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# Competition between mixed malaria parasite strains could influence drug resistance

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Scientists have documented for the first time how competition among different malaria parasite strains in human hosts could influence the spread of drug resistance.

"We found that when hosts are co-infected with drug-resistant and drug-sensitive strains, both strains are competitively suppressed," says Mary Bushman, lead author of the study and a PhD candidate in Emory University's Population Biology, Ecology and Evolution Graduate Program. "Anti-malarial therapy, by clearing drug-sensitive parasites from mixed infections, may result in competitive release of resistant strains."

*Proceedings of the Royal Society B* published the research, led by the labs of Jaap de Roode, an evolutionary biologist at Emory, and Venkatachalam Udhayakumar, a malaria expert from the Centers of Disease Control and Prevention's Division of Parasitic Diseases and Malaria.

Almost half of the world's population is at risk for malaria, a complex disease caused by five species of *Plasmodium* parasites that are transmitted to humans by 30 to 40 different species of mosquitoes that all behave differently. The current study focused on *Plasmodium falciparum*, the most common malaria parasite on the continent of Africa and the one responsible for the most malaria-related deaths globally.

*P. falciparum* has developed resistance to former first-line therapies chloroquine and sulfadoxine-pyrimethamine. "We're now down to our last treatment, artemisinin combination therapy, or ACT, and resistance to that recently emerged in Southeast Asia," Bushman says. "If ACT resistance continues to follow the same pattern, the world may soon be without reliable antimalarial drugs."

People infected with *P. falciparum* often have multiple strains of the parasite - especially in high-transmission areas such as sub-Saharan Africa where infectious mosquito bites occur frequently. Many people have developed partial immunity, making asymptomatic infections common and further complicating control efforts.

The researchers knew from previous work, by de Roode and others, that competition between mixed strains of malaria parasites in laboratory mice are a crucial determinant to the spread of resistance. "In the mouse studies we found that drug-sensitive parasites suppress resistant parasites," de Roode says. "We also found that by clearing these sensitive parasites with drugs, the resistant parasites had a big advantage, growing up to high numbers and transmitting to mosquitoes at high rates. Ever since doing that work, I have wanted to see if the same could apply to humans."

The researchers drew from 1,300 blood samples of untreated children with malaria from Angola, Ghana and Tanzania. They extracted DNA of malaria parasites from the blood samples and used polymerase chain reaction (PCR) technology to determine the densities of drug-resistant strains and drug-sensitive ones. About 15 percent of the blood samples had mixtures of both types.

The results showed that in mixed-strain infections, densities of chloroquine-sensitive and chloroquine-resistant strains were reduced in the presence of competitors. They also showed that, in the absence of chloroquine, the resistant strains had lower densities compared with sensitive strains.

"The results were really clear cut, which rarely happens in human studies," Bushman says. "We found almost complete consistency between the three data sets."

Currently, Bushman says, the tendency is to use "one-size-fits-all" strategies for controlling malaria but more tailored approaches are needed.

A strategy of mass drug administration might be effective, for example, in a place with a low prevalence of malaria and less likelihood of mixed-strain infections. That same strategy, however, might actually boost drug resistance without reducing the burden of disease in areas where most of the population is infected with multiple strains of malaria parasites.

"The epidemiology of malaria infection is different for different places and different conditions," Bushman says. "We

hope that our work will spur development of new strategies to minimize resistance while maximizing the benefits of control measures."

More questions must be answered to guide the development of these new strategies.

"As a first step," de Roode says, "we need to determine if the observed suppression of resistance in humans also results in reduced transmission to mosquitoes."

Another limitation of the current study was that it was focused entirely on blood samples from children that had not been treated with drugs. "We need to find out if drug treatment of people infected with malaria removes competition and gives resistance a boost, as we have found in mice before," de Roode says.

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Source:
Emory Health Sciences

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