BEING SMARTER THAN THE BUGS: THE ROLE OF (META)POPULATION DYNAMICS IN THE CONTROL OF INVASIVE MOSQUITOES AND THE PATHOGENS THEY TRANSMIT

By

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ABSTRACT OF THE DISSERTATION

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the control of invasive mosquitoes and the pathogens they transmit

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Mosquito-borne pathogens continue to afflict human populations around the world. Currently, our best methods for combatting the majority of them focus on controlling the vector species that transmit these pathogens. In the absence of systematic protocols developed by careful scientific research, current control methods vary significantly across space at multiple scales, and are reactively executed in response to various entomological and epidemiological indices. The resulting spatiotemporal patchwork of mosquito control across the local, regional, and global landscape provides the immediate potential to generate metapopulation dynamics in both mosquito vector species and the pathogens they transmit. In this dissertation, I explore these largely unstudied, novel dynamics, with the goal of illuminating ways in which mosquito control methods can better protect the global health landscape from mosquito-borne pathogens.

In chapter one, I examine the timing of larval control when triggered by different types and scales of surveillance information, and how well each surveillance type informs intervention that effectively reduces human infections. In

chapter two, I explore how the spatial distribution of larval control across a landscape causes and interacts with mosquito metapopulation dynamics to determine the efficacy of control efforts. In chapter three, I compare the efficacies of adulticide treatment and larval control in reducing the number of human infections in different entomological contexts. Ultimately, all three chapters demonstrate that local context determines when and where different types of mosquito control should be used, and highlight the need for further basic and applied research on vector mosquitoes in order to develop cost-effective, context-specific programs for the control of mosquito-borne viruses.

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INTRODUCTION

Anthropogenic change has altered spatial processes, increasing the risk of disease outbreaks in humans, wildlife, livestock, and crops around the world. International travel increases the spread of pathogens across the globe, and urbanization increases the rate at which infected and susceptible human hosts encounter each other (Tatem et al. 2006, Kilpatrick and Randolph 2012). Habitat loss leads to high population densities of wildlife at the small, intact sites, increasing intraspecific transmission of pathogens (Hess 1996, Altizer et al. 2011). Habitat destruction and fragmentation also reduce the prevalence of top predators in anthropogenic landscapes, and epidemiological models indicate that this predator removal may increase the number and proportion of prey hosts infected with a disease across a landscape (Ostfeld and Holt 2004). Some conservation efforts, such as translocations, also effectively increase pathogen dispersal over long distances, as well as human transport of wildlife in international trade (Daszak et al. 2001, Brunner et al. 2015). All of these changes contribute to the "pathogen pollution" that is linked to numerous emerging infectious diseases in wildlife and humans (Daszak et al. 2001, Cunningham et al. 2003).

International trade and travel have also enabled invasions of weedy species that quickly thrive in new habitats by outcompeting native species (McKinney and Lockwood 1999) or occupying previously empty niches. The yellow fever mosquito (*Aedes aegypti*) and Asian tiger mosquito (*Aedes albopictus*) exemplify this situation (Juliano and Lounibos 2005), and are efficient vectors of numerous viruses that

have caused recent epidemics throughout the world, such as yellow fever, dengue, chikungunya, West Nile, and Zika (Gratz 2004, Chouin-Carneiro et al. 2016). They have become globally invasive, putting immunologically naïve human populations at risk of these novel pathogens. Thus, more effective methods and research into best practices are needed to control the abundance of invasive mosquitoes and the pathogens they transmit.

Many invasive mosquito species are highly synanthropic, preferring to inhabit urban environments with high densities of human blood meal sources, and/or making use of human-altered habitats. Though thought to be limited in dispersal ability (Reiter 2007), females find and oviposit in small pools of standing water that are present throughout urban habitats (i.e., in tires and corrugated extension spouts (Unlu et al. 2013, 2014)). Importantly, the heterogeneous nature of control interventions must affect the dispersion of mosquitoes across urban and suburban landscapes, likely generating source-sink dynamics as some areas are controlled more often and with different methods than others (Auger et al. 2008). Control efforts may thus alter and/or create metapopulation dynamics in both the mosquitoes and the pathogens they transmit.

Vector control may engender a situation akin to the traditional blinking lights model of metapopulations. In this model, patches in a metapopulation "blink" in and out of existence due to the interplay between patch colonization and extinction rates (Hanski 1991). Though similar, the metapopulation dynamics created by control are distinct from this model because they impose extrinsic causes of patch "extinctions." A vector metapopulation's viability in this context depends on the interaction

between metapopulation dynamics (life history traits such as reproductive capacity, extinction proneness, and dispersal ability) and landscape dynamics (rate and spatial arrangement of control efforts, in this context) (Keymer et al. 2000, Akçakaya and Radeloff 2004). When considering the viability of a vector-borne pathogen, epidemiological parameters, such as intrinsic and extrinsic incubation periods and host immune responses, must also be considered, as well as demographic characteristics of the host population.

Current control methods either target the immature stages that develop in small pools (herein referred to as "larval control") or target the terrestrial adults. Larval control is commonly implemented by emptying and cleaning any water-holding containers that are suitable oviposition sites, or by applying larvicides to pools that cannot be emptied. Because adult mosquitoes are not limited to the discrete, aquatic habitats that immatures occupy, area-wide application of adulticide is the primary method employed when targeting adults. Control methods targeting immatures likely alter mosquito ecology and metapopulational dynamics differently from methods targeting adults. Thus, they likely also have different impacts on human disease risk.

In order to be successful, control efforts should reduce the population of infected mosquito vectors to below the thresholds required to maintain ongoing circulation (i.e., beneath the reproductive threshold, R_0), causing local extinctions of the pathogens they transmit. However, once control ceases and the vector population recovers, human travel can easily reintroduce the pathogen, causing a new local outbreak (Adams and Kapan 2009). The ways in which control efforts

create or alter the metapopulation dynamics of both vector and pathogen have gone largely unexplored in epidemiological modeling. A more robust understanding of the mechanisms operating in vector metapopulations in both the presence and absence of vector control may be crucial as pathogens continue to emerge and spread.

Due to its theoretical nature, my dissertation and its conclusions cannot yet be directly applied to real-world control efforts. However, I hope my research will ignite discussions among scientists, local governments, and mosquito control professionals about when and where different methods of control should occur, as well as the importance of considering ecological context, in order to implement more cost-effective methods that better protect the public from vector-borne diseases.

Chapter one

The type, quality, and frequency of mosquito and disease surveillance is extremely varied at all scales, with municipalities, counties, states, and countries often working independently to combat pathogens and vectors that ignore these artificial boundaries. The resulting spatiotemporal variability in control across a landscape likely alters mosquito metapopulation dynamics. Surveillance information might include epidemiological data on the incidence of reported human infections or the number of mosquitoes that test positive for a certain pathogen. Surveillance may also involve collection of ecological/entomological data on the abundance of immature or adult mosquitoes. In my first chapter, I examine the

efficacy of larval mosquito control when triggered by these different types and scales of surveillance information across a landscape. The results highlight the importance of implementing control measures in the early stages of an outbreak. Ideally, control should begin *before* an outbreak occurs, indicating that epidemiological surveillance information is an inherently ineffective trigger for control implementation when the goal of the vector control program is to reduce human disease risk.

Chapter two

Spatial processes have been largely ignored in the past when considering how to effectively allocate limited resources available for mosquito control. For my second chapter, I explore how the spatial distribution of larval mosquito control across a landscape affects how well control efforts reduce human infections with a mosquito-borne pathogen. The results demonstrate the potential to improve the cost-effectiveness of vector control by distributing control efforts in particular patterns to manipulate mosquito metapopulation dynamics. However, the ideal way of distributing control largely depends on the demography of the local mosquito population, so information on local dynamics is necessary to develop effective site-specific control distributions. Additional complications arise if areas deemed important locations for implementing control are on privately owned land, since government agencies cannot enact control measures there without the landowner's consent. Because of this, citizen cooperation will likely be critical to implementing control that effectively protects the health of all citizens.

Chapter three

For my third chapter, I compare the efficacy of adulticide treatment with that of larval control, using various biting rates and adult mosquito death rates. Despite little evidence demonstrating its efficacy, mosquito control agencies typically spray adulticides as the initial emergency response to combat mosquito-borne pathogens. Methods targeting adult mosquitoes inherently create different mosquito population dynamics from methods targeting immature mosquitoes, though the different demographic processes created by these two approaches have rarely been investigated. The results of this chapter suggest that mosquito population context does play a pivotal role in determining whether adulticide treatment or larval control better reduces human infections. For instance, larval control, as opposed to adulticide treatment, may better reduce outbreaks of highly transmissible viruses, and/or of pathogens vectored by aggressively-biting mosquitoes. Thus, methods targeting immatures should perhaps be implemented in emergency situations rather than methods targeting adults.

The importance of being urgent: the impact of surveillance target and scale on mosquito-borne disease control

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ABSTRACT

With the emergence or re-emergence of numerous mosquito-borne diseases in recent years, effective methods for emergency vector control responses are necessary to reduce human infections. Current vector control practices often vary significantly between different jurisdictions, and are executed independently and at different spatial scales. Various types of surveillance information (e.g., number of human infections or adult mosquitoes) trigger the implementation of control measures, though the target and scale of surveillance vary locally. This patchy implementation of control measures likely alters the efficacy of control. We modeled six different scenarios, with larval mosquito control occurring in response to surveillance data of different types and at different scales (e.g., across the landscape or in each patch). Our results indicate that: earlier application of larvicide after an escalation of disease risk achieves much greater reductions in human infections than later control implementation; uniform control across the landscape provides better outbreak mitigation than patchy control application; and different types of surveillance data require different levels of sensitivity in their collection to effectively inform control measures. Our simulations also demonstrate a potential logical fallacy of reactive, surveillance-driven vector control: measures stop being implemented as soon as they are deemed effective. This false sense of security leads to patchier control efforts that will do little to curb the size of future vector-borne disease outbreaks. More investment should be placed in collecting high quality information that can trigger early and uniform implementation, while researchers

work to discover more informative metrics of human risk to trigger more effective control.

INTRODUCTION

Container-inhabiting mosquitoes in the genus *Aedes*, specifically *Ae. aegypti* and *Ae. albopictus*, are competent carriers of many flaviviruses, including Zika, dengue, yellow fever, and chikungunya (Gratz 2004, Chouin-Carneiro et al. 2016, Weger-Lucarelli et al. 2016). They are also notoriously difficult to control because they thrive in urban and suburban settings where the immatures develop in water-holding containers present in homes and backyards (Powell et al. 2013, Unlu et al. 2013, 2014). Previous attempts to eradicate *Ae. aegypti* (the yellow fever mosquito) from its invasive range in the Americas were successful only in the short-term; within a few years after eradication had occurred across large portions of Central and South America, they began recolonizing and soon achieved numbers greater than their pre-eradication campaign abundances (Reiter 2001). Although invasive *Aedes* are very difficult to eradicate once they become established in a new area, reducing their abundance during outbreaks can significantly reduce the number of humans who become infected (Lorenzi et al. 2016). Especially for newly emerging or re-emerging mosquito-borne viruses like Zika, most human populations are highly susceptible to the virus and vaccines are not yet ready for use. Therefore, control of vector populations before and during outbreaks remains the best direct

means available of limiting the size of outbreaks, which may continue to emerge in the coming years (Manore et al. 2017).

Although vector control interventions and implementation methods vary widely between local agencies (NACCHO 2016), many implement Integrated Mosquito Management (IMM) techniques (Rose 2001) that target the larval and adult stages at different times. In the absence of mosquito-borne infectious disease circulation in the local human population, mosquito control efforts tend to target the aquatic larval stage via source reduction, through both draining/elimination of oviposition sites and larvicide application to water-holding containers in active use (e.g., bird baths, recycling cans) (Fonseca et al. 2013). However, source reduction is difficult to implement for control of container-inhabiting species because their larval habitats are often abundant, cryptic, and/or on privately owned land. During active outbreaks, common practice has included application of adulticide in and around areas with high prevalence of human infection (WHO 1997). Unfortunately, these chemical control methods have become less effective in recent years due to the evolution of resistance to multiple types of insecticides in mosquito populations worldwide (Corbel et al. 2017). Alternative, non-chemical control methods are being developed and tested (Hoffmann et al. 2011, Yakob and Walker 2016), but they will likely need to be part of a larger IMM strategy in order to provide effective outbreak prevention or mitigation within a broader eco-evolutionary context (Agusto et al. 2012, Yakob et al. 2017).

While trying to discover and implement the most effective emergency vector control regimes (e.g., Unlu et al. 2016; Gaff et al. 2015), scientists and mosquito

control specialists rarely consider the fact that different agencies enact control measures in response to different types and scales of information. Private citizens may be bothered by the abundance of mosquitos in their own house or yard (Dickinson and Paskewitz 2012), and enact bottom-up control on that small scale, while local/municipal vector control agencies enact mosquito control measures across their own jurisdictions, and state/national/global health agencies may implement larger scale, top-down control measures.

Critically, control efforts at these various spatial scales are frequently implemented reactively, only after a certain surveillance threshold is reached. Reactive control can occur in response to surveillance of different potential risks, such as the number of adult mosquitoes in a small area, or the number of human arbovirus cases in a larger region. At small scales (households to neighborhoods), during times of high risk of mosquito-borne viral outbreaks, surveillance of the number of adult mosquitoes is collected from appropriate traps in districts that can afford them. At larger scales (counties to states), surveillance of the number of human arbovirus cases is more common, though inadequate support for these systems threatens the capacity to identify outbreaks before they become epidemics (Hadler et al. 2015). Thus far, little attention has been paid to the reactive nature of many control efforts, and the differences caused by focusing on different triggers for control. These independently-motivated actions, triggered and enacted at different, often overlapping, spatial scales of control create a broad patchwork of vector control that needs to be considered in order to implement effective control across all spatial scales.

Mosquito control efforts are also often implemented only after human infections have been detected or mosquito populations have peaked (Eisen et al. 2009, Unlu et al. 2016). Although proactive control of mosquito populations before introduction of a pathogen into the landscape reduces outbreak size and public health costs more effectively than reactive control (Eisen et al. 2009, Vazquez-Prokopec et al. 2010), the funds necessary to implement these measures often diminish in the absence of an outbreak (McKenna 2016).

While both adulticidal and larvicidal control efforts are in common use, we restricted our consideration here to purely larval control strategies, though work is underway to contrast our findings with outcomes from other methods. Because we were modelling only short-term control measures, we chose to use larval control since it hinders mosquito population growth more immediately, while single applications of adulticide only reduce the adult population until larvae mature and replace it. In addition, commonly used larvicides can be delivered to larval habitats in slow-dissolving briquettes that remain effective for long periods, preventing immediate compensation (Skovmand et al. 2009). Larval vector control at a large spatial scale can be accomplished either through the tremendous effort of mosquito control experts and citizen volunteers to implement widespread spot treatment by emptying, overturning, or removing containers providing larval habitat; or by using newly developed aerosolized sprays designed to activate in pools of standing water (Faraji and Unlu 2016). While both metapopulation theory and pest management practice posit that such area-wide and uniform control would best reduce vector populations (Levins 1968, Vreysen et al. 2007), it rarely occurs, due to the small

scale of the information obtained by vector control agencies, variability in skill and engagement among these agencies, cost limitations (Shepard et al. 2014), and environmental contamination concerns (Zhong et al. 2010). Instead, control efforts occur on a smaller scale, with patchy distributions of spot treatment across the landscape (Unlu et al. 2013).

We present a mathematical model of mosquito-borne viral transmission to explore how the various triggering mechanisms for initiation of control alter the spatial patchiness in control coverage and ultimately impact the effectiveness of outbreak mitigation efforts.

METHODS

We used a simple grid landscape of 20 (five by four) identical patches to form the spatial basis of our model. Within this landscape, the location and movement of mosquitoes were modeled explicitly to capture the metapopulation dynamics that result from differences in surveillance and control and affect disease transmission. Humans were assumed to be mobile enough that a mosquito in any patch can bite any human (see Table 1 for a list of additional assumptions).

