24 hours (Culbert et al, 2017). For *Aedes aegypti* mosquitoes, similar findings from Chung et al., 2018 show that overnight air transport after chilling to a temperature between 7 and 14°C resulted in the highest survival rate when mosquitoes were compacted to 240 individuals/cm^3, even though this resulted in partial damage to mosquito wings and scales (Chung et al, 2018). Additionally, Zhang et al., 2020 showed that *Aedes albopictus* mosquitoes can maintain high survival rates after chilling to either 5 or 10°C for a maximum of 24 hours (Zhang et al, 2020).

Shipping eggs is generally cheaper and typically bears less of a regulatory burden than the shipment of live adults. For those interventions relying upon the shipment of eggs from international or regional production hubs, Aedes eggs can be desiccated and packaged for long-distance transport between 1 and 6 months depending on the species (Kauffman et al, 2017), but Anopheles eggs are more temperamental, seeing changes to sex ratio and survivorship among adults after 15 days of storage (Mazigo et al, 2019). If mosquitoes are being delivered internationally via shipments, the costs for specialized shipping requirements and fees must be considered.

Release

In-country transportation to release sites has historically been accomplished via ground transportation (IAEA, 2018), meaning that large variable costs can be accrued in personnel-hours, vehicle costs, and fuel surcharges. Some groups have posited the use of drone technology or light aircraft for targeted airborne release of live mosquitoes (Chung et al, 2018), but this solution has not yet been implemented at scale, and comes with its own array of financial and technical considerations. The release of adults compared to the placement of eggs will impact cost estimates for programs, as will the size of the release grid and the frequency with which releases are planned. The specific dimensions of a release grid are tied generally to the flight range of the mosquito in question, along with the size of the at-risk area the intervention is designed to affect. Additionally, whether an intervention is self-limiting, or self-sustaining as in the case of future gene drive applications will determine the need for repeated releases within an area over time, or if just one release will be appropriate to allow the intervention to spread throughout a wild mosquito population.

Post-Intervention

The post-intervention phase of a mosquito release program includes significant proportions of the overall program cost, accounting for nearly one quarter of programmatic costs for a recent World Mosquito Programme city-wide scaled deployment of Wolbachia-infected Aedes mosquitoes in northern Australia (O'Neill et al, 2019). Most of this cost category is driven by post-release monitoring of environmental, entomological, and epidemiologic outcomes critical to evaluating programmatic success and monitoring any unintended effects of the release program.

One aspect of post-intervention monitoring that will impact cost depending on the mosquito and intervention in question is the size of the intervention area that must be monitored. If the release area is spread out over a larger rural area for a mosquito with a wide flight range, the costs of environmental, entomological, and epidemiological monitoring will all likely be increased when compared to a smaller, more urban area, or for mosquitoes that do not range widely from where they hatch. Similarly, an intervention like gene drive that may have more uncertainty in the geographic range of its spread will likely require monitoring in an expanded geographic buffer that includes jurisdictions adjacent to the release area. This may include cross-border monitoring of environmental, entomological, and epidemiological endpoints that will substantially increase costs for release programs.

Environmental Monitoring

Much of the cost related to post-intervention environmental monitoring will be determined by the biosafety regulations in the countries where release operations occur. The costs may also differ substantially due to the specific mosquito release intervention being evaluated. As discussed in the pre-intervention phase, molecular gene drive technologies whose spread is not well characterized in the field will have more stringent, and therefore more expensive, requirements around monitoring for unintended environmental effects. However, it is generally expected that gene drive releases will be less likely to result in persistent ecological selection pressures than self-limiting mass releases such as Wolbachia interventions, which will have to be accounted for in post-release ecological niche monitoring activities (WHO, 2014).

