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 (Chouin-Carneiro et al., 2016; Gratz, 2004; 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., 2014, 2013). 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, as well as 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:

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

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

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

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

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

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

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 1. Assumptions of the model.

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 2. Variables used in model equations.

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*	3	Per capita birth rate of mosquitoes (after density-independent mortality)
K*	350	Carrying capacity of juvenile mosquitoes in each pool
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	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. Parameter definitions and values used in model simulations.

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 (Edman et al., 1998; Trpis and Hausermann, 1986).

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.

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 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.

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).

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

Table 5. Results from 5000 runs of each scenario.

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 lead 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 (Adams and Kapan, 2009; Gujral et al., 2007; 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" (Kampen et al., 2015; Silvertown, 2009), 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 (Fonseca et al., 2013; Regis et al., 2008; 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.

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Figure Captions

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.

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.

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