We constructed the following discrete-time SIR-type difference equation model using variables and parameters defined in Tables 2 and 3:

$$M_{j,p,t} = (1 - Treat_{p,t})\left(\left(M_{j,p,t-1}(1 - \mu_j)\right)(1 - g) + v\left(M_{n,p,t-1} + M_{i,p,t-1}\right)\left(1 - \frac{M_{j,p,t-1}}{K}\right)\right) \quad (1)$$

$$M_{n,p,t} = \left(M_{n,p,t-1} + \sum_{\forall q \neq p} M_{n,q,t-1} D_{q,p} - \sum_{\forall p \neq q} M_{n,p,t-1} D_{p,q} - rcT_{hm}H_{i,t-1}M_{n,p,t-1}\right)(1 - \mu)$$
$$+ gM_{j,p,t-1}\left(1 - \mu_j\right) \quad (2)$$

$$M_{i,p,t} = \left(M_{i,p,t-1} + \sum_{\forall q \neq p} M_{i,q,t-1} D_{q,p} - \sum_{\forall p \neq q} M_{i,p,t-1} D_{p,q} + rcT_{hm}H_{i,t-1}M_{n,p,t-1}\right)(1 - \mu) \quad (3)$$

$$H_{s,t} = H_{s,t-1} - H_{s,t-1}rcT_{mh} \sum_{\forall p} M_{i,p,t-1} \quad (4)$$

$$H_{i,t} = H_{i,t-1} + H_{s,t-1}rcT_{mh} \sum_{\forall p} M_{i,p,t-1} - \gamma H_{i,t-1} \quad (5)$$

$$H_{r,t} = H_{r,t-1} + \gamma H_{i,t-1} \quad (6)$$

Equations 1-3 describe the number of female pre-adult (or "juvenile" to avoid confusion with patch designation in variable indices), naïve/uninfected adult, and infected adult female mosquitoes, respectively, in patch p on day t. All immature, pre-reproductive stages are incorporated into the juvenile compartment. Equations 4-6 describe the number of susceptible, infected, and recovered humans on day t. Human demography was not included because we assume that the model will be run for a short enough timeframe that the human population size (1000 individuals) does not change. The adult mosquito dispersal matrix was generated using a probability of adult mosquito dispersal out of each patch of 0.1. For each patch p, this dispersal probability was divided by the number of patches adjacent to patch p, so that there was an equal probability of dispersing from patch p to each adjacent

patch q. Dispersal only occurred between adjacent patches to reflect the limited mobility of *Aedes* mosquitoes (Trpis and Hausermann 1986, Edman et al. 1998).

Since it has been demonstrated that the order of events for discrete-time models affect the outcome (Bodine et al. 2012, Massaro et al. 2013), we provide the order of our model dynamics as follows: On day t, adult mosquitoes from day t-1 lay eggs in their current patch up to the juvenile carrying capacity, then either: die and are removed from the population; remain in their current patch; or disperse to an adjacent patch. All compartment transitions also occur simultaneously after egg laying, based on the previous day's abundances (juvenile mosquitoes grow to become uninfected adults, uninfected mosquitoes become infected, susceptible humans become infected, and infected humans recover).

Each run of the model proceeded for 200 days without disease or control to bypass transient population dynamics before surveillance and control implementation began. We chose to begin surveillance before disease introduction to mimic how control agencies may respond to knowledge of an increased risk of arboviral outbreaks (e.g., from a national media report on mosquito-borne viruses), before any pathogen is known to be circulating. After the seventh day of surveillance in each run, one human became infected, and each simulation then continued for 150 days post-infection (156 total days of surveillance) to examine the short-term dynamics immediately following the introduction of a pathogen into the system.

Incorporating surveillance and reactive control into simulations

To reflect the diversity of current mosquito control practices and examine potential alternatives, we simulated six scenarios with different triggers for the implementation of control efforts (Table 4). To examine the relationship between the threshold level of the surveillance data that triggers control and how effectively each scenario reduces human infections, we first ran each of the four surveillance scenarios 1000 times at each of 10 different thresholds. We then ran all six scenarios for 5000 Monte Carlo realizations at a single threshold.

For each run in all scenarios (except for S-None), 16 out of the 20 patches were stochastically selected to participate in surveillance and control for all 156 days of each simulation. This level of participation was chosen as an arbitrarily high level to simulate more effective control conditions. Surveillance occurred daily in participating patches; on each day t that the surveillance target met or exceeded the threshold level, treatment was applied on days $t+1$ through $t+11$. Treatment affected only juvenile mosquitoes and was assumed to be completely effective for ten days after the initial application, so that there were no juveniles in treated patches. Treatment ceased only after ten consecutive days on which the surveillance target remained below the threshold for triggering control.

L-Inf: Large-scale human infection surveillance. This scenario simulated how county, state, or federal agencies might use the larger-scale information available on human epidemiology. Control was implemented when the total number of humans infected on day t exceeded the threshold for control in that run. All participating patches were then treated starting on day $t+1$ through day $t+11$, regardless of any

local differences between patches. Thus, all participating patches were either untreated or treated at any given time (Figure 1b).

S-Ad, S-Juv, and S-Inf: Small-scale mosquito surveillance. In all three of these scenarios, control occurred in each participating patch individually, based on surveillance information from each patch (Table 4), simulating how individuals or local municipalities might use smaller-scale information about mosquitoes. Control occurred in patch p when the variable being assessed in patch p on day t was above the threshold for control in that run. Only patch p was then treated on day $t+1$ through day $t+11$, so some participating patches may be treated on a given day, while others may not be, depending on local dynamics (Figure 1a).

L-None and S-None: No surveillance and large- or small-scale control. To determine whether surveillance-based treatment is more effective than control that is uninformed by any ecological or epidemiological data, we also examined the effect of treating patches without any surveillance information to guide the timing of control. In each run of L-None, the 16 participating patches were treated on days 2-137 (~70% treatment coverage) to simulate large-scale control implementation immediately after learning of the risk for disease introduction. To evaluate the efficacy of small-scale control implementation in response to increased risk, in each run of S-None, each of the 20 patches was treated on 109 stochastically selected days of the 156-day simulation (also ~70% treatment coverage) beginning on day two.

Analysis

Since one of the primary goals of vector control is to mitigate human disease risk, we report results using the percent reduction in human infections, calculated for each run as the percent difference between the number of human infections in that run and the number of human infections when the model is run without any surveillance or control.

Because different scenarios cause different amounts of the landscape to be controlled over time, we also determined the percent of the landscape that was treated over the 156 days of each simulation, calculated as the total number of days that all patches were treated in that run, out of all 3,120 possible days of treatment (20 patches × 156 days).

RESULTS

Threshold sensitivity

For human and mosquito infection surveillance (L-Inf and S-Inf, respectively), efficacy of control initially declined very steeply, even between the very sensitive thresholds of just one and two infected individuals, though mosquito infection surveillance was much less effective than human infection surveillance across all thresholds (Figure 2). Even slightly higher thresholds delay the onset of control enough to significantly reduce control efficacy in these scenarios. Control in

response to the number of juvenile or adult mosquitoes was much more effective at lower thresholds than the disease surveillance scenarios because of treatment application prior to disease introduction, which lowers the reproductive number of the pathogen by lowering the abundance of the vector. The adult mosquito surveillance scenario (S-Ad) achieved the greatest reduction in human cases for the two most sensitive thresholds tested before rapidly declining in response to progressively higher thresholds. Juvenile mosquito surveillance (S-Juv) achieved about a 70% reduction in human cases for the eight lowest thresholds before precipitously dropping in efficacy when using the two highest thresholds.

Comparison of surveillance scenarios at a single threshold

All of the following results for the surveillance scenarios use thresholds of 1 human or mosquito infection (for L-Inf and S-Inf), or 10% of the baseline abundance of the adult mosquito population in each patch (for S-Ad) or the juvenile mosquito population in each patch (for S-Juv). Due to these low thresholds, our simulations represent best-case circumstances of highly accurate and efficient monitoring and control programs.

Simulations with control in all participating patches in response to one human infection (L-Inf) lead to a 57.3% mean reduction in total human infections, with a range of 54.9-59.5% (Figure 3, Table 5). In all runs with this scenario, 71.8% of the landscape was controlled over the course of the simulation, since all

participating patches were treated starting on day 17 (10 days after disease introduction) through all 156 days of surveillance (Figure 4a).

Simulations with control in each participating patch when adult mosquito abundance exceeded 10% of the baseline (S-Ad) lead to an 85.6% mean reduction in human infections, with a range of 82.0-87.7%. The high efficacy of this scenario is due to control occurring before disease introduction since the surveillance target concerned ecological rather than epidemiological dynamics. Control coverage ranged from 74.3-79.0% because adult populations periodically dropped below the threshold for control (Figure 4b), depending on the locations of the participating patches in each run.

Enacting control when the number of juvenile mosquitoes exceeded 10% of the baseline (S-Juv) achieved a mean reduction of 73.4% and a range of 70.7-75.4%. In this scenario, because the direct effect of treating the larval habitats caused the juvenile populations to fall to zero (below the threshold for triggering control), all participating patches were untreated on the same day, every 11 days, once the previously applied larvicide was no longer in effect (Figure 4c). Because these dynamics occurred in all runs, this scenario essentially caused the accidental emergence of large-scale control, leading to 71.8% control coverage in all runs. The lapses in control every 11 days caused periodic spikes in mosquito abundance that made this scenario less effective than S-Ad at this control threshold.

Control in each participating patch in response to one mosquito infection (S-Inf) was the least effective scenario. Despite treating an average of 65.6% of the larval habitats over all 156 days of surveillance, it led to a mean reduction in human

infections of just 31.2% and a range of 28.4-34.6% (Figure 3, Table 5). This is because it took up to 25 days after disease introduction (day 32 of surveillance) for the virus to infect mosquitoes in all participating patches, so treatment did not occur in many of these patches until later in the course of the outbreak (Figure 4d).

Scenarios without surveillance

Treatment in both L-None and S-None began on day 2, rather than on day 3 as it did in S-Ad and S-Juv, because, once aware of the risk of disease introduction, control is enacted on the following day, without a lag for collecting surveillance information. L-None achieved an average of 87.5% infection reduction, the highest of any of the scenarios tested, and the smallest range of just 2.5 percentage points.

The results of S-None demonstrate a strong negative linear relationship (R^2=0.862) between the average timing of control implementation and the reduction in human infections (Figure 5), indicating that implementing larval control measures earlier in the course of the spread of the disease is vitally important to reducing outbreak size. Average human infection reduction was 71.0%, but ranged from 66.2-75.0% even though 69.9% of the landscape was treated in all 5000 runs, with differences in efficacy largely due to when treatment occurred.

DISCUSSION

The scenarios that yielded the fewest human infections after 150 days of arbovirus transmission had larvicide treatment in participating patches beginning before or soon after disease introduction and largely remaining in effect throughout the simulations (Figure 4). This result suggests that, where early detection of an outbreak is possible, collecting surveillance information continuously throughout the course of an outbreak may not be necessary, and in fact may be a waste of resources that should instead be put toward immediate and consistent control efforts as soon as the risk of an arbovirus outbreak increases, though risk assessment would still be necessary to determine when emergency control efforts can cease. However, it should be noted that, because we modelled a theoretical landscape with a ubiquitous human population, these results are not immediately applicable to current vector control programs across scales. Rather, we hope this research sparks a discussion among local governments, mosquito control experts, and researchers about how control regimes across numerous independent jurisdictions can best limit surveillance and treatment application costs while remaining effective.

Scenarios in which control began before disease introduction achieved much greater reductions in human infection than scenarios in which control was only implemented after arbovirus was already circulating. Surveillance information on vector ecology and population dynamics may thus provide more effective triggers for control than surveillance information on epidemiological dynamics that, by nature, only trigger control after disease introduction. Indeed, an increase in dengue infections in Singapore over the past few decades has coincided with a shift in the

focus of surveillance from vector populations to human infection cases (Ooi et al. 2006). However, the resources needed for vector surveillance are often only available when the risk of disease introduction is both known and acknowledged, and may only be provided after active transmission has been confirmed. This creates an impossible situation for underfunded mosquito control agencies, which cannot enact control without surveillance information to trigger it, and cannot acquire surveillance information without the resources to collect it.

The small-scale surveillance scenarios demonstrate another limiting factor in the success of vector control programs. The results from these scenarios imply an intuitive, but often neglected, fallacy of threshold-based, surveillance-driven vector control: the more effective the measure is in the short-term, the sooner it stops being implemented, and the less effective it is in the long-term. For instance, in the runs of S-Ad that yielded infection reductions on the lower end of that scenario's range, mosquito populations in some patches would dip below the threshold for applying further control measures, leading to lapses in treatment that caused greater production of adult mosquitoes. The fluctuations in the number of treated patches in the S-Juv simulations (Figure 4c) similarly demonstrate lapses in control due to short-term control success. Although our simulations were not tailored to explore this particular problem, they nonetheless reveal the potential for threshold-based programs to interpret surveillance data as premature implications of successful outbreak mitigation. The ability of vector control in reducing arboviral outbreaks could be greatly improved with more accurate metrics of human disease risk, such as those that incorporate surveillance data from multiple targets and

consider human behavioral exposure and other socioecological factors (Gujral et al. 2007, Adams and Kapan 2009, Kilpatrick and Pape 2013, Stewart Ibarra et al. 2014, Stewart-Ibarra et al. 2014, Stone et al. 2017), rather than using the direct impacts of control measures to approximate their efficacy.

The threshold results from S-Juv demonstrate another potential inefficiency of surveillance-driven control: for some surveillance targets, extensive and highly sensitive surveillance may not achieve infection reductions any greater than would less costly, moderately sensitive methods (Figure 2). Thus, results from this scenario under our model assumptions suggest that control in response to juvenile mosquito abundance may be a good option if surveillance data are not guaranteed to be particularly accurate, because it achieves similar infection reductions when using either highly sensitive or intermediate control thresholds. Information on larval mosquito abundance is easily obtained by "citizen scientists" (Silvertown 2009, Kampen et al. 2015), who could assist mosquito control experts with surveillance data collection, thus reducing costs for local municipalities. Because moderate data sensitivity is sufficient to inform control efforts in this scenario, a slight loss in accuracy in data collected by citizen scientists would not reduce the efficacy of control efforts informed by this information.

Unlike those of S-Juv, the threshold sensitivity results from L-Inf revealed a steep initial decline in the reduction in infections achieved, with a drop in efficacy of 15 percentage points between control thresholds of just one and two human infections (Figure 2). The higher reductions achieved using the lowest control threshold are due to earlier implementation of larvicide treatment; the only change

in control implementation at higher thresholds is the delaying of treatment application, which allowed mosquito populations to remain high and transmit more of the virus to the human population. If highly sensitive human infection surveillance causes quicker implementation of control measures, then collecting this information is well worth the costs.

Implementing small-scale larval control in response to surveillance of adult mosquito infections (S-Inf), however, was consistently the least effective of the surveillance methods simulated, even when using the most sensitive threshold. Thus, when implementing larval control measures only, the costs of labor, equipment, and laboratory testing associated with obtaining this information may outweigh the benefits. Ongoing work is examining whether other methods, such as adulticide treatment, in response to mosquito infection surveillance may provide worthwhile benefits.

Our results reveal numerous advantages to large-scale surveillance and control, particularly with anticipatory implementation before disease introduction (as in L-None) rather than responsive implementation after transmission has begun (as in L-Inf). Although L-Inf yielded lower efficacy than the anticipatory scenarios, it achieved greater infection reductions at all thresholds than S-Inf (the other responsive scenario), due to earlier uniform implementation of control in all participating patches (Figure 4). This suggests that even when anticipatory methods are not possible, implementation of control early in an outbreak can still prevent many people from acquiring infections. L-Inf was also the only scenario in which there were no gaps in treatment once it began (Figure 4), which would prevent the

mosquito populations from compensating for the decreased density of immatures in each treated larval pool.

The two large-scale control scenarios (L-Inf and L-None) had the smallest ranges in efficacy (Figure 3, Table 5), indicating that the homogenous/uniform control inherent to large-scale implementation yields more predictable outcomes that are less dependent on the location of the participating patches than small-scale control. In the small-scale scenarios, the runs on the lower end of each scenario's efficacy range exhibited patchier control implementation (due to spatial effects that will be examined in future efforts), while the more effective runs better approximated the uniformity of the large-scale scenarios. This suggests that when the locations of participating patches can be carefully chosen to lead to spatially and temporally homogenous control measures across the landscape, small-scale surveillance and control can yield similar treatment uniformity to purposeful large-scale control. However, when some areas of the landscape cannot be treated for a reason unrelated to mosquito and epidemiological dynamics (e.g., inaccessibility, private land, protected wildlife areas), small-scale surveillance may yield patchier implementation of control measures that are less effective than the uniform control implemented using large-scale surveillance. Engagement of private citizens to actively participate in local efforts, such as data collection from ovitraps, can make these more effective uniform methods more economically and logistically feasible (Regis et al. 2008, Fonseca et al. 2013, Ryan et al. 2015).

The theoretical nature of this model highlights the real-world inefficiencies that plague the efficacy of responses to vector-borne disease outbreaks at any scale.

In our simulations, treatment of larval habitats occurs one day after the surveillance

data threshold is reached; in reality, control efforts may not be implemented for

many weeks due to inadequate surveillance and funding. Also, because large

proportions of those infected with dengue or Zika experience no or mild symptoms

(Sikka et al. 2016), many people may need to be infected before anyone would seek

medical care and testing. It may then take months and multiple laboratory tests to

confirm and report a human diagnosis, though there are fewer hurdles to testing

and reporting mosquito infections in areas with sufficient resources (Lindsey et al.

2012). Despite the utility of the CDC's ArboNET system for arboviral incidence

reporting (Marfin et al. 2001), the time currently required to test for arbovirus

postpones the implementation of control measures in response to this information,

significantly reducing the efficacy of these responses (Figure 5). Thus, while our

current systems of surveillance remain in place, implementing control in response

to epidemiological surveillance would likely not be as effective in reality as it is in

this model. Future research should incorporate these inefficiencies in surveillance

data collection and control implementation into simulations, as well as more

complex ecological dynamics assumed absent here, including: co-infection with

multi-strain pathogens in a metapopulation framework; evolution of insecticide

resistance in mosquito populations; and insecticide effectiveness across a range of

environmental variables.