Entomological Monitoring

Entomological monitoring for mosquito release involves costs associated with capturing mosquitoes in a systematic fashion from the release area in question, as well as identifying and sorting them by sex and species before examining target species individuals for evidence of intervention effect. Potential indicators for entomological monitoring include vector population size, transgene frequency, and the ability to support pathogen replication (WHO, 2014). Costs associated with the establishment of an appropriate capture grid may vary based on the species of mosquito in question, as the flight range and dispersal patterns of individuals varies by species. The initial study area will have been created with these factors in mind, and if an intervention is targeting a wide-ranging mosquito in rural areas like *Anopheles gambiae*, this will create additional cost burdens compared to monitoring activities for interventions against urban or peri-urban mosquitoes such as *Aedes aegypti* with more comparatively contained diffusion patterns.

Another mosquito-specific variation in cost for entomological monitoring will be tied to the actual capture of mosquitoes. While mosquitoes can be reliably sampled from pre-placed traps in or around human dwellings, as well as artificial standing water containers, Anopheles mosquitoes may require capture both inside and outside of houses. While Anopheles are generally more common, their male mating swarm behavior at dusk limits efficient capture of large numbers in the wild due to the need to find local swarming sites and collect samples with a sweep-net. This has to be performed by someone who has been trained to do it at identified study capture sites and can only realistically happen at scale during one limited time-window per day, when the mosquitoes form mating swarms in the early evening. This means that substantial up-front investment in training for community collectors, or substantial costs in both time and capital must be devoted to sending collectors around a potentially vast capture area where they are able to hit a very limited number of sites per day. While lower-cost options are available for mosquito capture in these settings, such as sentinel traps or egg-collection techniques, they are not likely to produce the same yield and may produce a biologically biased sample of mosquitoes for study.

The mosquito modification technology that is being evaluated is a key component in considering entomological monitoring costs. Once the mosquitoes are captured and sorted, any additional analysis that needs to occur for measuring uptake of the intervention will add to program costs. For example, if a sterile male intervention's monitoring plan is to measure rates of population depletion, that will likely incur fewer costs than a Wolbachia program which needs to determine what proportion of captured mosquitoes have been colonized by the Wolbachia. Similarly, the endpoints for an eventual application of gene drive technology may present additional costs in monitoring if captured mosquito genomes must be sequenced to measure the spread of the intervention within a target population.

Epidemiological Monitoring

Epidemiological monitoring activities include the detection of lowered incidence of infection or clinical disease in human populations associated with the mosquito release area. Reductions in infections are often measured alongside decreased morbidity and mortality relating to the diseases of interest. If a field trial aims to detect decreasing infection incidence, this will be achievable with a smaller and less expensive cohort compared to field trails that aim to detect decreasing incidence of disease, as clinical disease development is not guaranteed in all those infected (WHO, 2014).

The costs of detecting these endpoints are often bound to the time it takes to detect a meaningful difference from base-rates of disease, which is most easily detected in high-transmission settings. If there are very few cases in a release area, then a field trial will take longer to show a detectable decrease in cases over time. This is a key consideration when projecting costs for a mosquito release intervention for malaria, which is highly endemic in many areas, as compared to dengue, which is less predictable in its transmission across different settings. Seasonality and year-to-year variations also differ between disease and geographic contexts, all of which affect the length of time needed to conduct a strong epidemiologic evaluation of an intervention. Finally, disease monitoring will be highly dependent on the existing local clinical infrastructure that can be accessed for disease detection, which would have important cost implications.

SECONDARY INPUTS: BENEFIT AREAS

In the following section, several secondary inputs that are critical to determining the cost-effectiveness and cost-benefit outcomes of implementing and scaling up a mosquito release intervention are described in detail. These estimates will come from published peer-reviewed articles, where available. Each estimate will include uncertainty intervals and will allow for implementers of mosquito release programs who may want to adjust these parameters and understand the impact on the cost and benefit outcomes.

