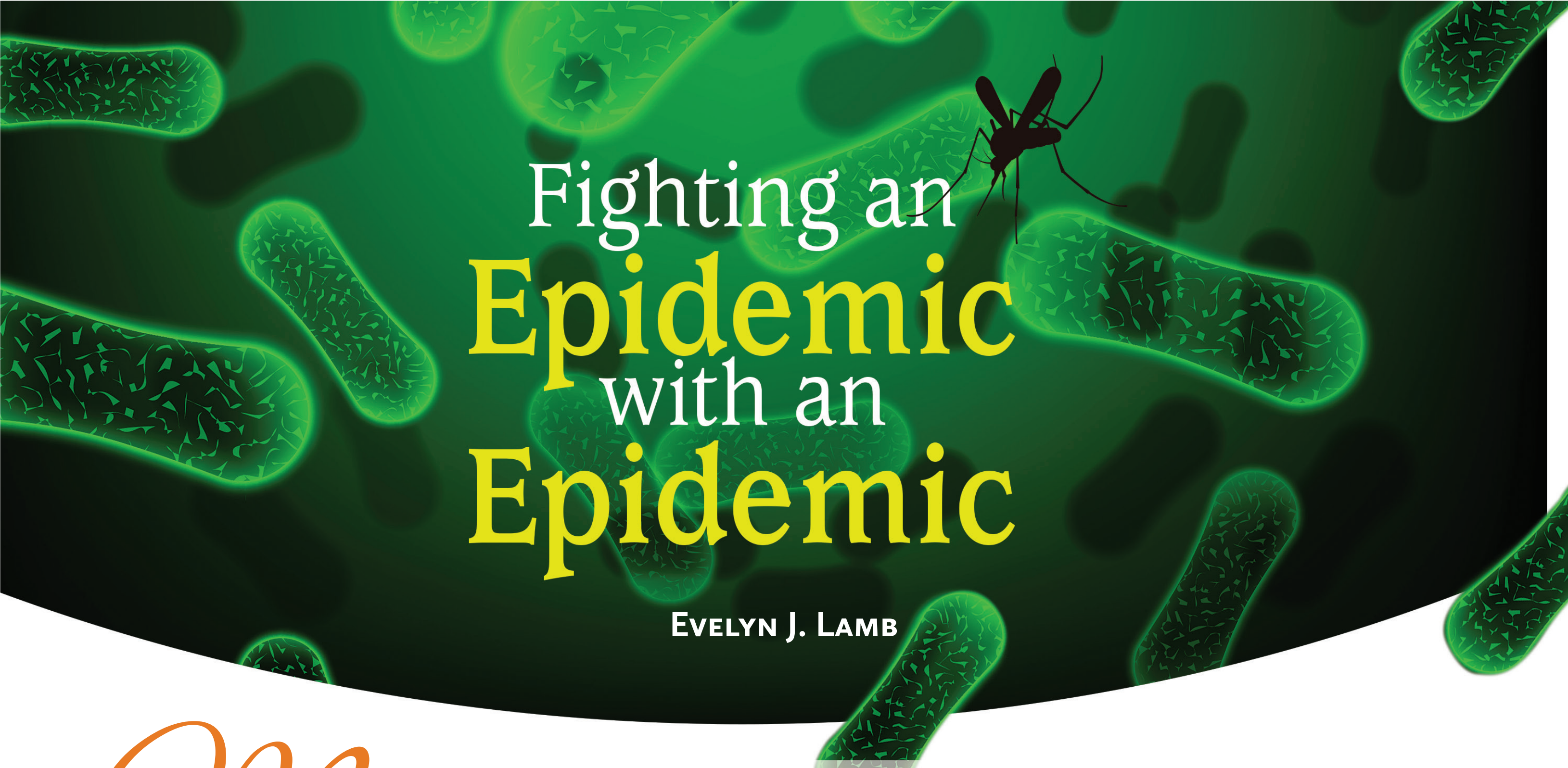

Fighting an Epidemic with an Epidemic

Evelyn J. Lamb

Mosquitoes are the deadliest animal in the world, killing almost twice as many humans as the next deadliest, humans themselves. Malaria, dengue fever, chikungunya, Zika, West Nile, and yellow fever infect millions and kill hundreds of thousands of people a year. Needless to say, mosquito mitigation is an important focus of many local and global health organizations.

Strategies for mosquito population control include killing adult and larval mosquitoes and reducing their breeding ground, but such interventions are costly and must be repeated, and mosquitoes can evolve resistance to the insecticides. The mosquito *Aedes aegypti* (see figure 1), the vector for several diseases, was almost eradicated in the Americas in the 1930s, but the small number that remained repopulated the territory, and the diseases they caused never fully disappeared. Genetically engineered sterile mosquitoes have been considered in some places, but genetic modification is a controversial option.

Infecting Mosquitoes

Several years ago, researchers started looking at the possibility of controlling disease-causing mosquito populations using non-lethal infection with *Wolbachia pipientis* (referred to as *Wolbachia*), a species of bacteria that infects, sometimes symbiotically, most insect species.

