

The original antigenic sin: How childhood infections could shape pandemics

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University of Pittsburgh School of Medicine virologists conducted an experiment to learn about the transmission of pandemic diseases, like influenza and COVID-19. Through experiments in ferrets that mimic real-world conditions for humans, they shed more light on how proximity, masks or other barriers, time spent with someone who is infectious, and pre-existing immunity from vaccines or prior infection may influence the likelihood of someone contracting a virus.

University of Pittsburgh-led study sheds light on the factors that influence viral transmission. Credit: UPMC

A child's first influenza infection shapes their immunity to future airborne flu viruses—including emerging pandemic strains. But not all flu strains spur the same initial immune defense, according to new findings published today by University of Pittsburgh School of Medicine virologists in the journal *PLOS Pathogens*.

"These results are relevant right now to the COVID-19 pandemic," said senior author Seema Lakdawala, Ph.D., assistant professor of microbiology and molecular genetics at Pitt. "They may explain age-based distributions of SARS-CoV-2 disease severity and susceptibility.

"Having flu once does not make you immune to all future influenza viruses," she said. "Nor does having had the original SARS virus in 2003 or any of the 'common cold' coronaviruses in circulation necessarily mean you can't get infected with SARS-CoV-2. But your susceptibility to infection might be different than someone who has never encountered a coronavirus."

Lakdawala and her colleagues devised an experiment using ferrets—which previous studies

have shown have a similar susceptibility and immune response to flu as humans—and mimicked real-world, human conditions. The experiment was designed to test the concept of "The Original Antigenic Sin," which is when a person's first exposure to a pathogen imprints on their immunity to all future infections.

This phenomenon is seen in the populations affected by previous flu epidemics and pandemics. For example, the 2009 H1N1 flu pandemic disproportionately affected people ages 5 to 24, suggesting that older people had been exposed to a previous strain of flu that gave them lasting immunity, protecting them from the newer strain.

In the ferret experiment, the scientists infected different groups of ferrets who had never had the flu with one of two different [strains](#) of influenza—seasonal H3N2 flu or the 2009 pandemic H1N1 flu—and waited three months to allow the immune system to calm down and develop a more mature immunity to whichever strain they were exposed to.



Assistant professor of microbiology and molecular genetics, University of Pittsburgh School of Medicine. Credit: Nate Langer/UPMC

Next, the ferrets with H3N2 immunity were exposed to ferrets contagious with H1N1 virus, and the ferrets with H1N1 immunity were exposed to ferrets contagious with H3N2 virus.

The scientists mimicked human workdays and weekends, comingling the contagious ferrets with their peers for 8 hours per day over five-day periods—much the way humans who work in cubicles would mix—or continuously over two days, similar to a family weekend.

The ferrets with previous H1N1 infection had protection against airborne transmission of H3N2 flu from a contagious peer. But ferrets with previous H3N2 infection didn't have the same level of protection against H1N1 and got infected at the same rate as an animal without prior immunity.

"This was really surprising," said Lakdawala. "Our immunity can shape how susceptible we are to subsequent infections, but that is not uniform. We have long ignored that not every strain of a virus is going to transmit through a population in the same way. That's important to understand when preparing for future pandemics."

The experiment did not reveal why the ferrets with previous H1N1 infection were protected against H3N2, nor why prior H3N2 infection didn't block H1N1. But the scientists did find that the immunity was not due to neutralizing antibodies, which are antibodies acquired following vaccination or infection that specifically target and neutralize a defined pathogen. This finding indicates the immunity was likely driven by the adaptive immune response—meaning that the previous H1N1 [infection](#) primed the [immune system](#) to be on the lookout for H3N2 and quickly eliminate it.

Future study is needed to reveal the precise immunological mechanism underlying such an [immune response](#), but Lakdawala said that doesn't mean public health authorities should wait to put the findings into action, especially in the midst of the COVID-19 [pandemic](#). Understanding the different ways that infections affect people based on prior exposure could be leveraged to target age-based interventions or vaccination programs.

More information: Le Sage V, Jones JE, Kormuth KA, Fitzsimmons WJ, Nturibi E, Padovani GH, et al. (2021) Pre-existing heterosubtypic immunity provides a barrier to airborne transmission of influenza viruses. *PLOS Pathogens* (2021). [DOI: 10.1371/journal.ppat.1009273](https://doi.org/10.1371/journal.ppat.1009273)

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