      The extent and methods of vector and arbovirus surveillance and control

vary widely between jurisdictions in the United States (Lindsey et al., 2012;

NACCHO, 2016). This likely leads to patchy implementation of control regimens that

lack the urgency and uniformity of the more effective scenarios simulated here. This lack of uniformity also pervades the research that has been done on the effectiveness of various vector control approaches. Thus, while it would be useful to compare our results with more real-world studies, the current literature contains little overlap in study design, making it difficult to compare the results of these disparate approaches (Bowman et al. 2016). Increased standardization in methods, investment in proactive approaches, and communication about vector population dynamics locally, nationally, and internationally could significantly reduce the public health risks of Zika virus and other current and future vector-borne infectious diseases.

CONCLUSIONS

In our simulations, vector control implemented in anticipation of an arboviral outbreak was much more effective at reducing the number of human infections than control efforts that began after disease introduction. Thus, surveillance information on mosquito ecology and demography may more effectively inform control application than information on epidemiology that inherently can only trigger treatment after disease transmission has begun. Uniform control applied consistently across space and time can further mitigate outbreaks more than patchy control application, indicating that large-scale efforts informed by landscape-wide surveillance, or even well-positioned small-scale implementation,

may be more effective than haphazard small-scale efforts enacted in each patch independently. For some surveillance targets, only very sensitive and accurate information can notify control agencies of an escalating risk quickly enough for them to implement effective control, so limited resources would be well spent on collecting high quality surveillance data. However, other types of surveillance data may still effectively inform control without requiring high sensitivity in their collection. Critically, rather than responding to a true measure of control efficacy and risk level, some control efforts triggered by surveillance may instead foster a false sense of security that leads to ineffective or prematurely relaxed efforts (c.f. Arosteguí et al. 2013, Gubler 2002, Reyes-Castro et al. 2017) . Further research on the previously neglected topics of surveillance target and scale in mosquito-borne disease control can help determine economical methods to both collect high quality surveillance information and implement continuously effective responses, especially in regions where the best outcomes require the participation and cooperation of many local jurisdictions.

Table 1. Assumptions of the model.

Topic	Assumptions
Landscape	• All patches are identical, with equal connectivity between all adjacent patches. • The landscape is completely isolated. • Humans move homogeneously throughout the landscape.
Control	• Surveillance is 100% accurate and results are immediate enough to inform the following day's actions. • Treatment to each larval development ("breeding") pool is completely effective for exactly 10 days. • Source reduction via larvicide application is the only control measure implemented.
Epidemiology	• The single arbovirus strain is only transmitted horizontally and only between mosquitoes and humans. • Recovery causes complete life-long immunity in humans; mosquitoes do not recover from infection. • Transmission of the virus is immediate; there is no latency/exposed period. • No viral evolution occurs. • Viral infection has no effect on mosquito life history.
Mosquito population	• Mosquito feeding on humans has no effect on birth or death rate, and both are constant throughout mosquito lifetime. • No evolution occurs in the mosquito population, including no evolution of resistance to treatment. • Oviposition of non-diapause eggs occurs daily. • A fixed percent of mosquitoes in each patch disperse to an adjacent patch each day; dispersal is not density-dependent. • No regulation of the adult population occurs, only density-dependent regulation of the juvenile population. • Juveniles cannot grow and die on the same day; eggs cannot be laid and die on the same day.

Table 2. Variables used in model equations.

Variable	Definition
M_j	Number of juvenile (pre-adult) mosquitoes
M_n	Number of adult naïve (uninfected) female mosquitoes
M_i	Number of adult infected female mosquitoes
H_s	Number of susceptible humans
H_i	Number of infected humans
H_r	Number of recovered humans
p and q	Patch identifiers
t	Day identifier

Table 3. Parameter definitions and values used in model simulations.

Parameter	Value(s)	Definition
Treat	0=untreated 1=treated	Matrix of control schedule in each patch
$\mu^{\wedge}$	1/20	Per capita death rate of mosquitoes (after density-independent mortality)
ν^*	3	Per capita birth rate of mosquitoes (after density-independent mortality)
K^*	350	Carrying capacity of juvenile mosquitoes in each pool
$g^{\wedge}$	1/10	Growth rate of mosquitoes from juvenile to adult
D^*	$\sum_{\forall q \neq p} D_{p,q} = 0.1$	Matrix of mosquito dispersal probabilities between pools
$r^{\wedge}$	0.3	Biting rate
c^*	0.003	Scaling constant (to enable reasonable pace of outbreak amid a ubiquitous human population)
T^*	$T_{mh} = 0.08$ $T_{hm} = 0.07$	Transmission probabilities per bite from mosquitoes to humans (T_{mh}) and humans to mosquitoes (T_{hm})
$\gamma^{\wedge}$	1/4	Recovery rate of humans

All rates are in days.
*=Assumed for model exploration
$^{\wedge}$=Modified from (Erickson et al. 2010)

Table 4. Summary of the surveillance and control scenarios simulated. "L" stands for large-scale and "S" for small-scale control implementation. "Inf" refers to surveillance of the number of human or mosquito infections, "Ad" refers to adult mosquito surveillance, and "Juv" to immature mosquito surveillance.

Scenario	Focus of Surveillance	Scale of Surveillance and Response	Number (Percent) of Patches Participating	Range of Threshold Values Tested
L-Inf	Infected humans	Whole landscape	16 (80%)	1-10 infected humans
S-Ad	Adult mosquitoes	Individual patch	16 (80%)	10%-100% baseline* adult abundance
S-Juv	Juvenile mosquitoes	Individual patch	16 (80%)	10%-100% baseline* juvenile abundance
S-Inf	Infected mosquitoes	Individual patch	16 (80%)	1-10 infected mosquitoes
L-None	None	Whole landscape	16 (80%)	N/A
S-None	None	Individual patch	20 (100%)	N/A

* Baselines are average per patch abundances in the 10 days before surveillance begins.

Table 5. Results from 5000 runs of each scenario.

Scenario	Control Threshold/Trigger	Mean reduction in human infections	Range of human infection reduction	Proportion of landscape treated over time	First day of treatment
L-Inf	1 infected human	57.3%	54.9-59.5%	All 0.718	17
S-Ad	10% adult baseline	85.6%	82.0-87.7%	0.743-0.790	3
S-Juv	10% juvenile baseline	73.4%	70.7-75.4%	All 0.718	3
S-Inf	1 infected mosquito	31.2%	28.4-34.6%	0.642-0.664	25-32
L-None	On days 2-137	87.5%	86.2-88.7	All 0.697	2
S-None	On 109 stochastically selected days	71.0%	66.2-75.0%	All 0.699	2

Figure 1. Representations of control implementation over time in small-scale and large-scale surveillance scenarios. Grey squares receive larvicidal treatment, while white squares do not. (a) The small-scale control of S-Ad, S-Juv, S-Inf, and S-None yields patchier control, with the number and location of treated patches changing over time. (b) The large-scale control of L-Inf and L-None yields spatially uniform control, with all participating patches either treated or untreated at each time step.
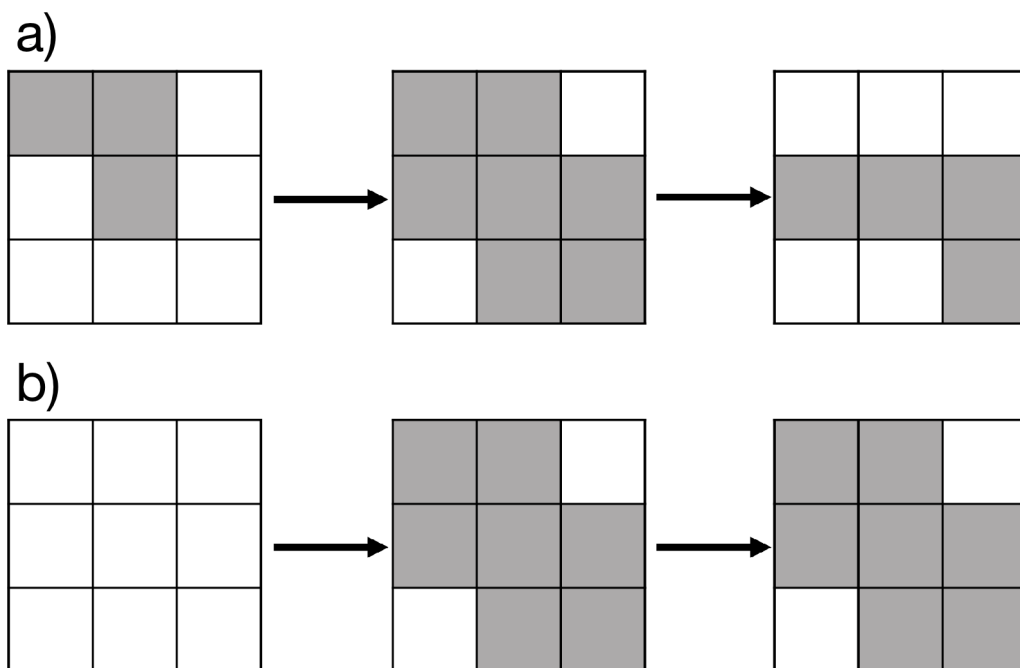
Figure 2. Average infection reduction at each threshold level tested, for scenarios using surveillance. Shaded regions indicate two standard deviations around the mean. Top panel: results from scenarios L-Inf and S-Inf, using threshold numbers of infections to trigger treatment. Bottom panel: Results from scenarios S-Ad and S-Juv, using threshold proportions of baseline abundance to trigger treatment.
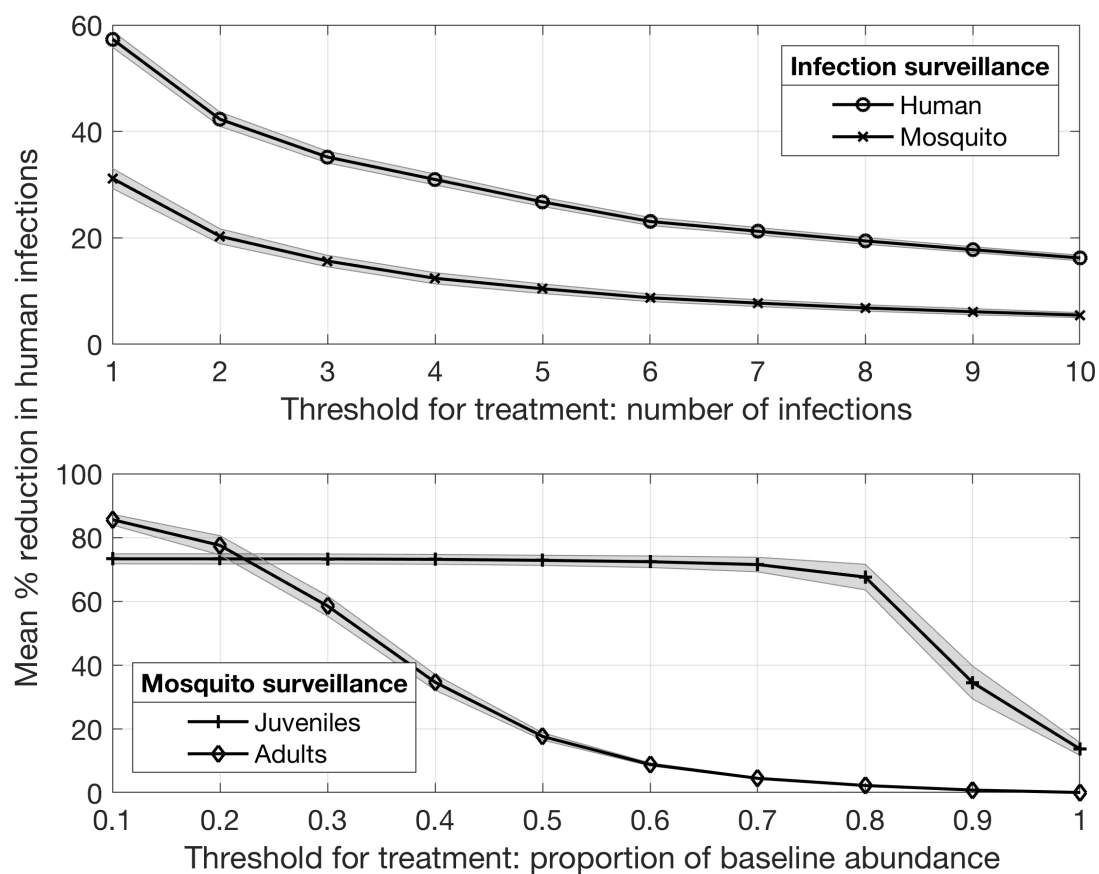
Figure 3. Box-and-whisker plots of human infection reduction in all six scenarios. Whiskers extend to the upper and lower adjacent values.
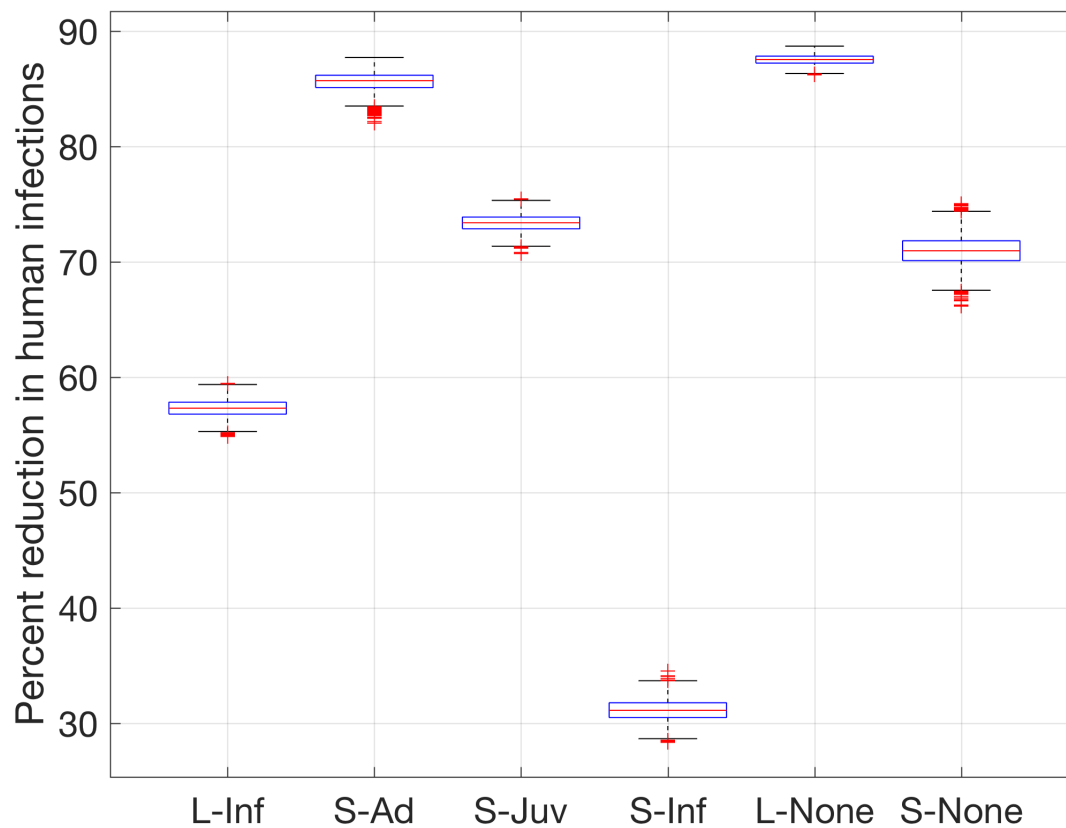
Figure 4. Number of patches receiving treatment in surveillance scenarios on each of the 156 days of surveillance and control. Blue dotted lines indicate introduction of one infected human. (a) L-Inf (large-scale human infection surveillance); (b) S-Ad (small-scale adult mosquito surveillance); (c) S-Juv (small-scale juvenile mosquito surveillance); (d) S-Inf (small-scale mosquito infection surveillance). Because S-Ad and S-Inf have slightly different numbers of patches treated each day in each run, one representative run from each scenario was chosen for the figure. Effectiveness percentages are the average percent reduction in human infections under that scenario, compared to implementing no control measures.
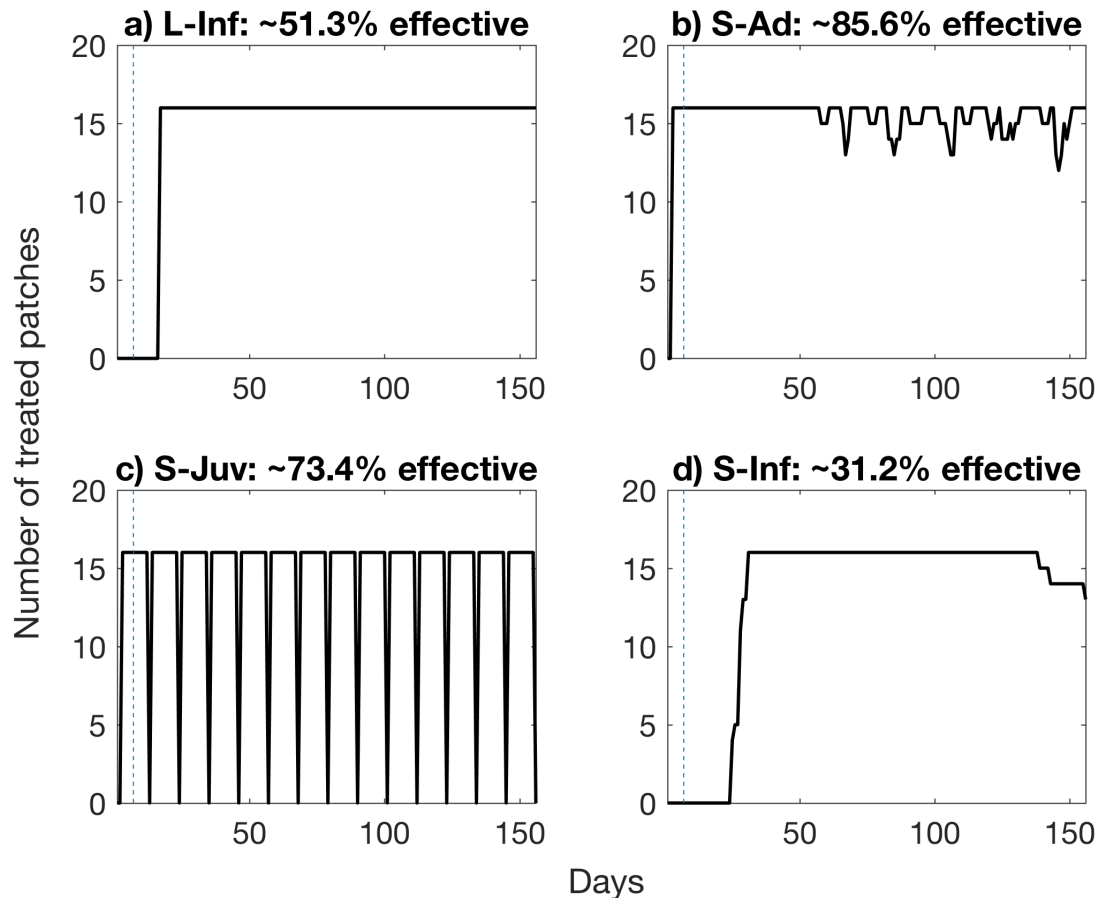
Figure 5. S-None demonstrates the importance of early vector control in reducing outbreak size. All patches in each run were treated on 109 days of the 156-day simulation. The x-axis shows the average day number on which treatment occurred in all 20 patches in each run, with the left side indicating earlier average treatment, and the right side indicating later average treatment across the landscape.

