In nature, an imperfect immune system drives the evolution of deadly pathogens

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A healthy male house finch forages in the snow. Credit: Bob Vuxicnic

As annual flu shot patrons know, immune systems are not perfect and

must be constantly reinforced to protect against rapidly evolving pathogens.

New research shows that, in the case of a common backyard bird, imperfect immunity to a dangerous pathogen that causes "bird pink eye" actually makes the pathogen stronger and more dangerous for its next victim. The findings—from a multi-university team led by Virginia Tech—were published March 2 in the journal *Science*.

Unlike humans, wild birds do not receive vaccines and must rely on their natural immune systems to protect them from pathogen attacks. Immune systems have "memories" that allow organisms to recognize past abusers and ward them off. However, in the case of partial immunity, these memories aren't always perfect and some pathogens make it through the door.

Dana Hawley, an associate professor of biological sciences in the College of Science who led the work, has long studied mycoplasmal conjunctivitis in house finches—a disease similar to "pink eye" in humans. In 2015, she determined that birds that eat at feeders are more likely to be infected with the disease, which causes red, swollen eyes and often blindness that results in death.

An increase in the severity of finch pink eye in recent years alerted Hawley and her collaborators to a potential link between bird immunity and pathogen virulence. She partnered with colleagues specializing in microbiology and modeling to measure how bacterial strains of varying strength fared in finches with or without pre-existing immunity to the pathogen.

The lab experiments showed that stronger or more virulent strains have a leg up for several reasons. One of the most surprising was that virulent strains generate more complete memory responses in finches, leaving

weaker strains with few hosts to infect. In contrast, weaker strains produce only partial immune memory, leaving the door open for more virulent strains to invade.

Results from that experiment were then modeled to reveal how a pathogen might move through an entire population of finches. The model showed that pathogen strains that came to dominate in an experimental population with incomplete immunity were almost twice as harmful as those that dominate in the absence of immunity. Thus, incomplete immunity is likely what's driving the evolution of more harmful strains of the finch bacteria in nature.

"Our results are not just important for finches. Many human pathogens and other animal pathogens also cause only incomplete protection against reinfection. Thus, the potential is there for the host immune response to favor more harmful strains in many types of hosts. The immune response is an incredibly powerful agent of protection for hosts, but in this case, imperfection can be deadly," said Hawley who is an affiliate of the university's Global Change Center, an arm of the Fralin Life Science Institute.

"The shift to favor more harmful pathogens that we observed in the modeling results is a very dramatic increase, suggesting that immune responses have key effects on the evolution of this pathogen and others," said Arietta Fleming-Davies, co-first author on the paper and currently an assistant professor of biology at the University of San Diego. "What I found unique about working on this study was that the patterns in the experimental data were so strong—no matter how we looked at it, the same important immune effect popped out."

"This is really groundbreaking since most of what we know about host-pathogen co-evolution is in the context of interventions like vaccinations," said Ariel Leon, a doctoral student in Hawley's lab and co-

author on the paper. "Additionally, this research provides valuable insight into what is driving pathogens to become more dangerous in wild animals, which we know to be important sources of emerging infectious diseases in humans."

"The experiments reported in the *Science* paper explain elegantly why pathogen virulence increased once the disease had become established," said André Dhondt, co-author, Edwin H. Morgens Professor of Ornithology and director of Bird Population Studies at the Cornell Lab of Ornithology. "Curiosity-driven research on birds can generate insights that are relevant for human health."

"This study provides convincing evidence from a natural bird system that we should be looking at the relationship between the virulence of the primary infection and the strength of the memory response that the host generates," said Ann Tate, an assistant professor of biological sciences at Vanderbilt University who was not involved in the research. "When the two are correlated, lower virulence strains could be their own worst enemies, creating a population of hosts that are resistant to them but not the higher virulence strains that remain. The burning question now is, in which and how many disease systems are microbial virulence and the strength of host memory correlated? This is most likely in cases where microbial numbers or microbe-induced damage act as a kind of adjuvant for the generation of immune memory, and those conditions are likely to be met for a number of important human and animal infections."

More information: A.E. Fleming-Davies at University of San Diego in San Diego, CA el al., "Incomplete host immunity favors the evolution of virulence in an emergent pathogen," *Science* (2017). science.sciencemag.org/cgi/doi … 1126/science.aao2140

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