The math of malaria: Drug resistance 'a numbers game' of competing parasites

August 28 2018, by Carol Clark

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A new mathematical model for malaria shows how competition between

parasite strains within a human host reduces the odds of drug resistance developing in a high-transmission setting. But if a drug-resistant strain does become established, that same competition drives the spread of resistance faster, under strong selection from antimalarial drug use.

"It's basically a numbers game," says Mary Bushman, who developed the model for her Ph.D. thesis in Emory University's Population Biology, Ecology and Evolution Graduate Program. "When you already have multiple strains of malaria within a population, and a drug-resistant strain comes along, it will usually go extinct simply because it's a late-comer. Whichever strain is there first has the advantage."

PLOS Biology published the findings, a computational framework that modeled a malaria epidemic across multiple scales: Transmission of parasites from mosquitos to humans, and the dynamics of parasites competing to infect blood cells while they also battle the immune system of a human host.

After creating the model, Bushman ran simulations tracking malaria in a population for roughly 14 years. The simulations included 400 theoretical people who were randomly bitten by 12,000 mosquitos that were infected with malaria parasites classified as either drug resistant or drug susceptible. Various levels of treatment with antimalarial drugs were also part of the simulations.

"Our model holds strong relevance for infectious diseases beyond malaria," says Jaap de Roode, an evolutionary biologist at Emory and senior author of the paper. "We hope this research gives others a method to look at disease dynamics across scales of biological organisms to learn how drug resistance develops in a range of pathogens."

The study's authors also include Emory biologist Rustom Antia (a specialist in infectious disease modeling) and Venkatachalam

Udhayakumar, a malaria expert from the Centers of Disease Control and Prevention's Division of Parasitic Diseases and Malaria.

The researchers are now working to develop their specific model for malaria into a generalized software tool for infectious diseases. "Computer models can sometimes give you insights that would be too difficult to get in a real-world setting," says Bushman, who is now a post-doctoral fellow in the Antia lab.

Malaria occurs in poor, tropical and subtropical areas of the world, although most of the global death toll consists of children from sub-Saharan Africa. People infected in this high-transmission area often have multiple strains of the parasite and, by the time they have reached adulthood, they have usually developed partial immunity.

"It's a baffling disease," Bushman says. "Malaria has been studied for more than 100 years, much longer than most diseases, but there is still a lot that we don't understand about it.

Malaria is caused by several species of Plasmodium parasites that are transmitted to humans by mosquitos. Plasmodium falciparum, the most common malaria parasite on the continent of Africa, is the one responsible for the most malaria-related deaths globally.

P. falciparum has developed resistance to former first-line therapies chloroquine and sulfadoxine-pyrimethamine. Resistance has also emerged in Southeast Asia to the third and last available treatment, artemisinin combination therapy, or ACT.

One of the mysteries about malaria is why drug-resistant strains tend to emerge first in low-transmission areas, like Southeast Asia, and not appear until much later in Africa, where transmission is high.

Previous research led by de Roode and Bushman showed that when people are co-infected with drug-resistant and drug-sensitive strains of malaria, both strains are competitively suppressed.

For the current paper, the researchers wanted to get a more detailed understanding of these dynamics. Some evidence had shown that within-host competition could suppress resistance, while other studies showed that it could ramp resistance up.

"It was a little bit of a puzzle, why the findings were conflicting," Bushman says.

The new model, driven by evidence for how malaria parasites work within the immune system and the blood cells they infect, provided a solution to the puzzle.

"Some previous models were based on the assumption that when you put two strains of malaria into a host, they split 50-50," Bushman says. "But our model showed that the system is asymmetrical. When you put two strains in a host they virtually never split 50-50."

The late-comer will usually go extinct, which explains why in high-transmission areas drug resistant strains are at a big disadvantage. But in low transmission areas, such as Southeast Asia, a drug resistant strain has a better chance of arriving first in a host and getting established.

The new model also showed how once a drug-resistant strain becomes established in a high transmission area, it will spread much faster than it would in a low transmission area.

"The distinction between establishment and spread just jumped out of the data," Bushman says. "Our model validated both sides of the argument—that within-host dynamics of competing parasites could both

repress and accelerate the spread of resistance. The phenomena are occurring at different stages of the process so they both can happen."

The results offer a new explanation for why chloroquine resistance arrived relatively late in Africa, appearing in Kenya and Tanzania in 1978, but then spread rapidly across the continent.

More information: Bushman M, Antia R, Udhayakumar V, de Roode JC (2018) Within-host competition can delay evolution of drug resistance in malaria. PLoS Biol 16(8): e2005712. doi.org/10.1371/journal.pbio.2005712

Provided by Emory University