(Meta)population dynamics determine effective spatial distributions of mosquito-borne disease control

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ABSTRACT

Recent epidemics of mosquito-borne dengue and Zika viruses demonstrate the urgent need for effective measures to control these diseases. The best method currently available to prevent or reduce the size of outbreaks is to reduce the abundance of their mosquito vectors, but there is little consensus on which mechanisms of control are most effective, or when and where they should be implemented. Although the optimal methods are likely context-dependent, broadly applicable strategies for mosquito control, such as how to distribute limited resources across a landscape in times of high epidemic risk, can mitigate (re)-emerging outbreaks. We used mathematical simulations to examine how the spatial distribution of larval mosquito control affects the size of disease outbreaks, and how mosquito metapopulation dynamics and demography might impact the efficacy of different spatial distributions of control. We found that the birth rate and mechanism of density-dependent regulation of mosquito populations affected the average outbreak size across all control distributions. These factors also determined whether control distributions favoring the interior or the edges of the landscape most effectively reduced human infections. Thus, understanding local mosquito population regulation and dispersion can lead to more effective control strategies.

INTRODUCTION

Mosquitoes that lay their eggs in peri-domestic water-filled containers have become invasive across the globe (Juliano and Lounibos 2005, Schaffner et al. 2013), and can transmit a diversity of viruses that have caused recent viral epidemics throughout the world, such as yellow fever, dengue, chikungunya, West Nile, and Zika (Gratz 2004, Chouin-Carneiro et al. 2016). These and other vector-borne diseases will likely continue to emerge and spread with increasing globalization and urbanization (Tatem et al. 2006, Kilpatrick and Randolph 2012). Thus, effective emergency measures will be necessary to protect affected populations from mosquito-borne diseases and their potentially tragic lasting effects, such as neurological birth defects in children born from women infected with the Zika virus (Rasmussen et al. 2016).

The mechanisms and patterns of vector population regulation are integral to the metapopulation dynamics of vectors and the diseases those vectors transmit (White et al. 2011, Smith et al. 2013, Godfray 2013). Intraspecific competition for resources among pre-adults of many invasive mosquito species is thought to impose significant regulation on many populations (Juliano 2007). The effect of conspecific density on oviposition site selection by gravid females appears to be highly context-dependent (Wasserberg et al. 2014, Day 2016); the presence of conspecifics may signify high habitat quality and attract greater oviposition, or signify high larval competition and deter further oviposition in favor of less competitive larval development sites (Onyabe and Roitberg 1997, Kiflawi et al. 2003, Wong et al. 2011,

Fonseca et al. 2015). Wasserberg et al. (2014) suggest a negative parabolic relationship between conspecific density and oviposition rate, with the highest oviposition rates in pools with intermediate densities that balance the risks and rewards of both density extremes.

Despite their public health importance, existing mosquito control strategies are highly variable in effort, resources, and methods used (Hadler et al. 2015), leading to patchy and inconsistent control measures across both space and time. According to metapopulation theory, this likely creates a rescue effect in which mosquito metapopulations, and thus the reservoir of mosquito-borne diseases, are maintained in untreated refuges that then act as sources when new uncontrolled sites become available (Grenfell and Harwood 1997). Although many critical mosquito species display low dispersal ability (Trpis and Hausermann 1986), mosquito-borne disease can be transmitted over long distances in either infected humans (Stoddard et al. 2009, Stone et al. 2017) or in infected mosquitoes that often get transported via human travel networks (Eritja et al. 2017). Research that considers the effects of both mosquito and human movement in a metapopulation context would enable the application of more targeted and effective approaches and allow for more accurate epidemiological and entomological predictions.

Empirical work indicates that focusing treatment efforts in highly productive "hot spots" can reduce mosquito populations at minimal cost (Smith et al. 2013, Faraji and Unlu 2016, Unlu et al. 2016), but this requires existing knowledge about the productivity of local mosquito populations, as well as coordinated comparisons of this information across space. Any time an arbovirus outbreak occurs, emergency

vector control measures need to be implemented quickly; the time it takes to identify hot spots can postpone the implementation of control measures, leading to larger outbreaks (Schwab et al. 2017). Also, due to complex oviposition site selection dynamics, applying control measures only in hot spots may leave a sufficient abundance of immature mosquitoes in the remaining larval pools to maintain transmission of mosquito-borne diseases in some ecological contexts (Wasserberg et al. 2014). The development of standardized, effective best practices to employ during time of high epidemic risk could significantly reduce outbreaks sizes.

While consistent control application over large contiguous areas would reduce mosquito populations better than smaller-scale approaches (Levins 1968, Hendrichs et al. 2007), large-scale treatment of entire landscapes is rarely possible because of insufficient resources (Hadler et al. 2015), environmental contamination concerns, inability to access private properties, and a lack of coordination among local jurisdictions. The synanthropic nature of some species, particularly *Ae. aegypti* and *Ae. albopictus*, has added to these logistical control difficulties; small pools of water that are ubiquitous in urban and domestic environments provide ideal sites for oviposition by females and subsequent development of immatures. The resulting spatial and temporal heterogeneity in control efforts may reduce the temporal correlation of mosquito population dynamics between nearby areas, contributing to the long-term persistence of mosquito-borne disease even while reducing the size of each individual outbreak (Bolker and Grenfell 1996, Grenfell and Harwood 1997, Bjørnstad et al. 1999).

We focus solely on insecticidal methods targeted at the aquatic pre-adult stages, which we refer to as "larval control" for the remainder of this manuscript. There is growing evidence that low residue adulticides, currently preferred as they minimize non-target effects and resistance evolution, are not particularly effective and are only active for a few days. In contrast, some larvicides can remain effective for months (Skovmand et al. 2009). However, strong density-dependence among juveniles has been shown to cause larval control efforts to fail to reduce adult mosquito populations. This may be due to compensation or overcompensation, in which control efforts that kill a proportion of juveniles allow competition for resources among the remaining juveniles to relax (Legros et al. 2009). In some circumstances, this allows a greater proportion of these larvae to develop into adults than if the site had remained uncontrolled and thus denser and more resource-limited. Understanding the ecological and demographic contexts under which compensation and overcompensation occur would inform more effective and more economical methods of control (Juliano 2007).

Here, we use a theoretical discrete-time SIR-type difference equation model to examine how the spatial distribution of mosquito control alters the efficacy of control in reducing human infections, and how mosquito metapopulation dynamics and demography might impact the efficacy of different spatial control distributions. Work by Lutambi et. al. found that spatial clustering of certain control interventions may be less effective at reducing biting mosquito abundance than less clustered distributions (Lutambi et al. 2014). We build on this foundation by also

incorporating mosquito-borne disease transmission into our simulations, as well as two different potential types of simple density-dependence.

METHODS

The model presented here builds on a model previously employed by Schwab et al. (2017) to explore the efficacy of different types of surveillance data to trigger effective control.

We used a simple grid landscape of 20 (five by four) identical patches to form the spatial basis of our model. Within this landscape, the location and movement of mosquitoes were modeled explicitly to simulate metapopulation dynamics of both the vector and the disease, but humans are assumed to be mobile enough that a mosquito in any patch can bite any human (see Table 1 for a list of additional assumptions).

The equations for female juvenile/pre-adult ($M_{j,p,t}$), naïve/uninfected adult ($M_{n,p,t}$), and infected adult ($M_{i,p,t}$) mosquitoes in patch p on day t are:

$$M_{j,p,t} = \left(1 - Treat_{p,t}\right)\left(\left(M_{j,p,t-1}(1 - \mu_j)\right)(1-g)\right.$$

$$\left. + \, v(x^{\alpha_{p,t}})\left(M_{n,p,t-1} + M_{i,p,t-1}\right)\left(1 - \frac{M_{j,p,t-1}}{K}\right)\right) \tag{1}$$

$$M_{n,p,t} = \left(M_{n,p,t-1} + \sum_{\forall q \neq p} M_{n,q,t-1}\,D_{q,p} - \sum_{\forall p \neq q} M_{n,p,t-1}D_{p,q} - rcT_{hm}H_{i,t-1}M_{n,p,t-1}\right)(1-\mu_a)$$

$$+ \, gM_{j,p,t-1}\left(1 - \mu_j\right) \tag{2}$$

$$M_{i,p,t} = \left(M_{i,p,t-1} + \sum_{\forall q \neq p} M_{i,q,t-1} D_{q,p} - \sum_{\forall p \neq q} M_{i,p,t-1} D_{p,q} + rcT_{hm}H_{i,t-1}M_{n,p,t-1} \right)(1 - \mu_a) \qquad (3)$$

The equations for susceptible ($H_{s,t}$), infected ($H_{i,t}$), and recovered ($H_{r,t}$) humans on day t are:

$$H_{s,t} = H_{s,t-1} - H_{s,t-1}rcT_{mh} \sum_{\forall p} M_{i,p,t-1} \qquad (4)$$

$$H_{i,t} = H_{i,t-1} + H_{s,t-1}rcT_{mh} \sum_{\forall p} M_{i,p,t-1} - \gamma H_{i,t-1} \qquad (5)$$

$$H_{r,t} = H_{r,t-1} + \gamma H_{i,t-1} \qquad (6)$$

Parameter definitions and values used are in Table 2. The adult mosquito dispersal matrix was generated using a probability of adult mosquito dispersal out of each patch of 0.1. For each patch p, this dispersal probability was divided by the number of patches adjacent to patch p, so that there was an equal probability of dispersing from patch p to each adjacent patch q. Mosquitoes could only disperse to an adjacent patch to reflect the limited dispersal ability of many container-breeding species (Trpis and Hausermann 1986).

Before each simulation, we ran the model for 200 days without disease or control so that the behavior of the mosquito populations was caused by model dynamics and not by initial conditions. On day 1 of each simulation, surveillance of human infections began, though disease was not yet introduced into the landscape. At the end of day 7 (after control decisions have been made), one human became

infected with an arbovirus, initiating disease transmission on day 8. The simulation then proceeded for 150 days with disease (156 total days with surveillance).

The order of events on each day of the simulation is as follows: On day *t*, adult mosquitoes from day *t-1* lay eggs in their current patch, with the number of eggs regulated by the designated juvenile density-dependence mechanism (see below). Then, a proportion of both juvenile and adult mosquitoes die and are removed from the population. All compartment transitions then occur simultaneously, using the number of mosquitoes from day *t-1* that are still alive (juvenile mosquitoes grow to become uninfected adults, uninfected mosquitoes become infected, susceptible humans become infected, and infected humans recover).

Mosquito demography

To examine how the interplay of within-patch mosquito demography and between-patch dispersal affect control outcomes, we ran our simulations under four different demographic circumstances: logistic density-dependence (LDD) with a high and a low birth rate, and nonlinear/multiphasic density-dependence (MPDD) with a high and a low birth rate. In all forms of density-dependence used, only the juvenile populations in each patch are directly regulated.

We incorporated logistic density-dependence by setting α=0 in Equation 1, so that the number of juveniles added to each pool is unaffected by *x*. We incorporated multiphasic density dependent population regulation by setting α=1 when the number of juveniles in a patch reached 80% of carrying capacity or above,

thereafter restricting juvenile increase to only a proportion (x) of the unrestricted LDD-based increase. We used these extreme parameters in order to examine a very different demographic situation from simple logistic growth. Biologically, dynamics similar to those in MPDD could arise if high larval densities not only increase larval competition for resources, but also attract more predators, increase disease transmission, and/or repel female oviposition.

Incorporating control into simulations

To capture the patchiness of mosquito control efforts, and the many potential spatial distributions of control that this patchiness creates, we ran the model 5000 times, with 16 out of the 20 patches (80%) arbitrarily selected at the start of each run to participate in disease surveillance and control in that simulation. Treatment affected only juvenile mosquitoes and was assumed to be completely effective, so that when the value of *Treat* in patch p on day t equaled 1, Equation 1 equaled 0 and there were no juveniles in that patch on that day.

In our simulations, larval control occurred when there was at least one infected human in the landscape on day t (the efficacy of this and other surveillance scenarios were examined elsewhere (Schwab et al. 2017)). All 16 participating patches were then treated starting on day *t+1* through day *t+11*, regardless of any local differences between patches, so that all participating patches were either untreated or treated on any given day. Due to this low threshold for triggering control, and the high level of participation among the patches, our simulations

represent best-case scenarios of effective monitoring programs and well-funded

control agencies.

Quantifying the spatial distribution of control effort

   To quantitatively compare the spatial patterns of treatment in each run, we

created a metric based on Simpson's Evenness Index that we call insulation ($\Im$). We

computed this metric in each run by first calculating Simpson's evenness index

(Smith and Wilson 1996) of the number of participating patches in each of 20

different spatial windows in the landscape, with each window containing one focal

patch and all of its adjacent patches (Figure 1). To have the highest evenness value

of 1, all patches in that window participated in control in that run; the fewer patches

in that window that participated, the lower the evenness value. To get a metric of

the control distribution across the whole landscape (Equation 7), we summed all of

the evenness values from each window and subtracted that sum from 20 (the

number of patches) such that insulation is equal to:

$$\Im = |p| - \sum_{\forall p} \frac{n_p}{w_p}$$

where $|p|$ is the total number of patches, p is the patch identity, n_p is the number of

participating patches in the window for patch p, and w_p is the total number of

patches in the window for patch p (1 + the number of patches adjacent to patch p).

In the 20-patch landscape we simulated, this metric essentially quantifies whether the spatial distribution of control effort favored patches located on the edges of the landscape (high insulation, e.g., Figure 2a) or patches that are centrally located in the landscape (low insulation, e.g., Figure 2b). The same total amount of control occurred in all runs; only the distribution of this control was allowed to vary.

Because the goal of this research was to determine how spatial processes involved in mosquito control impact the number of humans who contract mosquito-borne disease, we report results using the percent reduction in human infections, which was calculated by first determining how many humans become infected in each demographic circumstance when there is no control implementation, then calculating what percent of this number of humans did not become infected in each run.

RESULTS

Human infections were reduced the most in runs using MPDD and the higher birth rate, followed by MPDD and LDD with the lower birth rate, and reduced the least in runs with LDD and the higher birth rate (Table 3).