Effectiveness

Our method for assessing cost-benefit implications will utilize several scenarios with varying effectiveness. For example, a recent modelling study indicated that a nationwide *Wolbachia* population replacement program was estimated to avert 86.2% (95% Uncertainty interval 36.2-99.9%) of dengue cases (O'Reilly et al. 2019). However, given the wide uncertainty interval in the example above, and effectiveness that may be affected by population density and other covariates, there will be a range, or several effectiveness estimates included as options for this work.

For mosquito release intervention, it is expected that epidemiologic impact evaluation efforts would take place before scaling up. As such, our work will rely on estimates of efficacy and effectiveness from studies (i.e., mosquito release intervention randomized trials), rather than relying on mosquito release programs to routinely collect epidemiological data. Most randomized trials with epidemiological outcomes include detection of lowered incidence of infection or clinical disease in human populations associated with large mosquito release area. Reductions in infections are often measured alongside decreased morbidity and mortality relating to the diseases of interest. Release programs may choose to conduct epidemiological evaluations as part of routine implementation.

Establishment in Population and Transmission

Though entomological monitoring is expected to be part of the implementation costs, entomological endpoints will be included as options linked to cost-implications for our methods. Estimates from prior randomized trials, vector competence studies, and mathematical modeling on the ability of a specific mosquito intervention to establish itself in the mosquito population and reduce disease transmission will be included. For example, several dengue transmission models have been conducted and shown that Wolbachia-infected mosquitoes can replace wild-type *Aedes aegypti* populations and persist for 7 years (Hoffmann et al. 2011). Further, other studies of Wolbachia-infected mosquitoes have shown a substantial reduction in dengue virus transmission (Ferguson et al. 2015; Ndii et al. 2015; Carrington et al. 2018). Each of these input parameters could be included with uncertainty intervals to understand several scale-up scenarios with varying population establishment and virus or parasite transmission rates.

Spatial Population Density and Disease Burden

Population and disease burden are important determinants of the cost of releasing mosquitoes, as mentioned above. Previous Wolbachia-infected mosquito interventions for dengue control have indicated that for areas with higher population density, and therefore larger mosquito populations, the number of mosquitoes required per release is higher than in areas with smaller native mosquito populations (O'Neill et al. 2018). Spatially explicit estimates of population and cases of disease will also be critical as secondary inputs to determine outputs such as the number of people covered by the intervention, the cases averted by the intervention, and outcomes such as cost per person covered and cost per case averted. Spatial estimates of vector-borne diseases are available through sources such as the Institute of Health Metrics and Evaluation and the Malaria Atlas Project.

High resolution human population distributions are widely available through sources such as WorldPop (Tatem et al. 2017). These estimates rely on satellite, census, survey, and cell phone data to produce geospatial population density estimates. Dengue, malaria, and other vector-borne diseases have limited disease surveillance and are largely underreported due to scarce data on the number of cases in communities, particularly for mild and asymptomatic cases. Given limited surveillance, several methods have been employed to improve burden estimates, including surveys that measure occurrence, incidence, and seroprevalence, and approaches such as ecological niche modelling (Messina et al. 2014; Brady et al 2014; Ong et al. 2018; Bhatt et al. 2013). Modelled estimates of population density and cases will be critical components of our cost-benefit estimations as they will provide estimates regarding reach (i.e., the number of people reached by the intervention in a specific geography) and the potential cases that could be averted in specific geographies by the intervention.

Disease Severity Estimates

In addition to estimating the case burden of dengue, malaria, and associated vector-borne diseases, sources that disaggregate by case severity of the disease of interest will be sought. Cases will include non-medically attended cases, ambulatory cases, hospitalized cases, and fatal cases. These designations are as follows: Not medically attended refers to an illness interrupting routines but not resulting in formal health seeking for treatment. Not medically attended cases may seek treatment at a pharmacy or be left untreated. Ambulatory cases include those that have severe enough symptoms to warrant formal medical treatment in an outpatient facility, whereas hospitalized cases are severe enough to warrant hospital admission. Fatal cases refer to cases where the cause of death is determined to be the vector-borne disease. To calculate the burden of disease in each area, the distribution of case severity will be established to the furthest extent possible. Each of these types of cases will be investigated to determine the distribution of case severity across diseases, populations, and geographies. However, if there are not recent or reliable estimates, healthcare utilization rates from nationally representative surveys such as the Demographic Health Surveys will be used. For each type of case, data on the Disability Adjusted Life Years (DALYs) and Years of Life Lost (YLL) for fatal cases could be accessed, which would be important secondary inputs for determining the cost per DALY averted or the cost per YLL averted, indicators which are considered the gold standard for economic evaluations.