Aedes aegypti do not harbor *Wolbachia* in the wild, yet when they are infected, they are not able to pass diseases such as dengue fever on to humans. The infection can shorten mosquito life spans and reduce their number of offspring, but it is not generally fatal to mosquitoes. “They can live, they can fly around happily, but they cannot transmit viruses to human beings,” says Zhuolin Qu, an applied mathematician at Tulane University.

If *Wolbachia* became endemic in *Aedes aegypti*, it would reduce the number of humans harmed by certain infectious diseases at a lower cost than continual spraying and without the pushback of genetic engineering. “I think it’s the most promising mitigation effort we’ve seen since vaccines were developed for yellow fever,” says Qu’s Tulane colleague James Hyman.

Adult mosquitoes do not pass the bacteria to each other; infection occurs only through maternal-fetal transmission from an infected female mosquito. (If an infected male mosquito mates with an uninfected female mosquito, the offspring are nonviable.)

Modeling the Infection

In research published last year in the *SIAM Journal of Applied Mathematics*, Hyman, Qu, and Ling Xue of Harbin Engineering University in China developed a mathematical model of *Wolbachia* infection in *Aedes aegypti* with an eye to determining how to create a self-sustaining infection in a population. Mathematically, they used a multicompartment model including nine differential equations.

In epidemiology, the basic reproductive number R_0 (“R-naught”) is used to quantify the infectiousness of a disease and, in this case, encapsulates the difficulty of creating a *Wolbachia* epidemic in a mosquito population. The R_0 of an infection is the average number of individuals an infected individual will infect. For example, measles in humans has an R_0 of around 12–18, making it highly infectious, while the flu has an R_0 of around 2–3.

Figure 1. *Aedes aegypti*.

Scientists do not make too much of the precise R_0 value for a disease; instead, the number is more useful as a piece of qualitative information. A disease with an R_0 greater than 1 is likely to become an epidemic, while a disease with an R_0 less than 1 will tend to die out naturally.

When it comes to *Wolbachia* in *Aedes aegypti*, R_0 is a problem. Researchers estimate that it is less than 1 based both on model parameters and on the fact that the infection does not occur naturally in the species, as it probably would if R_0 were greater than 1. The low R_0 is a strike against establishing an epidemic in *Aedes aegypti*.

But the threshold condition interpretation of R_0 is a simplification. It assumes one infected individual is released into a population with no other infections. In reality, the dynamics are different when there is a high background rate of infection.

The researchers were discouraged by the low R_0, but they regained hope when they analyzed the stable states in their model. One stable state is a disease-free equilibrium: with a low number of infected individuals, the infection is cleared from the population. Another is a complete-infection equilibrium in which, true to the name, the entire population has *Wolbachia*. Lab experiments show that maternal transmission of *Wolbachia* is not perfect, so this state is not possible in real mosquitoes. Finally, they found that even with incomplete maternal transmission, endemic equilibria were possible where infected and uninfected mosquitoes could coexist.

The precise conditions necessary for creating these endemic equilibria depend on model parameters including R_0 and the fitness cost of the infection. *Wolbachia* infection leads to lower lifespans for mosquitoes and a reduced number of offspring, meaning uninfected mosquitoes can outcompete their infected kin. Different strains of *Wolbachia* have different fitness costs, so researchers find themselves in the slightly ironic position of identifying *Wolbachia* strains that are less harmful to mosquitoes to keep a larger proportion of the population infected.

Future Directions and Future Infections

Eventually, the researchers hope to advise public health officials on how to most effectively deploy *Wolbachia*-infected mosquitoes, but they are not yet at the point of putting their research to the test in the real world. Jumping the gun is a real risk when it comes to using their work in the field. One of Hyman's favorite phrases is "the easiest person to fool is yourself." He and his team are cautious about putting too much trust in their model and consequently giving ineffective or harmful advice.

"The current model is useful qualitatively," Qu says. "The absolute numbers may not be accurate, but the insights we can get based on the model are still useful."

Before their research starts informing real-world tests, they want to refine the model they have, obtaining more accurate values for their parameters and figuring out how to quantify the uncertainty in the model, but they also want to develop more sophisticated models that will reflect conditions more accurately.

For example, their model does not take the spatial distribution of mosquitoes into account. The researchers are working on developing new partial differential equation models that will allow them to gain a more nuanced understanding of how a *Wolbachia* infection could behave in a mosquito population. Hyman adapts a Picasso quote: "Models are lies that help us see the truth."

They also have their sights on malaria, the most deadly of the mosquito-borne illnesses, but it is caused by *Anopheles* mosquitoes, not *Aedes aegypti*. Researchers have only recently started investigating whether *Wolbachia* could be effective for *Anopheles*. Hyman and his team will be able to use the model they developed for *Aedes aegypti*, but the parameters will be different for the different mosquito species and *Wolbachia* strains, so their conclusions for malaria could be completely different.

Hyman started working with vector-borne illness in the 1990s, when one of his students, who was Kenyan, pointed out that a mere 1-percent reduction in the number of deaths a year from malaria would save tens of thousands of lives. "What other mathematical result is there where if you get a 1 percent improvement, you save 10,000 people?" Hyman asks.

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