Simulations using LDD demonstrated negative linear relationships between insulation and infection reduction (Figure 3a-b), indicating that low insulation achieves greater reductions in these circumstances (e.g., Figure 2b). However, Figure 3a shows that the smallest reductions in human infections occurred in runs

with medium insulation values, suggesting a non-linear interaction between the insulation metric used here and control efficacy in this circumstance. Overall, the greatest reductions in LDD circumstances were more likely to be achieved when the four non-participating patches were in the corners or on the edges of the landscape (Figure 4a-b), and the central patches all participated. Regardless of the location of the participating patches, LDD with the lower birth rate always achieved greater reductions than LDD with the higher birth rate. In all LDD simulations with the higher birth rate, treatment in all participating patches began after 10 days of disease transmission (Table 3). This is the earliest implementation of control among the four circumstances tested, due to greater vector abundance causing more human infections to occur sooner (Figure 5). In LDD with the lower birth rate, treatment began one day later (after 11 days of disease transmission), because lower vector abundances from the lower birth rate reduced the effective rate of transmission.

The results from simulations using MPDD were markedly different from those of the LDD circumstances. With the lower birth rate, the location of the participating patches had little effect on human infection reduction (Figure 3d, Figure 4d). Interestingly, these simulations with the lower birth rate were always less effective than MPDD with the higher birth rate (Figure 5). With the higher birth rate, infection reduction had a positive linear relationship with insulation in this circumstance (Figure 3c), indicating that high insulation of control distribution (i.e., participation of edge patches favored over that of interior patches as in Figure 2a) achieves the greatest reductions in human infections. Figure 4c demonstrates that,

for MPDD with the higher birth rate, simulations achieved greater average reductions when the control distribution favored the participation of edge patches, and especially of corner patches, rather than the participation of interior patches. However, Figure 3c shows that the greatest reductions were achieved in runs with medium insulation values, again suggesting a non-linear interaction between insulation and control efficacy in this circumstance, as with LDD and the higher birth rate. Despite achieving greater reductions than the other circumstances, control measures were only implemented after 15 days of disease transmission, the latest among the four circumstances.

DISCUSSION

Current ideas about the effects of landscape configuration on pest control focus largely on biological control in agroecosystems, and the role of landscape complexity in maintaining natural enemy populations (Tscharntke et al. 2007, Chaplin-Kramer et al. 2011). However, it is difficult to apply this body of knowledge to the control of anthropophilic mosquito species that thrive in urban areas, and a comparable understanding of the role of landscape configuration on mosquito metapopulation dynamics is lacking. Thus, finding effective spatial distributions for mosquito control requires more specialized consideration. Our simulations approach this line of research, and ultimately demonstrate that the distribution of control across a landscape differentially affects control efficacy in different ecological contexts. These results suggest that there may not be a "one size fits all"

emergency control plan for effectively preventing or mitigating mosquito-borne disease outbreaks in all circumstances.

In both circumstances using logistic density-dependence in the juvenile mosquito populations (LDD), simulations with control distributions displaying low insulation patterns achieved the greatest reductions in human infections. When the four non-participating patches were on the edges of the landscape, they received lower subsidies of immigrating adults and started out at lower abundances of both adults and juveniles. This caused their oscillating juvenile populations to have smaller overshoots of carrying capacity with low insulation (top two rows of Figure 6) than with high insulation (top two rows of Figure 7). With fewer adult mosquitoes in the landscape in the long-term, fewer human infections occurred. Conversely, in high insulation simulations that favored the participation of edge patches over that of central patches, mutual population amplification between the non-participating patches increased the number of adult mosquitoes, reducing the efficacy of control measures.

In contrast, simulations with high insulation patterns achieved greater reductions when using multiphasic density-dependence (MPDD) and the higher birth rate. Preferentially treating edge patches over interior patches enhanced control efficacy in this circumstance because these patches started out with higher abundances and received dispersing adults from more patches, causing their juvenile populations to remain consistently above the threshold for oviposition restriction (see patch 6 in Figure 6). In low insulation simulations, however, the lower density of juveniles in non-participating patches, and the lack of adult

dispersal between non-participating patches, caused the juvenile populations to more quickly decline to below 80% of carrying capacity. Once juvenile abundance dipped below this threshold, oviposition restrictions were no longer in place, causing the number of juveniles to then surpass the threshold again, then rapidly decline again to below the threshold due to the imposed oviposition restrictions (Figure 7).

Unlike the other three circumstances, the location of the participating patches had little effect on the efficacy of MPDD simulations with the lower birth rate (Figure 3d, Figure 4d). This lower birth rate was not low enough to completely negate the effects of MPDD by always keeping juvenile populations below the threshold, but also not high enough to cause sufficient population amplification to maintain juveniles above the threshold, even in centrally-located patches. Thus, the juvenile populations in the non-participating patches continued to fluctuate or began fluctuating soon after control implementation (Figures 6 and 7).

Many researchers have posited that mosquito control efforts may fail to reduce mosquito populations because of compensating or overcompensating density-dependence (Agudelo-Silva and Spielman 1984, Yakob et al. 2008, White et al. 2010); when control measures reduce mosquito abundance, they also reduce the burden of larval competition, which both theory and empirical data suggest may allow populations to compensate or overcompensate by producing that many or more additional mosquitoes. With the multiphasic density-dependence examined here, certain spatial patterns of control implementation cause the non-participating patches to synergistically prevent compensation on a larger scale through mutual

population amplification that causes decreased oviposition in untreated patches. This finding suggests that detailed knowledge of local mosquito metapopulation and demographic dynamics can inform mosquito control programs about where to focus limited resources to better protect people throughout the landscape from mosquito-borne diseases.

Despite the theoretical possibility that compensation and overcompensation may render larvicide application ineffective or counterproductive, we see no evidence in any of our simulations of larval control leading to greater adult mosquito production. This may be due to the high level of participation and/or the assumption of completely effective larvicide, such that treated patches contain no pre-adults, but simulations that relax these assumptions also all yield fewer human infections than implementing no control (Schwab et al. unpublished data). These simulations suggest that any control may reduce disease prevalence better than no control, though the cost-effectiveness of implementing uninformed control remains unclear.

Although we only modeled the short-term effects of emergency responses to a single pathogen introduction event, further research examining these dynamics over longer time scales may reveal important eco-evolutionary impacts of the spatial distribution of mosquito control. For instance, local disease extinctions in areas participating in mosquito control measures may inadvertently increase mosquito and/or disease metapopulation persistence by desynchronizing regional population dynamics and enabling recolonization of previously controlled patches (Fox et al. 2017). In addition, certain spatial and temporal patterns of insecticide

application could help maintain low levels of insecticide resistance in vector populations by promoting the survival of susceptible individuals in untreated refuges (Carriere et al. 2012).

Integrated vector management (IVM) programs that combine numerous approaches will likely be vital to future arbovirus control efforts (Yakob et al. 2017). In our simulations, the higher birth rate lead to greater mosquito production and less effective larval control measures than the lower birth rate when using logistic density-dependence (Figure 5). Thus, mosquito control efforts that effectively reduce birth rate, such as release of insects carrying a dominant lethal gene (RIDL) (Phuc et al. 2007, Carvalho et al. 2015), may improve control efficacy in populations regulated by logistic density-dependence, and the simultaneous use of multiple control measures may lead to the fewest infections. However, some combinations of approaches may partially counteract each other, and would be best implemented only after careful consideration of local mosquito ecology. For instance, simulations using multiphasic density-dependence (MPDD) were more effective with the higher birth rate than with the lower birth rate (Figure 5), so adding RIDL to a larvicide application regime could lead to more human infections than larvicide application alone in these circumstances.

These results demonstrate that site-specific knowledge of mosquito metapopulation dynamics can inform more effective distributions of mosquito control measures. However, the mechanisms of population regulation in natural populations of invasive mosquitoes remain poorly understood (Legros et al. 2009, Walsh et al. 2011). This dearth of knowledge currently prevents the use of

mathematical models to establish effective emergency control regimes uniquely tailored to particular ecological contexts. In addition to the empirical work needed to understand mosquito population dynamics, further theoretical research should expand on this simple model to explore the efficacy of different control distributions in simulations that incorporate more complex landscape configurations and density-dependent effects on the fitness of eclosing adults. A more thorough understanding of the mechanisms regulating mosquito populations, as well as the spatial dynamics created by different configurations of control, can lead to more effective measures for controlling mosquitoes and the diseases they transmit.

Table 1. Assumptions of the model.

Topic	Assumptions
Landscape	All patches are identical, with equal connectivity between all adjacent patches.
	The landscape is completely isolated.
	Humans move homogeneously throughout the landscape.
Control	Surveillance is 100% accurate and results are immediate enough to inform the following day's actions.
	Treatment to each larval development pool is completely effective for exactly 10 days.
	Source reduction via larvicide application is the only control measure implemented.
Epidemiology	The single arbovirus strain is only transmitted horizontally and only between mosquitoes and humans.
	Recovery causes complete life-long immunity in humans; mosquitoes do not recover from infection.
	Transmission of the virus is immediate; there is no latency/exposed period. No viral evolution occurs.
Mosquito population	Mosquito feeding on humans has no effect on birth or death rate, and both are constant throughout mosquito lifetime.
	No evolution occurs in the mosquito population, including no evolution of resistance to treatment.
	Oviposition of non-diapause eggs occurs daily; the maximum number of eggs oviposited per day in patch i is a function of the carrying capacity of patch i.
	A fixed percent of mosquitoes in each patch disperse to an adjacent patch each day; dispersal is not density-dependent.
	No regulation of the adult population occurs, only density-dependent regulation of the juvenile population.
	Eggs/juveniles cannot be laid and die on the same day.

Table 2. Parameter definitions and values used in model simulations.

Parameter	Value(s)	Definition
Treat	0 = untreated 1 = treated	Matrix of control schedule in each patch
μ^	1/20	Per capita death rate of mosquitoes (after density-independent mortality)
ν*	Low = 3 High = 5	Average number of eggs laid per female per day (after density-independent mortality)
α	LDD: $\alpha_{p,t} = 0$ MPDD: $M_{j,p,t-1} < 0.8K \Rightarrow \alpha_{p,t} = 0,$ $M_{j,p,t-1} \geq 0.8K \Rightarrow \alpha_{p,t} = 1$	Triggering mechanism for multiphasic density-dependence
x	0.1	Proportion of eggs still laid when $\alpha_{p,t} = 1$
K*	350	Daily availability under carrying capacity of additional juvenile mosquitoes that can be added to each pool at stability
g^	1/10	Growth rate of mosquitoes from juvenile to adult
D*	$\sum_{\forall q \neq p} D_{p,q} = 0.1$	Matrix of mosquito dispersal probabilities between pools
r^	0.3	Biting rate
c*	0.003	Scaling constant (to enable reasonable pace of outbreak amid a ubiquitous human population)
T*	$T_{mh} = 0.08$ $T_{hm} = 0.07$	Matrix of transmission probabilities per bite from mosquitoes to humans (T_{mh}) and humans to mosquitoes (T_{hm})
γ^	1/4	Recovery rate of humans

All rates are in days.

*=Assumed for model exploration

^=Modified from (Erickson et al. 2010)

Table 3. Control efficacy and spatial effects depend on mosquito population dynamics.

Density-dependence	Logistic (LDD)		Multiphasic (MPDD)	
Birth rate	High	Low	High	Low
Mean % reduction in infections ± SD	52.0% ± 0.96	67.4% ± 0.66	81.5% ± 0.73	73.8% ± 0.36
Range in % reduction in infections	48.4-54.8%	65.0-69.0%	79.2-84.2%	72.3-75.0%
Days of disease transmission before treatment begins	10	12	15	13
Slope of regression line between $\Im$ and % reduction	-1.73	-1.46	1.28	0.018
R^2 of regression line between $\Im$ and % reduction	0.540	0.815	0.534	0.0004

Figure 1. **Simulated landscape with patch numbers**. Each box represents the spatial window used for calculating control insulation for each of the two starred patches.