Cost of Illness Estimates

Once burden and case severity are determined, these estimates will be linked with existing data on financial and economic cost of illness for vector-borne disease across countries, which are widely available (Beatty et al. 2011; Suaya et al. 2009; Hailu et al. 2017). Financial costs will include direct medical costs, including the cost of medication, treatment, and healthcare costs and direct non-medical costs, including food or transportation. Sources that describe the cost contributions for each financial cost (e.g., households, the government, insurance, etc.) will be utilized. Economic costs may include both short term indirect losses such as lost wage or opportunity costs during illness, and long-term economic losses such as lost work productivity. For costs of fatal illness, estimates that use methods such as the human capital approach to estimate the economic value of a human life lost prematurely based on expected productivity and adjusted for GDP will be accessed (Shepard et al. 2016).

Standard of Care and Associated Costs

To estimate the incremental effectiveness and cost of mosquito release programs compared to existing interventions, the existing standard of care for vector-borne diseases must be established in each relevant geography. These will vary by context but will include interventions such as insecticide-treated bed nets, indoor residual spraying, and antimalarial drugs for malaria, and insecticides and vaccines for dengue (WHO, 2020). Further, associated costs for the standard of care across geographies will have to be quantified. Estimates will come from existing government and non-governmental organization expenditures related to global malaria and dengue efforts, and other resources should as WHO-CHOICE for unit costs (Evans et al. 2005).

OUTPUTS & OUTCOMES

Outputs

Outputs will provide information on coverage and reach (i.e., area and population) for each mosquito release intervention. Examples of outputs could include (but are not limited to) how many staff were trained, how many mosquitoes were produced, and how many mosquitoes were released.

Outcomes

Several cost and benefit outcomes can be estimated with the input parameters described. For cost outcomes, important estimates for understanding the impact will include the total cost of the mosquito release program, the cost per geography (e.g., cost per administrative unit, cost per km^2), the total cost per person covered, the total cost per case averted, the cost per DALY averted, and 10- or 20-year forecasted scale-up costs will be determined. Benefit outcomes will include cases averted, deaths averted, total health system costs averted (i.e., from hospitalized and ambulatory cases) including direct medical and non-medical costs, total economic costs averted (including indirect costs, and long-term economic losses from fatalities). In addition, incremental cost effectiveness ratios and cost-benefit ratios will be calculated. These are critical for comparisons and bench marking against existing interventions.

ADDITIONAL CONSIDERATIONS

Sensitivity Analyses and Economic Considerations

In addition to including uncertainty intervals for each primary and secondary inputs, sensitivity analyses will be included as part of our estimates. These will use a range of plausible values for each primary and secondary input parameter to assess the impact of variability on our estimates. This will help to address uncertainty in the estimates produced and allow for a range of estimates or several categories of estimates (i.e., a base case, optimistic, conservative) to be produced.

Several standard economic considerations will be included in the analyses, including standard discounting. These are particularly important for benefit outcomes across varying time periods, and with interventions, such as mosquito releases, where there is a delay between the initial program costs and the time that the effects and benefits accrue. Similarly, if the cost of interventions is estimated across years, special considerations for inflation and differences in price levels for the same goods or labor could be taken into account.

