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# Sustained bacterial outbreak in mosquitoes limits spread of life-threatening diseases

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Medical practitioners, such as those at the Centers for Disease Control and Prevention, frequently utilize mathematical models when determining how to best control the spread of mosquito-borne illnesses. Diseases such as chikungunya, dengue fever, malaria, and Zika virus can be life-threatening, and no effective vaccine currently exists. While most mitigation strategies aim to eliminate popular mosquito breeding sites through the use of insecticides, the accompanying costs, logistical difficulties, and resistance evolution make these treatment methods unsustainable.

*Wolbachia pipientis* is a maternally-transmitted bacteria that occurs naturally in over 60 percent of insect species. Certain strains of *Wolbachia* inhibit the transmission of disease-inducing pathogens to humans; this feature gives the microbe potential medical value, and scientists have been studying its effect on mosquitoes for years. Unfortunately, it is not naturally found in *Aedes aegypti* mosquitoes, the primary transmitters of mosquito-borne illnesses. If researchers wish to use *Wolbachia* to control the spread of these diseases, they must continually reintroduce it to wild mosquito populations. Such repeated introductio*SIAM Journal on Applied Mathematics* is strategically unfeasible.

In an article publishing next week in the , Zhuolin Qu, Ling Xue, and James Mac Hyman use an ordinary differential equation (ODE)-based model to calculate the most effective method of introducing a self-sustaining *Wolbachia* infection to a wild mosquito population. Their two-sex model accounts for the aquatic life stage, heterosexual transmission, and multiple pregnant states for female mosquitoes, thus capturing the entire transmission cycle. "If a stable *Wolbachia* infection can be established in wild mosquitoes, this will reduce the spread of mosquito-borne diseases," Qu said.

Past researchers have used a number of models to study the presence of *Wolbachia* in wild *A. aegypti* mosquito populations, though many did not distinguish between mosquitoes' varied life stages and the fitness costs that accompany Wolbachia. "Most previous models assumed that there is a fixed male/female ratio, and use this assumption to reduce the equations to a single-sex model," Qu said. "This is a good approximation for isolated wild mosquito populations, but is violated when releasing only infected male mosquitoes into a wild population. Our ODE model for *Wolbachia* transmission does not assume that there is a fixed ratio of males to females."

Qu et al. employ a multi-stage system of nine ODEs that integrate both genders, pregnant and non-pregnant females, and all life stages. They group the adult mosquito population into seven compartments based on infection state, pregnancy status, and fertility. Because female mosquitoes typically mate only once during their lifetime and store the sperm for multiple egg clutches, a successful two-sex model differentiates between non-pregnant (unmated) and pregnant (mated) females.

"The *Wolbachia* infection is transmitted vertically from an infected female mosquito to her offspring," Qu said. "A female mosquito usually mates successfully once, and if an uninfected female mosquito mates with an infected male mosquito, very few of her offspring survive. Because our compartmental model includes the heterosexual interaction of mosquitoes and multiple pregnant stages for females, it can be used to analyze the threshold condition required to sustain endemic Wolbachia for both perfect and imperfect maternal transmissions."

To reach the threshold at which enough mosquitoes are contaminated for a *Wolbachia* infection to persist, a model must surmount the shortened lifespan and decreased fecundity (egg-laying rate) that accompanies an outbreak and limits its permanence. "There are three coexisting equilibria for the proposed model: a stable zero-infection equilibrium, an unstable intermediate-infection endemic, and a stable high-infection endemic equilibrium (or complete infection for perfect maternal transmission)," Qu said. "These three equilibria are characterized by a backward bifurcation, with the unstable equilibrium points being the threshold condition for endemic *Wolbachia*. If the fraction of infected mosquitoes is below this threshold, then the population returns to a zero-infection state. If the fraction is above the threshold, then the infection spreads and eventually almost all of the mosquitoes are infected with *Wolbachia*."

After characterizing the threshold condition, the authors simulate and compare real-life mitigation strategies for employment prior to the release of *Wolbachia*-infected mosquitoes. "Because the threshold condition is characterized by a minimal fraction of mosquitoes that are infected, we could reduce the number of infected mosquitoes that must be released by first reducing the population of uninfected mosquitoes," Qu said. Tested strategies include indoor residual spraying, since *A. aegypti* tend to breed in or near houses; larval control, which targets water storage and container removal where mosquitoes often breed; sticky gravid traps/ovitraps, which attract and kill uninfected pregnant females as they prepare to lay eggs; and acoustic attraction, which reduces the number of uninfected males.

"Our simulations indicate that the pre-release mitigations that target pregnant females, such as residual spraying and sticky gravid traps, are more helpful than ones that target only males or the aquatic stage, given that pre-release mitigation stops once the release starts," Qu said. "Removing uninfected pregnant females greatly slows reproduction of the uninfected offspring, and the gap can be filled up mostly with the infected population."

Ultimately, monitoring both fitness cost and maternal transmission rate are key to establishing and sustaining a *Wolbachia* outbreak among wild mosquitoes. If researchers introduce enough infected mosquitoes to a natural population to surpass the threshold, the population levels out at a stable endemic *Wolbachia*-infected equilibrium. As a result, infected mosquitoes will be less likely to spread infectious diseases like dengue, chikungunya, and Zika to the humans they encounter.

Qu et al. recognize that they must further hone their model before their findings can truly guide policy efforts. For example, they assume that all parameters are constant for the sake of simplicity, but temperature, humidity, and other seasonal factors realistically vary. Incorporating seasonality in the model would offer a more accurate projection of multi-season success. "We are currently extending this model to include both spatial heterogeneity and temporal variations using partial differential equations that incorporate the diffusion of mosquitoes and seasonal variations," Qu said. "Hopefully it could offer more practical insights to help guide mitigation efforts for mosquito-borne diseases."

**More information:** Qu, Z., Xue, L., & Hyman, J.M. (2018). Modeling the Transmission of Wolbachia in Mosquitoes for Controlling Mosquito-Borne Disease. *SIAM Journal on Applied Mathematics*, 2018.

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