Figure 2. **Representations of spatial control distributions.** (a) demonstrates high insulation, and (b) demonstrates low insulation. Patches that participated in control efforts are shown in blue, while patches that did not participate are shown in white.
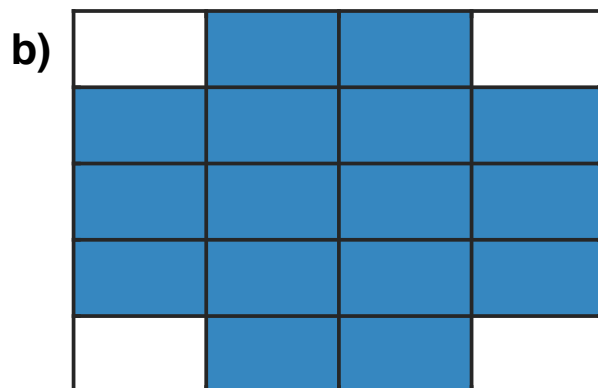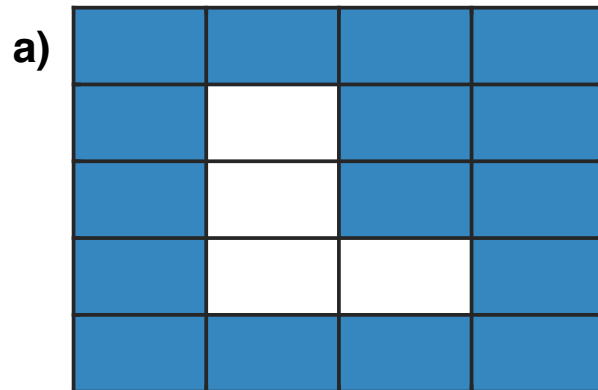
Figure 3. Scatter plots of control insulation and percent reduction in human infections in each of the four demographic contexts. Note the different scales of the y-axis. Each dot represents results from one simulation, with points on the left side of each plot from low insulation runs (more participation in the interior of the landscape), and points on the right side from high insulation runs (more participation on the edges). The linear regression lines are shown in black.
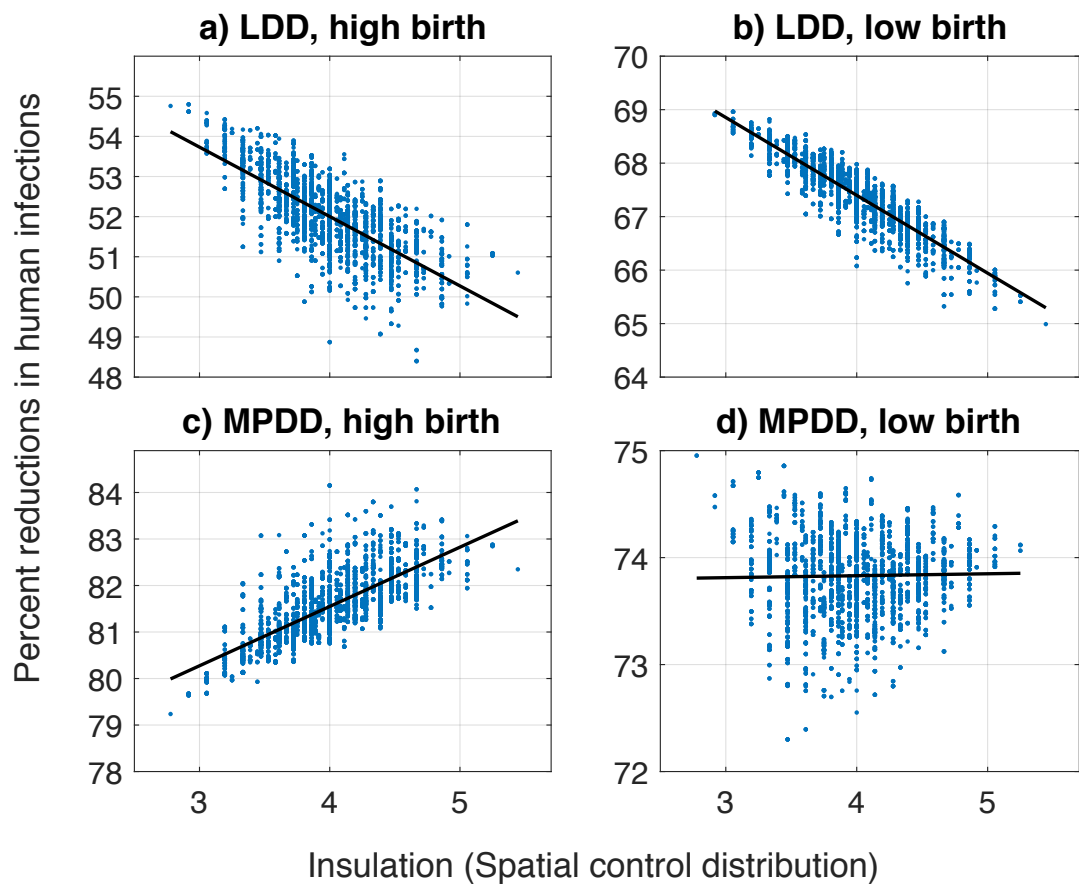
Figure 4. **Average benefit of patch participation in each circumstance**. The color of each block represents, for that patch, the average reduction when that patch participated divided by the average reduction when that patch did not participate. Values <1 (darker blue) signify that the average reduction was higher when that patch did not participate, this patch should remain untreated when resources are limited; values >1 (darker red) signify that the average was higher when that patch did participate, so ideally this patch should be involved in control implementation.
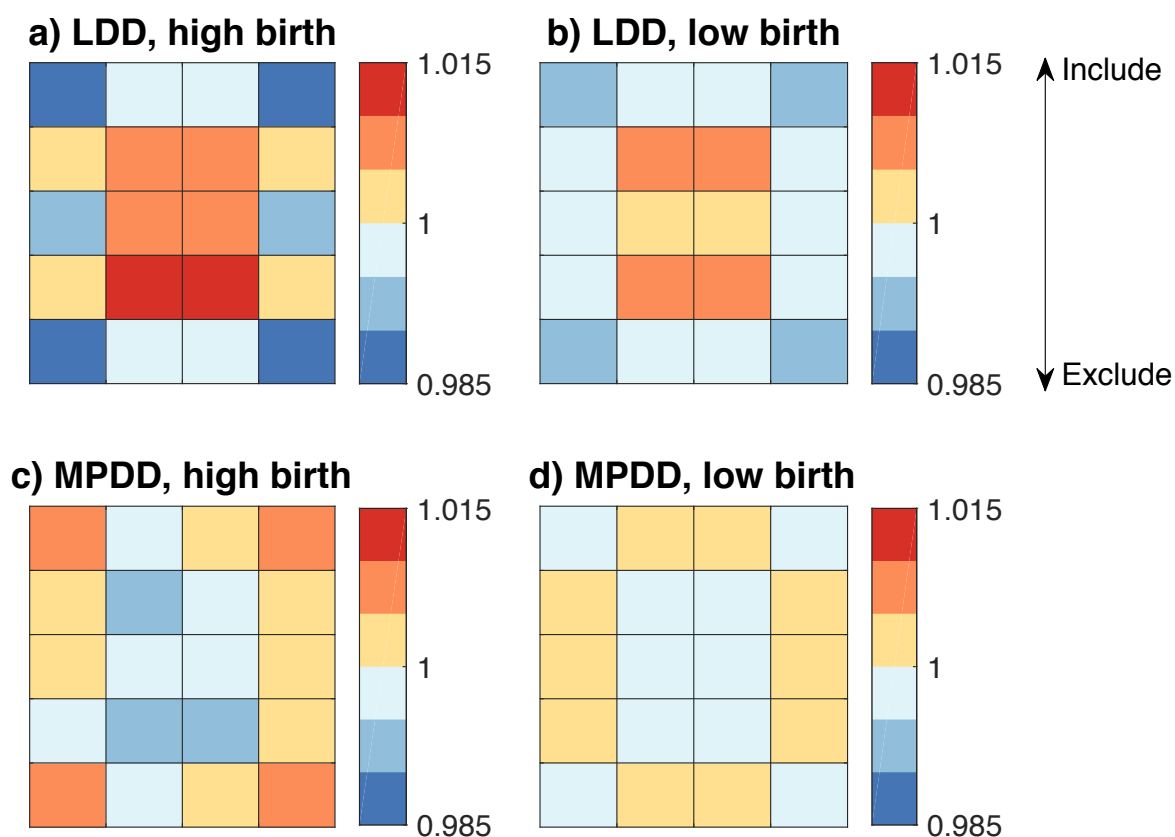
Figure 5. Average number of humans infected in each demographic circumstance on each of the 150 days of disease transmission. Shaded areas indicate two standard deviations around the mean number of infections each day.
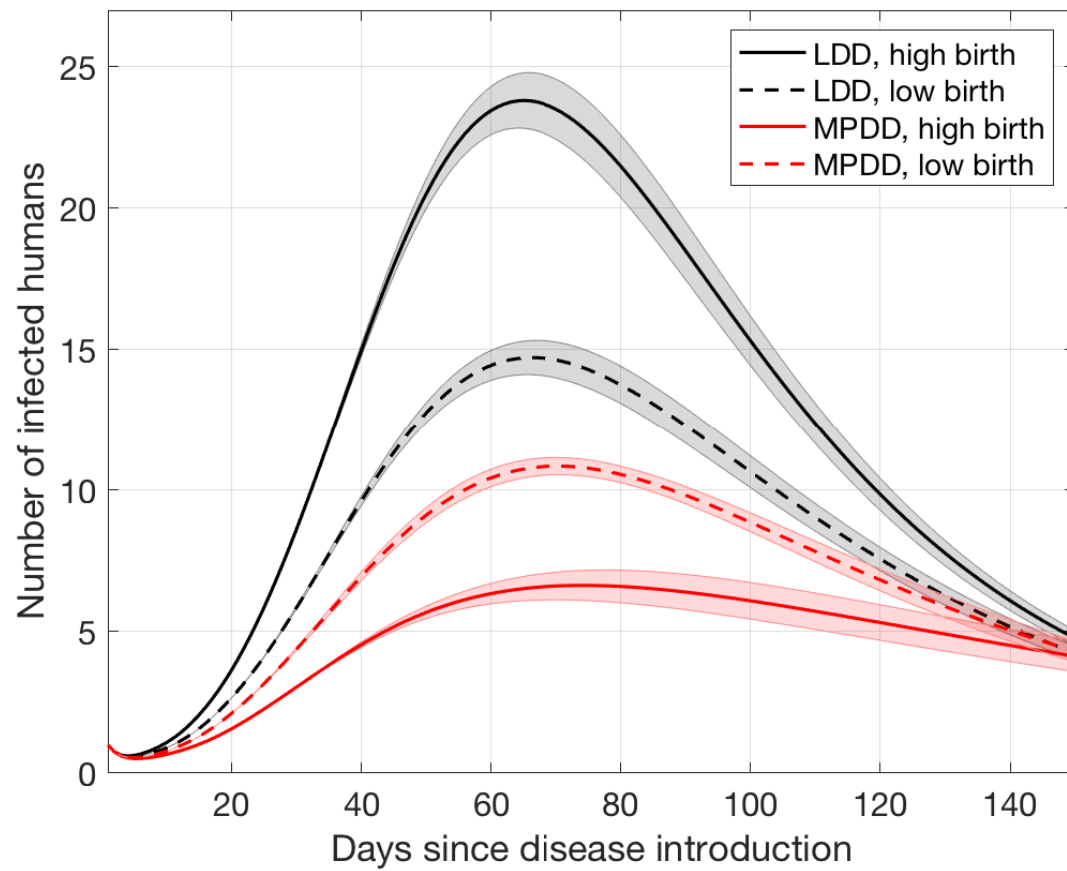
Figure 6. **The number of juveniles in each non-participating (NP) patch during the most effective runs of each circumstance**. The first column shows control distributions that yielded the greatest reduction in human infections for each demographic context, with white squares representing participating patches and non-white squares representing NP patches. Each row contains the graphs of the juvenile populations in NP patches for the circumstance labeled above the landscape depiction at the start of that row, with the line color of each graph corresponding to the location of that patch in the landscape depiction. The x-axis of all juvenile plots ranges from day 7 (day of disease introduction) through day 156, with grid lines marking days 40, 80, and 120. The y-axis of all juvenile plots ranges from 250-900 individuals, with grid lines marking every one hundred between 300 and 900.
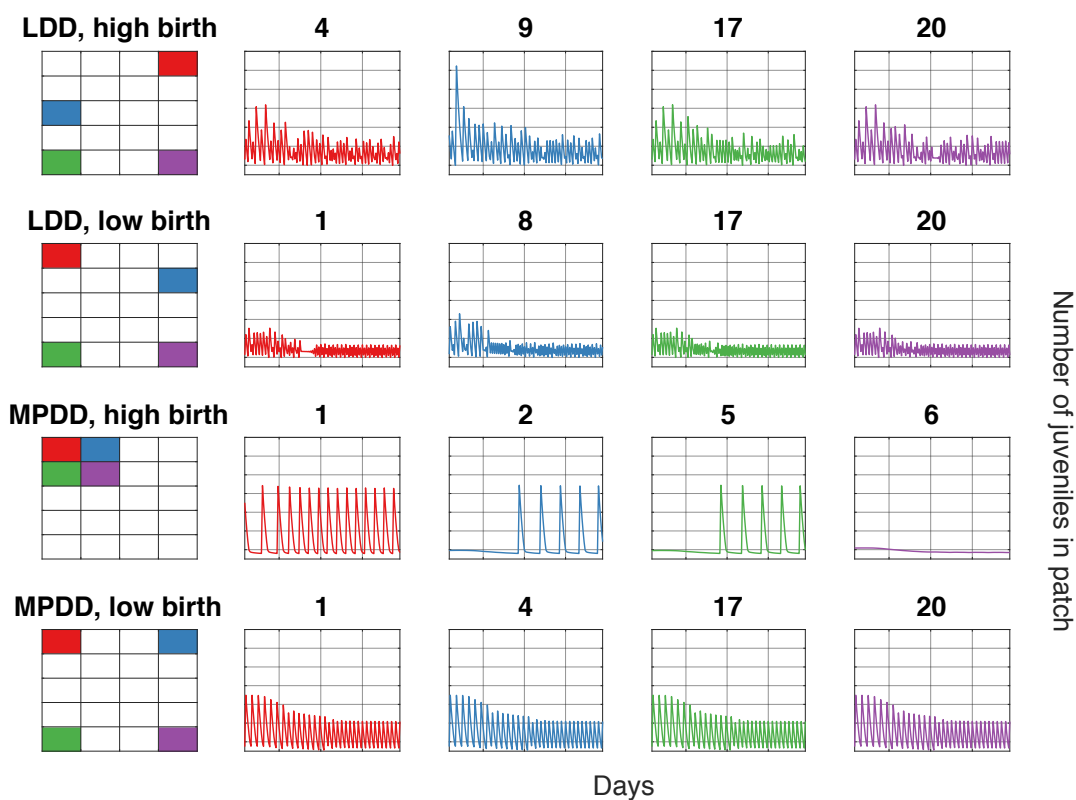
**Figure 7. The number of juveniles in each non-participating (NP) patch during the least effective runs of each circumstance**. The first column shows control distributions that yielded the lowest reduction in human infections for each demographic context, with white squares representing participating patches and non-white squares representing NP patches. Each row contains the graphs of the juvenile populations in NP patches for the circumstance labeled above the landscape depiction at the start of that row, with the line color of each graph corresponding to the location of that patch in the landscape depiction. The x-axis of all juvenile plots ranges from day 7 (day of disease introduction) through day 156, with grid lines marking days 40, 80, and 120. The y-axis of all juvenile plots ranges from 250-900 individuals, with grid lines marking every hundred between 300 and 900.
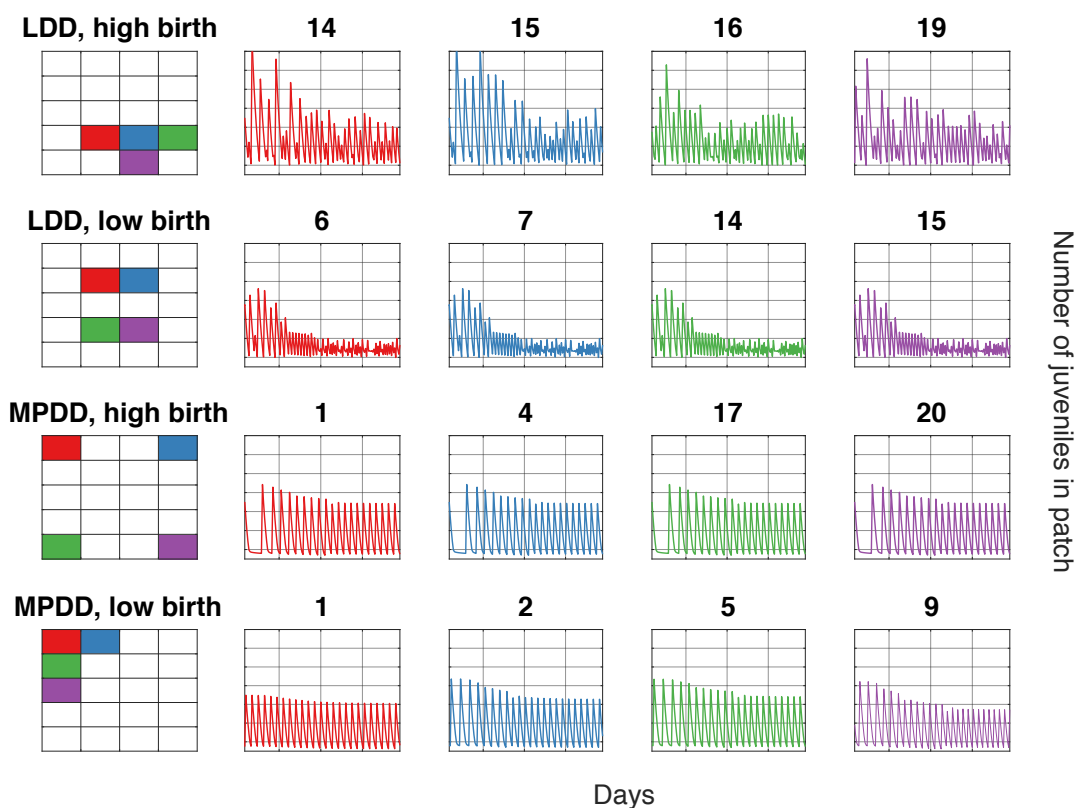
Adulticide or larval control, that is the question: how to take arms against a sea of mosquito-borne viruses?

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ABSTRACT

When faced with evidence of active transmission of mosquito-borne pathogens such as Zika virus and chikungunya, mosquito control agencies typically spray adulticides as the primary means of control. However, there exist little to no formal analyses of the relative efficacies of adult vs. larval control in reducing the risk of transmitting mosquito-borne viruses to humans. To address this deficiency, we present a mathematical model to test whether adulticide or larval control regimes yield greater reductions in the number of humans who acquire a mosquito-borne virus. To account for uncertainty in biting and demographic rates, as well as potential variability across populations, we simulated both types of control using various biting rates and adult mosquito lifespans. In our simulations, larval control more effectively reduced outbreak sizes when using higher biting and shorter lifespans, while adulticide better reduced human infections when using medium to low biting rates and higher lifespans. These results suggest that larval control interventions may be a better strategy to control outbreaks of particularly virulent viruses, viruses transmitted by highly aggressive mosquitoes, and/or under socioeconomic conditions that magnify contact. Much work remains to be done to determine what methods of mosquito control best protect human populations from mosquito-borne viruses in different epidemiological and ecological contexts.

INTRODUCTION

Vector control is the best method currently available for combatting the continued emergence of mosquito-borne pathogens (Lorenzi et al. 2016). While there are, of course, control measures that focus on non-lethal methods of control (e.g., Harris et al. 2012), for these first explorations, we restrict ourselves solely to targeted lethal efforts. Due to the physiological and habitat differences between mosquito life history stages, mosquito control efforts that target either adults or immature stages (eggs, larvae and pupae) differ significantly. Methods for the control of immatures (hereafter referred to as "larval control") include source reduction (removal and drainage of aquatic oviposition sites/larval development pools), biological control, and application of larvicides and pupicides. Adult-targeted efforts are mostly limited to adulticide applications.

"Container-breeding" species, namely *Aedes aegypti and A. albopictus*, transmit many pathogens, such as Zika, dengue, chikungunya, and yellow fever (Focks and Chadee 1997, Moore and Mitchell 1997, Focks et al. 2000, Gratz 2004, Reiter et al. 2006, Medlock et al. 2012). These often highly anthropophilic species thrive in urban environments and oviposit in small pools of standing water that can be abundant throughout urban habitats (Unlu et al. 2013). Due to the difficulty of locating and accessing these numerous oviposition sites, source reduction efforts to control container-breeding species are often quite time- and labor-intensive. Adulticide application is more commonly used to control these species, with the goal of eliminating any infected mosquitoes before an outbreak occurs.

We have a relatively poor understanding of the population dynamics of container-breeding mosquitoes, and there are conflicting results among the studies that have been done, especially regarding oviposition site selection (Wasserberg et al. 2014, Day 2016). In particular, very few studies have directly measured the effects of different control methods on the incidence of infection among mosquito or human populations (Esu et al., 2010; Farajollahi et al., 2012; but see Teng et al., 2007), so it is currently unclear whether targeting the juveniles or the adults more effectively curbs viral transmission. Despite the lack of available data, mosquito control professionals are under pressure to take action to protect the public. Adulticide spraying is usually the first, and sometimes only, control measure enacted to combat the transmission of mosquito-borne viruses (Mount et al. 1996, WHO 1997). However, there is little empirical evidence suggesting that this is an effective method by itself (Esu et al. 2010, Farajollahi et al. 2012, Bowman et al. 2016).

There is an "unspoken rule" in professional mosquito control that the best methods are the ones that kill the greatest number of adult mosquitoes, an understandable but possibly misguided notion that results in a bias towards adulticide applications (Mount et al. 1996). With this approach, the outcome of control efforts is clear: sudden declines in mosquito bites are seen as proof of successful control. But effective larval control methods work by *preventing* adult mosquitoes from emerging; they provide much less tangible evidence of success, making these methods less understandable to the public and to policymakers.