Limitations and Potential Challenges

Although rigorous costing methodologies such as inclusion of sensitivity analyses to account for uncertainty, it will be challenging to determine point estimates for many of the primary input parameters and secondary input parameters. This will be particularly challenging for lab-augmented mosquito technologies that have not been field tested or implemented yet (i.e., gene drive). Further, it may be particularly challenging to get reliable cost estimates and activity specifics (i.e., activities during planning, preparation, production, distribution, and release) that may be deemed sensitive by implementing partners. Lastly, it is unlikely that there will be estimates for all secondary input parameters (i.e., burden, cost of illness) across all settings of interest, which will require us to extrapolate estimates. For unavailable data, estimates from similar contexts and interventions may be used to enrich the existing data.

CONCLUSION

Several primary and secondary input parameters are required to develop a generalizable cost-benefit tool for mosquito release programs. In the next phase of this work, key cost areas in the pre-intervention, intervention, and post-intervention phases will be combined with secondary input parameters to develop a generalizable cost-benefit tool that can be used for new programs and is flexible across geographic settings, disease contexts, and vector population control interventions such as those described above. This tool will provide insights on the costs and benefits of mosquito release interventions, which are important in guiding planning, advocacy, implementation, and scale-up efforts. We will begin this effort by collaborating with mosquito release programs to access and establish estimates for the primary cost areas for two use cases: *Wolbachia* scale up for dengue control in Indonesia and gene drive implementation for malaria control in Burkina Faso. We will determine data requirements and seek out data sources for the secondary input parameters for dengue and malaria in the respective geographies. Once the two use cases are established, we will expand this work and develop a generalizable cost-estimation tool that is flexible across geographic settings, disease contexts, and mosquito release interventions.

REFERENCES

Beatty, M. E., Beutels, P., Meltzer, M. I., Shepard, D. S., Hombach, J., Hutubessy, R., ... & Kuritsky, J. N. (2011). Health economics of dengue: a systematic literature review and expert panel's assessment. *The American journal of tropical medicine and hygiene*, *84*(3), 473-488.

Bhatt, S., Gething, P. W., Brady, O. J., Messina, J. P., Farlow, A. W., Moyes, C. L., ... & Hay, S. I. (2013). The global distribution and burden of dengue. *Nature*, *496*(7446), 504-507.

Brady, O. J., Golding, N., Pigott, D. M., Kraemer, M. U., Messina, J. P., Reiner Jr, R. C., ... & Hay, S. I. (2014). Global temperature constraints on Aedes aegypti and Ae. albopictus persistence and competence for dengue virus transmission. *Parasites & vectors*, *7*(1), 1-17.

Carrington, L. B., Tran, B. C. N., Le, N. T. H., Luong, T. T. H., Nguyen, T. T., Nguyen, P. T., ... & Simmons, C. P. (2018). Field-and clinically derived estimates of Wolbachia-mediated blocking of dengue virus transmission potential in Aedes aegypti mosquitoes. *Proceedings of the National Academy of Sciences*, *115*(2), 361-366.

Chung, H.-N., Rodriguez, S. D., Gonzales, K. K., Vulcan, J., Cordova, J. J., Mitra, S., Adams, C. G., Moses-Gonzales, N., Tam, N., Cluck, J. W., Attardo, G. M., & Hansen, I. A. (2018). Toward Implementation of Mosquito Sterile Insect Technique: The Effect of Storage Conditions on Survival of Male Aedes aegypti Mosquitoes (Diptera: Culicidae) During Transport. Journal of Insect Science, 18(2).

Culbert, N. J., Lees, R. S., Vreysen, M. J. B., Darby, A. C., & Gilles, J. R. L. (2017). Optimised conditions for handling and transport of male Anopheles arabiensis: effects of low temperature, compaction, and ventilation on male quality. Entomologia Experimentalis et Applicata, 164(3), 276–283.

Dorigatti, I., McCormack, C., Nedjati-Gilani, G., & Ferguson, N. M. (2018). Using Wolbachia for dengue control: insights from modelling. *Trends in parasitology*, *34*(2), 102-113.

Eisen, L., Beaty, B. J., Morrison, A. C., & Scott, T. W. (2009). Proactive vector control strategies and improved monitoring and evaluation practices for dengue prevention. *Journal of medical entomology*, *46*(6), 1245-1255.

Evans, D. B., Edejer, T. T. T., Adam, T., & Lim, S. S. (2005). Methods to assess the costs and health effects of interventions for improving health in developing countries. *Bmj*, *331*(7525), 1137-1140.

Ferguson, N. M., Kien, D. T. H., Clapham, H., Aguas, R., Trung, V. T., Chau, T. N. B., ... & Simmons, C. P. (2015). Modeling the impact on virus transmission of Wolbachia-mediated blocking of dengue virus infection of Aedes aegypti. *Science translational medicine*, *7*(279), 279ra37-279ra37.

Gething, P. W., Casey, D. C., Weiss, D. J., Bisanzio, D., Bhatt, S., Cameron, E., ... & Lim, S. S. (2016). Mapping Plasmodium falciparum mortality in Africa between 1990 and 2015. *New England Journal of Medicine*, *375*(25), 2435-2445.

Gonzales, K. K., Rodriguez, S. D., Chung, H.-N., Kowalski, M., Vulcan, J., Moore, E. L., Li, Y., Willette, S. M., Kandel, Y., Van Voorhies, W. A., Holguin, F. O., Hanley, K. A., & Hansen, I. A. (2018). The Effect of SkitoSnack, an Artificial Blood Meal Replacement, on Aedes aegypti Life History Traits and Gut Microbiota. Scientific Reports, 8(1), 11023.

Gubler, D. J. (1989). Aedes aegypti and Aedes aegypti-borne disease control in the 1990s: top down or bottom up. *The American journal of tropical medicine and hygiene*, *40*(6), 571-578.

Hailu, A., Lindtjørn, B., Deressa, W., Gari, T., Loha, E., & Robberstad, B. (2017). Economic burden of malaria and predictors of cost variability to rural households in south-central

Ethiopia. *PLoS One*, *12*(10), e0185315.

Hoffmann, A. A., Montgomery, B. L., Popovici, J., Iturbe-Ormaetxe, I., Johnson, P. H., Muzzi, F., ... & O'Neill, S. L. (2011). Successful establishment of Wolbachia in Aedes populations to suppress dengue transmission. *Nature*, *476*(7361), 454-457.

IAEA. (2018). Co-ordinated Research Project on Mosquito Handling, Transport, Release and Male Trapping Methods (Research Coordination Meeting No. 3; Joint FAO/IAEA Division of Nuclear Techniques in Food And). IAEA.

Kauffman, E., Payne, A., Franke, M. A., Schmid, M. A., Harris, E., & Kramer, L. D. (2017). Rearing of Culex spp. and Aedes spp. Mosquitoes. Bio-Protocol, 7(17).

Lutrat, C., Giesbrecht, D., Marois, E., Whyard, S., Baldet, T., & Bouyer, J. (2019). Sex Sorting for Pest Control: It's Raining Men! Trends in Parasitology, 35(8), 649–662.

Mazigo, E., Kidima, W., Myamba, J., & Kweka, E. J. (2019). The impact of Anopheles gambiae egg storage for mass rearing and production success. Malaria Journal, 18(1), 52.

Messina, J. P., Brady, O. J., Golding, N., Kraemer, M. U., Wint, G. W., Ray, S. E., ... & Hay, S. I. (2019). The current and future global distribution and population at risk of dengue. *Nature microbiology*, *4*(9), 1508-1515.

Ndii, M. Z., Hickson, R. I., Allingham, D., & Mercer, G. N. (2015). Modelling the transmission dynamics of dengue in the presence of Wolbachia. *Mathematical biosciences*, *262*, 157-166.

Nguyen, T. H., Le Nguyen, H., Nguyen, T. Y., Vu, S. N., Tran, N. D., Le, T. N., ... & Hoffmann, A. A. (2015). Field evaluation of the establishment potential of wMelPop Wolbachia in Australia and Vietnam for dengue control. *Parasites & vectors*, *8*(1), 563.