There are many potential reasons why adulticide-focused mosquito control efforts may be less successful than expected and why larval control may be a more effective option. For instance, widespread and frequent usage of adulticides has led to extensive insecticide resistance in mosquito populations (Corbel et al. 2017). It is much more difficult to evolve resistance to source reduction efforts without vastly changing life history characteristics, and resistance to *Bti*, a commonly used larvicidal biological agent, is rare and potentially energetically costly (Tetreau et al. 2013). In addition, adulticide typically remains effective for a very short period of time, potentially allowing immatures to quickly replace the killed adults. This does likely reduce infection prevalence among adult mosquitoes, despite achieving only transient population reduction. On the other hand, larvicides can remain active for several weeks, even months (Skovmand et al. 2009), providing longer-term ultimate suppression of adult mosquito populations with a smaller labor cost. Adulticides can also have significant non-target effects, including on humans, so their use is tightly regulated. *Bti*, on the other hand, is specific to mosquitoes, black flies and other aquatic insect detritivores. Without extensive non-target effects, its use is not as heavily regulated, so it can be applied more often. Finally, adulticide application requires specific training and licensure, while container removal can be done by anyone and has thus been incorporated into successful public education initiatives (Fonseca et al. 2013).

The question we aim to address here is: under what circumstances would adulticide application better reduce human infections with a mosquito-borne virus than larval control? We employ a spatially explicit difference equation model,

simulating arboviral transmission between a mosquito metapopulation and a human population, in order to compare the efficacy in reducing human infections of mosquito control programs targeting either immature or adult life stages, across various biting rates and adult mosquito lifespans.

METHODS

We used a model previously employed in Schwab et al. 2017, Schwab et al. 2018 (in revision), and Lemanski et al. 2018 (in review). Model equations, as well as parameter definitions and values used in the present study, can be found in Appendix 1. For a more complete description of this model and its assumptions, see (Schwab et al. 2017).

In keeping with these previous studies, we made the following assumptions about the nature of the landscape. Simulations of this model were run on a grid landscape with 20 (five by four) identical patches. To incorporate metapopulation dynamics, adult mosquitoes could disperse to any adjacent patch each day, reflecting the limited dispersal ability of many container-breeding species (Trpis and Hausermann 1986). Humans, however, were assumed to be mobile enough that they created a homogenous and ubiquitous population; thus, a mosquito in any patch could bite any human.

To focus our study on mitigation of novel introduction or annual reintroduction of otherwise absent infections, surveillance of human infections

began on day 1 of the simulation, though disease was not yet introduced into the landscape. At the end of day 7 (after control decisions had been made), one human became infected with an arbovirus, initiating disease transmission on day 8. The simulation then proceeded for 150 more days (156 total days with surveillance).

The order of events on each day of the simulation was as follows: Adult mosquitoes laid eggs in their current patch. Then, proportions of both juvenile and adult mosquitoes died and were removed from the population. Adult dispersal and all compartment transitions then occurred simultaneously, using the number of mosquitoes from the previous day that remained alive (juvenile mosquitoes grew to become uninfected adults, uninfected mosquitoes became infected, susceptible humans became infected, and infected humans recovered).

Parameter combinations

To incorporate parameter sensitivity, we simulated both adulticide application and larval control using three different rates at which mosquitoes feed off of humans ("biting rates") and up to 14 different adult mosquito lifespans (Table 1). We ran the model 1000 times for each combination of control type (larval control or adulticide), biting rate, and adult mosquito lifespan. For the medium and high biting rates, we did not run the model with all 14 of the lifespans used with the high biting rate because, with the medium and low biting rates, the shorter lifespans limited the entomological inoculation rate, and hence the reproductive number of the disease declined to near or below one, so epidemics were either very small or did not occur.

For each combination of parameters, we calculated the average percent reduction in human infections. The number of humans infected in the absence of either adulticide or larval control can be found in Table 1. To address our question about the circumstances under which adulticide would more effectively curb disease transmission than larval control, we also subtracted, for each combination, the average percent reduction using larval control from the average percent reduction using adulticide.

Incorporating larval control and adulticide treatment

For both the larval control and the adulticide simulations, 16 out of the 20 patches in the landscape were arbitrarily selected at the start of each run to participate in human infection surveillance and control. When there was at least one infected human, control was triggered to begin in all 16 participating patches on the following day, with adulticide lasting one day and larval control lasting 10 days. Due to the regulations governing application of insecticides, most adulticides can only be applied at their maximum dosage about once per week, leading to temporary 40-90% reductions in adult *Ae. albopictus* populations in one study (Farajollahi et al. 2012). Since our simulations involve repeated applications more often, we assumed that smaller doses of adulticide were applied to treat patches, killing 10% of all adult mosquitoes (regardless of infection status) in all 16 participating patches for one day. We plan in future work to compare the benefit of high doses applied less often versus low doses applied more often. Larval control was assumed to be completely effective, so that when treatment was triggered, there were no juveniles

in any of the 16 participating patches for the following ten days. For simplicity, we assume that either adulticide application or larval control occur, though additional research should address the effects of combining these approaches.

RESULTS

Parameter sensitivity

Simulations using the high biting rate yield smaller infection reductions than simulations using the medium or low biting rate. Both larval control and adulticide can effectively reduce human infections at longer lifespans when using the low biting rate than when using the high biting rate (Figure 1). In addition to the effects of different biting rates, different lifespans also alter the efficacies of adulticide and larval control relative to each other, though each becomes more effective as lifespan decreases. Shorter life expectancies improve the relative efficacy of larval control until mosquitoes live for such a short time that preventing their eclosion becomes less beneficial (as occurs with lifespans corresponding to death rates higher than 0.12 in Figure 2). At the same time, shorter lifespans decrease the efficacy of adulticide treatment because adults already live for short enough periods of time that further decreasing their lifespan becomes less beneficial.

Adulticide versus larval control: high biting rate

When using the high biting rate and short adult mosquito lifespans (corresponding to death rates between 0.05 and 0.08), neither adulticide nor larval control effectively reduces human infections (Figure 1). When death rates are between 0.9 and 0.15, the efficacy of both control types increases, but larval control more effectively reduces human infections by seven to 50 percentage points than adulticide treatment, with larval control yielding fewer infections than adulticide by 50 percentage points with a death rate of 0.12 (Figure 2). When the death rates are between 0.16 and 0.18, both adulticide and larval control very effectively reduce human infections by up to 96.4%.

Adulticide versus larval control: medium biting rate

When using the medium biting rate and intermediate lifespans (corresponding to death rates between 0.05 and 0.08), adulticide more effectively reduces human infections than larval control by five to 29 percentage points, with the greatest differences at longer lifespans, when the efficacy of larval control remains below 25%. When death rates are between 0.09 and 0.11, both adulticide and larval control very effectively reduce human infections by up to 95.5%. (We do not include results for shorter lifespans due to lack of disease outbreak with those parameters – see Methods).

Adulticide versus larval control: low biting rate

When using the low biting rate and a death rate of 0.05, adulticide much more effectively reduces human infections than larval control (93.4% versus 47.2%, a

difference of 46.2 percentage points [Figures 1 and 2]). When the death rate is 0.06, the efficacy of larval control increases to 86.1%, but adulticide remains about 10 percentage points higher. When the death rates are 0.07 and 0.08, both adulticide and larval control achieve reductions of about 95%.

DISCUSSION

Vector control effectively reduces the transmission of vector-borne pathogens by limiting the inoculation rates of vector populations. There are many potential methods of controlling entomological inoculation rates, some of which work more directly and intuitively than others. We examine here the control methods that involve complex interactions of and between intraspecific vector population dynamics, interspecific vector-host dynamics, and epidemiological circumstances.

When there is active transmission of a mosquito-borne virus, or a high risk of active transmission, adulticide application is largely considered the most effective, and quickest acting, mosquito control method (Mount et al. 1996). However, our results suggest that with aggressively-biting mosquitoes and/or highly transmissible viruses (such that lower biting rates also yield rapid viral transmission), larval control can be more effective than adulticide application. This is expected to be the case when sufficiently high biting rates allow adult mosquitoes to quickly both bite an infected human and then transmit infection by biting a

second, susceptible human. It is more beneficial in these circumstances to prevent more adult mosquitoes from emerging at all by implementing larval control than to apply adulticide that reduces the number of adults that have already had the chance to engage in transmission of the virus.

However, the benefit of larval control may not be immediately apparent. For the first approximately 20 days of control in simulations using the parameter combination that yielded the greatest differential benefit of larval control, there are actually *more* new human infections with larval control than with adulticide (Figure 3, top panel). This occurs because larval control has no direct effect on adults, so adults that were present before control began remain alive for longer than they do in simulations with adulticide. This causes greater viral transmission until the prevention of eclosion due to larval control sufficiently reduces the adult population. If only short-term epidemiological data are available, adulticide would appear to more effectively reduce outbreaks than larval control, even though many fewer people would acquire the virus over longer timescales with larval control than with adulticide. Larval control is so effective here that the number of human infections drops below the threshold for triggering control. This causes control to cease around day 112, leading to a subsequent spike in the number of adult mosquitoes (Figure 4, top panel). This spike, in turn, causes more human infections (Figure 3, top panel), which triggers the continuation of larval control, which again reduces the number of adult mosquitoes. For more on the effects of triggering control based on different types of surveillance data, see (Schwab et al. 2017).

There are other areas of parameter space where the efficacy of adulticide greatly exceeds that of larval control. However, the mechanism of this differential benefit is quite different from the mechanism commonly believed to be at play by professionals choosing to treat an area with adulticide (i.e., that directly reducing the number of adults best reduces viral spread). When both the biting rate is low and the lifespan is long, adulticide treatment yields significantly fewer human infections than larval control (Figure 3, bottom panel), despite there actually being *more* total mosquitoes after day 50 with adulticide than with larval control (Figure 4, bottom panel). This occurs because both the biting and dying rates are low enough that being killed by adulticide prevents mosquitoes from otherwise having the time to bite two people and thus contribute to the number of infected humans. While larval control does eventually lead to reduced numbers of adults, they stay alive long enough to bite two people, leading to more human infections. In this case, the efficacy of adulticide treatment in reducing outbreak size would not be reflected in surveillance data of mosquito population sizes; only infection surveillance (of either humans or mosquitoes) would demonstrate this differential benefit.

Consideration of the spatial metapopulation dynamics created by mosquito control efforts introduces an additional level of complexity, causing variation in efficacy among simulations run with the same combinations of parameters. When the biting rates are medium to high, adulticide simulations yield much more variable results than larval control simulations (Figure 1). This suggests that the effect of adult-targeted control regimes will depend on the spatial distribution of adulticide

applications (for more on the effects of spatial distributions of larval control, see Schwab et al 2018, *in revision*).

Although not examined in this paper, mosquito control efforts always operate under strict economic constraints (Halasa et al. 2012, Lemanski et al 2018, *in review*). In the simulations presented here, larval control remains completely effective for ten days, while adulticide only works for one day. Thus, many fewer individual implementations of larval control need to occur to achieve the same number of days of treatment with adulticide. Fewer implementations of larval control translates to fewer hours spent by staff on control efforts, which could save financially strapped agencies significant sums of money, as long this occurs in a context conducive to effective larval control. However, these savings might be offset by the labor-intensive nature of finding and accessing larval containers. A thorough cost-effectiveness study comparing larval control and adulticide in a metapopulation context would be a useful next step.

The efficacy of mosquito control in reducing human infections largely depends on ecological context (Medlock et al. 2012, Schwab et al. 2018, *in revision*). Accurate empirical estimates of mosquito biting and lifespans would therefore be critical for mosquito control professionals to be able to determine which control methods would be most effective. Until we are able to accurately evaluate mosquito lifespans, we may be able to figure out where we are in parameter space by looking at how effective different strategies have been. We could then use that knowledge to amend our strategies and employ methods expected to be more successful in our particular context.

CONCLUSIONS

Quick and effective mosquito control measures remain the primary means of reducing human diseases caused by mosquito-borne viruses. Although adulticide is commonly applied as an emergency measure for controlling outbreaks of mosquito-borne pathogens, larval control more effectively reduced the total number of human infections than adulticide application in our simulations when using a high mosquito biting rate. Adulticide was more effective than larval control only when using lower biting rates. Thus, with aggressive mosquitoes or highly virulent pathogens, larval control may better reduce total outbreak sizes, while adulticide application may be more effective in other contexts. However, depending on the average lifespan of particular mosquito populations, there are cases in which adulticide and larval control will be expected to yield similar results. The ability to obtain accurate empirical estimates of mosquito demographic rates in individual jurisdictions will lead to better predictions for which methods of control would best reduce human risks from mosquito-borne viruses.

Due to the limitations imposed by economic constraints, continued theoretical and empirical research are needed to discover which mosquito control methods are most cost-effective in different ecological contexts. Because the short-term and long-term effects of control can be different from one another, assessment of control effectiveness via collection of surveillance information should continue

for as long as possible. In addition, our results demonstrate that trends may differ between epidemiological and population information, indicating that both are needed to fully understand the impacts of mosquito control on mosquito population abundances and ultimately on mosquito-borne pathogen transmission.

Table 1. Parameter combinations used in simulations with either adulticide treatment or larval control.

Biting rate	Adult mosquito death rate (corresponding lifespan in nearest whole days)	Number of human infections in the absence of control
High (0.83)	0.05 (20)	999.00
	0.06 (17)	999.00
	0.07 (14)	999.00
	0.08 (13)	998.99
	0.09 (11)	998.87
	0.10 (10)	998.00
	0.11 (9)	994.90
	0.12 (8)	986.92
	0.13 (8)	971.97
	0.14 (7)	947.06
	0.15 (7)	910.07
	0.16 (7)	858.05
	0.17 (6)	787.03
	0.18 (6)	685.26
Medium (0.48)	0.05 (20)	999.00
	0.06 (17)	998.60
	0.07 (14)	994.00
	0.08 (13)	977.35
	0.09 (11)	937.61
	0.10 (10)	860.74
	0.11 (9)	701.87
Low (0.33)	0.05 (20)	996.16
	0.06 (17)	974.29
	0.07 (14)	892.90
	0.08 (13)	628.24