Oki, M., Sunahara, T., Hashizume, M., & Yamamoto, T. (2011). Optimal timing of insecticide fogging to minimize dengue cases: modeling dengue transmission among various seasonalities and transmission intensities. *PLoS Negl Trop Dis*, *5*(10), e1367.

Ong, J., Liu, X., Rajarethinam, J., Kok, S. Y., Liang, S., Tang, C. S., ... & Yap, G. (2018). Mapping dengue risk in Singapore using Random Forest. *PLoS neglected tropical diseases*, *12*(6), e0006587.

O'Neill, S. L., Ryan, P. A., Turley, A. P., Wilson, G., Retzki, K., Iturbe-Ormaetxe, I., Dong, Y., Kenny, N., Paton, C. J., Ritchie, S. A., Brown-Kenyon, J., Stanford, D., Wittmeier, N., Jewell, N. P., Tanamas, S. K., Anders, K. L., & Simmons, C. P. (2019). Scaled deployment of Wolbachia to protect the community from dengue and other Aedes transmitted arboviruses. Gates Open Research, 2.

O'Reilly, K. M., Hendrickx, E., Kharisma, D. D., Wilastonegoro, N. N., Carrington, L. B., Elyazar, I. R., ... & Brady, O. J. (2019). Estimating the burden of dengue and the impact of release of wMel Wolbachia-infected mosquitoes in Indonesia: a modelling study. *BMC medicine*, *17*(1), 1-14.

Papathanos, P. A., Bourtzis, K., Tripet, F., Bossin, H., Virginio, J. F., Capurro, M. L., Pedrosa, M. C., Guindo, A., Sylla, L., Coulibaly, M. B., Yao, F. A., Epopa, P. S., & Diabate, A. (2018). A perspective on the need and current status of efficient sex separation methods for mosquito genetic control. Parasites & Vectors, 11(2), 654.

Ritchie, S. A., & Johnson, B. J. (2017). Advances in vector control science: rear-and-release strategies show promise… but don't forget the basics. *The Journal of infectious diseases*, *215*(suppl_2), S103-S108.

Shepard, D. S., Undurraga, E. A., Halasa, Y. A., & Stanaway, J. D. (2016). The global economic burden of dengue: a systematic analysis. *The Lancet infectious diseases*, *16*(8), 935-941.

Suaya, J. A., Shepard, D. S., Siqueira, J. B., Martelli, C. T., Lum, L. C., Tan, L. H., ... & Halstead, S. B. (2009). Cost of dengue cases in eight countries in the Americas and Asia: a prospective study. *The American journal of tropical medicine and hygiene*, *80*(5), 846-855.

Tatem, A. J. (2017). WorldPop, open data for spatial demography. *Scientific data*, *4*(1), 1-4.

World Health Organization. (2014). Guidance framework for testing of genetically modified mosquitoes. World Health Organization on behalf of the Special Programme for Research and Training in Tropical Diseases.

World Health Organization. (2020). *Vector-borne diseases*. World Health Organization.

Worrall, E., & Fillinger, U. (2011). Large-scale use of mosquito larval source management for malaria control in Africa: a cost analysis. Malaria Journal, 10(1), 338.

Yen, P. S., & Failloux, A. B. (2020). A Review: Wolbachia-Based Population Replacement for Mosquito Control Shares Common Points with Genetically Modified Control Approaches. *Pathogens*, *9*(5), 404.

Zhang, D., Xi, Z., Li, Y., Wang, X., Yamada, H., Qiu, J., Liang, Y., Zhang, M., Wu, Y., & Zheng, X. (2020). Toward implementation of combined incompatible and sterile insect techniques for mosquito control: Optimized chilling conditions for handling Aedes albopictus male adults prior to release. PLOS Neglected Tropical Diseases, 14(9), e0008561.