Figure 1. Average percent reductions in human infections using either adulticide or larval mosquito control methods. Shaded areas indicate two standard deviations around the mean. Top panel shows reductions when simulating a high biting rate, across 14 different adult mosquito death rates. Bottom panel (left) shows reductions when simulating a medium biting rate, across seven different death rates (reciprocal of the lifespans). Bottom panel (right) shows reductions with a low biting rate, across four death rates. Bottom panel graphs do not include higher death rates due to lack of disease outbreak with those parameters (see Methods).
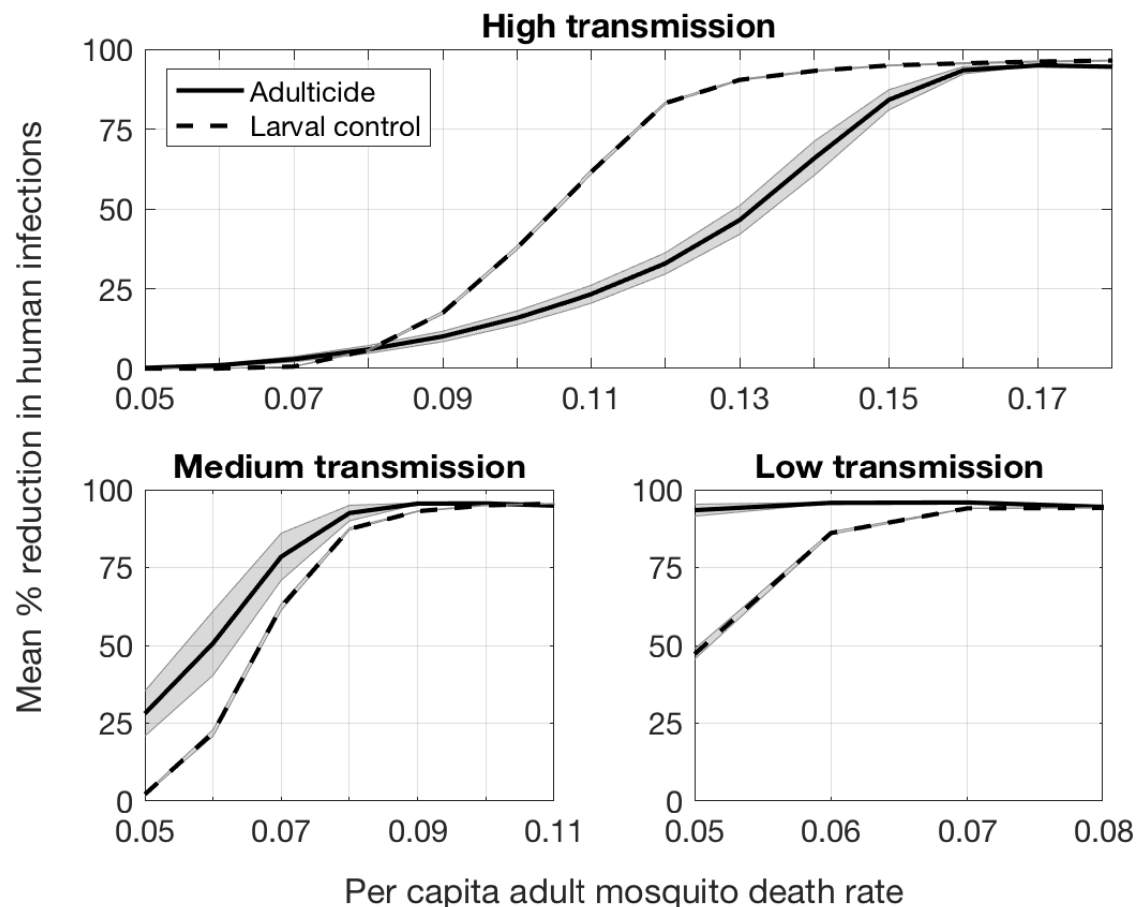
Figure 2. Average benefit of adulticide over larval control. Graphed values are the differences in average human infection reduction between adulticide and larval control: positive values indicate greater reductions with adulticide; negative values indicate greater reductions with larval control. Solid line with circles represents results with high mosquito biting, across 14 adult mosquito death rates (reciprocal of the lifespans). Dashed line with triangles represents medium biting across seven death rates. Dotted line with squares represents low biting across four death rates.
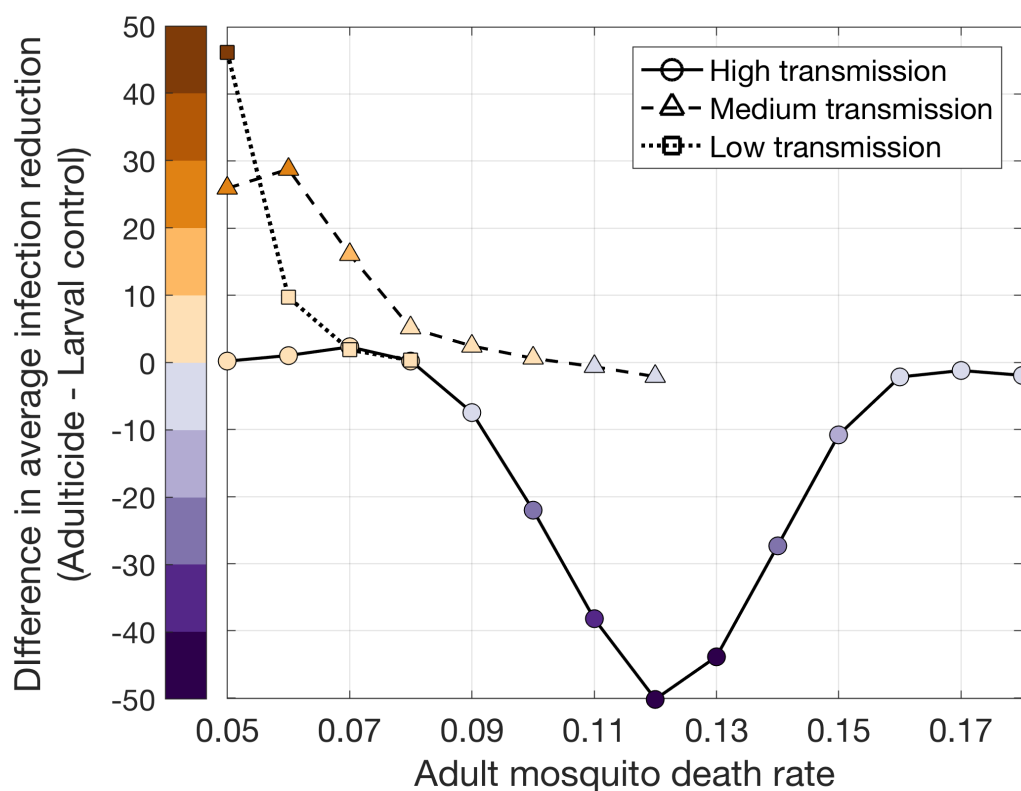
Figure 3. Number of new human infections each day using either adulticide or larval control with two different parameter combinations. Shaded areas indicate two standard deviations around the mean. Top panel shows new human infections when simulating a high biting rate and an adult mosquito death rate (reciprocal of the lifespan) of 0.12. Bottom panel shows new human infections when simulating a low biting rate and an adult mosquito death rate of 0.05. Pathogen introduction occurred on day 7 in both panels; control was triggered by detection of at least one human infection (first occurring on day 14 in the top panel and on day 17 in the bottom panel).
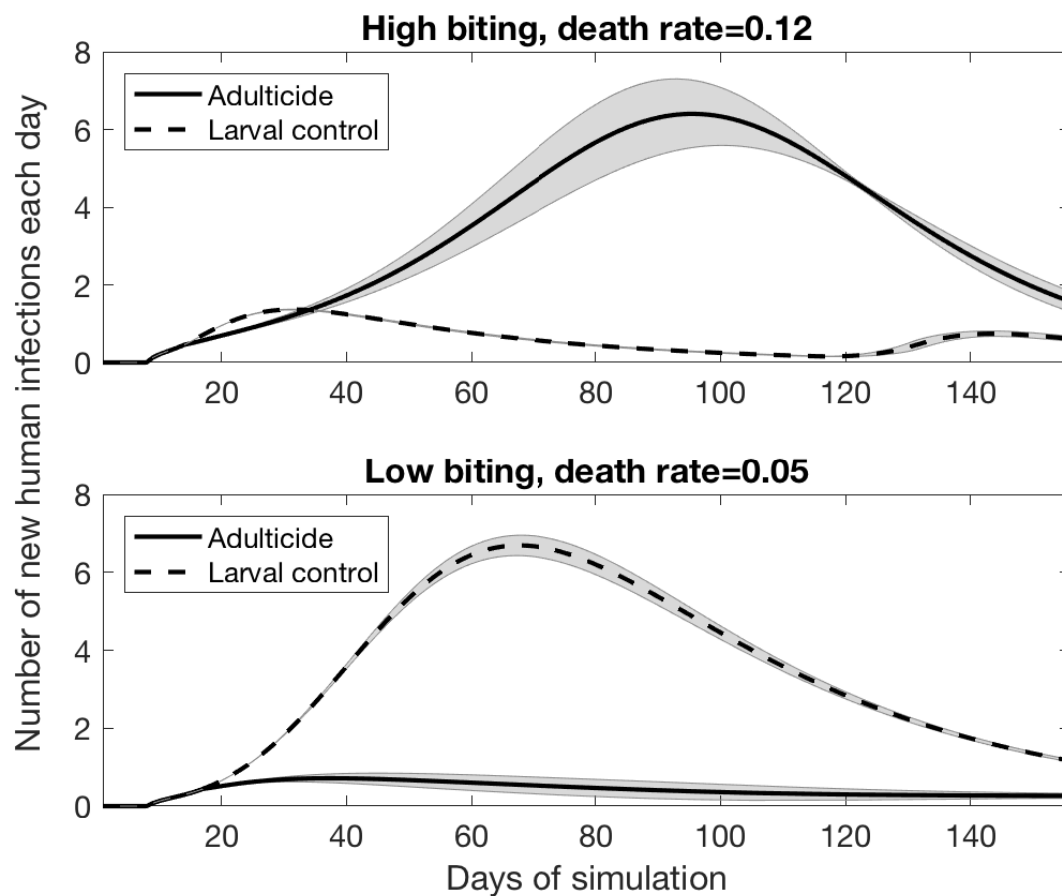
**Figure 4. Total number of adult mosquitoes in the landscape on each day using either adulticide or larval control with two different parameter combinations**. Shaded areas indicate two standard deviations around the mean. Top panel shows total adult mosquitoes when simulating a high biting rate and an adult mosquito death rate of 0.12. Bottom panel shows total adult mosquitoes when simulating a low biting rate and an adult mosquito death rate of 0.05. Pathogen introduction occurred on day 7 in both panels; control was triggered by detection of at least one human infection (first occurring on day 14 in the top panel and on day 17 in the bottom panel).
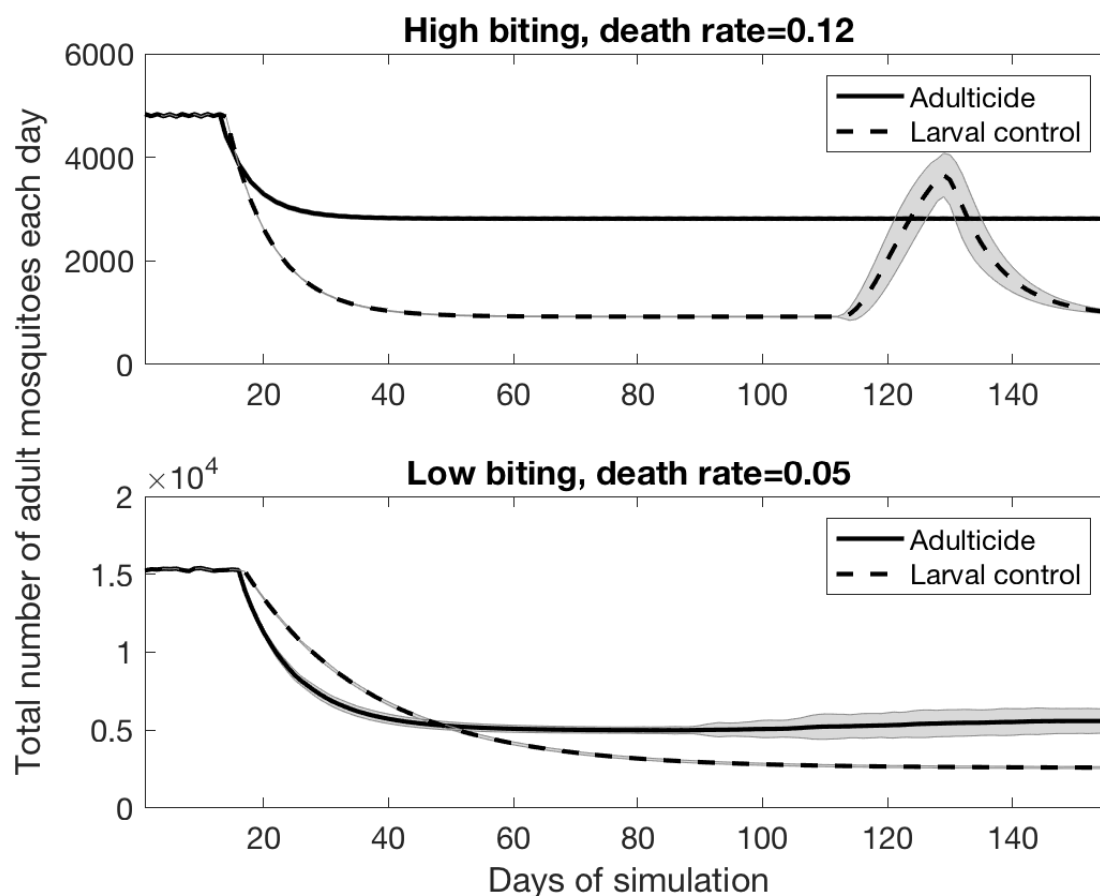
APPENDIX

As presented earlier and reproduced here for clarity, the equations for female juvenile/immature ($M_{j,p,t}$), naïve/uninfected adult ($M_{n,p,t}$), and infected adult ($M_{i,p,t}$) mosquitoes in patch p on day t are:

$$M_{j,p,t} = \left(M_{j,p,t-1}(1 - \mu_j)\right)(1 - g) + \nu\left(M_{n,p,t-1} + M_{i,p,t-1}\right)\left(1 - \frac{M_{j,p,t-1}}{K}\right) \tag{1}$$

$$M_{n,p,t} = \left(M_{n,p,t-1} + \sum_{\forall q \neq p} M_{n,q,t-1}\, D_{q,p} - \sum_{\forall p \neq q} M_{n,p,t-1} D_{p,q} - rcT_{hm} H_{i,t-1} M_{n,p,t-1}\right)(1 - \mu_a) \tag{2}$$
$$+ gM_{j,p,t-1}(1 - \mu_j)$$

$$M_{i,p,t} = \left(M_{i,p,t-1} + \sum_{\forall q \neq p} M_{i,q,t-1}\, D_{q,p} - \sum_{\forall p \neq q} M_{i,p,t-1} D_{p,q} + rcT_{hm} H_{i,t-1} M_{n,p,t-1}\right)(1 - \mu_a) \tag{3}$$

The equations for susceptible ($H_{s,t}$), infected ($H_{i,t}$), and recovered ($H_{r,t}$) humans on day t are:

$$H_{s,t} = H_{s,t-1} - H_{s,t-1} rcT_{mh} \sum_{\forall p} M_{i,p,t-1} \tag{4}$$

$$H_{i,t} = H_{i,t-1} + H_{s,t-1} rcT_{mh} \sum_{\forall p} M_{i,p,t-1} - \gamma H_{i,t-1} \tag{5}$$

$$H_{r,t} = H_{r,t-1} + \gamma H_{i,t-1} \tag{6}$$

To simulate adulticide treatment, multiply Equations 2 and 3 by $\left(1 - Treat_{p,t}\right)$.

To simulate larval control, multiply Equation 1 by $\left(1 - Treat_{p,t}\right)$.

Table A1. Parameter definitions and values used in model simulations.

Parameter	Value(s)	Definition
Treat	When untreated, $Treat_{p,d}=0$ When treated via larval control, $Treat_{p,d}=1$ When treated with adulticide, $Treat_{p,d}=0.1$	Matrix of control schedule in each patch
μ_j	0.05	Per capita death rate of juvenile mosquitoes (after density-independent mortality)
μ_a	0.05-0.18 (see Table 1 of main text)	Per capita death rate of adult mosquitoes (after density-independent mortality)
ν	3	Average number of eggs laid per female per day (after density-independent mortality)
K	350	Daily availability under carrying capacity of additional juvenile mosquitoes that can be added to each pool at stability
g	1/10	Growth rate of mosquitoes from juvenile to adult
D	$\sum_{\forall q \neq p} D_{p,q} = 0.1$	Matrix of mosquito dispersal probabilities between pools
r	0.83 (High) 0.48 (Medium) 0.33 (Low)	Biting rate
c	0.003	Scaling constant (to enable reasonable pace of outbreak amid a ubiquitous human population)
T	$T_{mh} = 0.08$ $T_{hm} = 0.07$	Matrix of transmission probabilities per bite from mosquitoes to humans (T_{mh}) and humans to mosquitoes (T_{hm})
γ	1/4	Recovery rate of humans

Table A2. Variables used in model equations.

Variable	Definition
M_j	Number of juvenile (immature) mosquitoes
M_n	Number of adult naïve (uninfected) female mosquitoes
M_i	Number of adult infected female mosquitoes
H_s	Number of susceptible humans
H_i	Number of infected humans
H_r	Number of recovered humans
p and *q*	Patch identifiers
t	Day identifier

CONCLUDING REMARKS

The work presented here highlights the complexity of the dynamics involved in improving vector-borne pathogen control, and the need for both basic and applied research on culicine vector species, improved communication between researchers and mosquito control professionals, and coordination between neighboring mosquito control districts. In order to increase support for vector control programs, future efforts should also aim to educate policy makers on disease and vector ecology.

In chapter one, I demonstrate potential inefficiencies in surveillance-driven control and emphasize the need to initiate control measures before or soon after pathogen introduction. In chapter two, I show how the ideal distribution of limited control resources depends on the demographic context. In chapter three, I compare the efficacy of control targeting either the immature or adult mosquito life stages, and establish the importance of considering ecological context here as well when deciding which method to employ. Together, these chapters reveal the importance of cooperation and coordination across multiple scales in order to gather sufficiently informative surveillance data and employ sufficiently comprehensive control measures. If an infected person enters a patch that does not conduct epidemiological surveillance, control measures will not be implemented until an epidemic is already underway and the pathogen has spilled over into adjacent patches. If landowners decline control application on property that is integral to effective resource distribution, more people across the entire landscape will acquire

infections. If anthropogenic nutrient enrichment alters community dynamics and ultimately affects mosquito demographic rates in a patch not conducting entomological surveillance, landscape-scale control decisions may not reflect the methods that would best reduce outbreaks of mosquito-borne viruses.

Future work expanding on my dissertation research should incorporate evolution of both hosts and pathogens (Urban et al. 2008). For instance, as insecticide resistance becomes increasingly commonplace, modeling how resistance evolves in a metapopulation context may reveal spatial and temporal patterns of insecticide application that reduce the strong selective advantage for resistance genes. I also plan to expand on some preliminary results demonstrating how a lack of coordination in larval control may be counterproductive and actually alter metapopulation dynamics in a way that causes more humans to become infected than when no control is implemented.

While my dissertation work aims to improve methods of vector control, the modeling framework developed here could easily be applied to conservation contexts instead, with the goal of reducing disease incidence in endangered metapopulations. Many emerging infectious diseases (EIDs) affect wildlife species with complex spatial structures and temporal patterns, such as Ranaviruses in amphibians that breed in temporary ponds (Gray et al. 2009); white-nose syndrome in hibernating bats in the northeastern Unites States (Frick et al. 2010); a protozoan parasite in migratory monarch butterflies (Altizer et al. 2011); and sudden oak death in forests of the western United States (Meentemeyer et al. 2011). Other diseases that fit this paradigm have great economic importance, such as Porcine

Epidemic Diarrhea and Asian Soybean Rust, while still others pose a health risk to

humans, as habitat loss and human encroachment increase the likelihood of

infections spilling over from wild to human and domesticated hosts (Daszak et al.

2001, Ostfeld and Holt 2004, Altizer et al. 2013). Modeling these epidemics using the

framework developed here may offer more realistic and accurate predictions than

current models that do not include metapopulation and patch dynamics, and lead to

more effective control measures (Meentemeyer et al. 2012).

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