Past encounters with the flu shape vaccine response

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New research on why the influenza vaccine was only modestly effective in recent years shows that immune history with the flu influences a person's response to the vaccine.

Low effectiveness of the flu vaccine is often blamed on problems with

how the vaccine is designed and produced. Sometimes the flu strains chosen for the vaccine are a poor match for those that end up circulating in the public, especially in years when the H3N2 strain predominates. The majority of flu vaccines given around the world are also grown in eggs, which can cause the virus to mutate and differ from circulating strains, and thus become less protective.

In 2012-13, the H3N2 component of the flu vaccine was effective in just 39 percent of people. That season, public health officials believed that adaptations in egg-grown vaccines were the problem. But in a new study published this week in the journal *Clinical Infectious Diseases*, researchers from the University of Chicago, Harvard University and others show that poor immune responses, not egg adaptions, may explain the low effectiveness of the vaccine that year.

"Egg adaptations have variable effects," said Sarah Cobey, PhD, assistant professor of ecology and evolution at UChicago and lead author of the study. "Sometimes they matter and sometimes they don't, but what seems to make the most difference is immune history."

What's at play seems to be a phenomenon known as "original antigenic sin." Flu vaccines are designed to get the immune system to produce antibodies that recognize the specific strains of the virus someone may encounter in a given year. These antibodies target unique sites on the virus, and latch onto them to disable it. Once the immune system already has antibodies to target a given site on the virus, it preferentially reactivates the same immune cells the next time it encounters the virus.

This is efficient for the immune system, but the problem is that the virus changes ever so slightly from year to year. The site the antibodies recognize could still be there, but it may no longer be the crucial one to neutralize the virus. Antibodies produced from our first encounters with the flu, either from vaccines or infection, tend to take precedence over

ones generated by later inoculations. So even when the vaccine is a good match for a given year, if someone has a history with the flu, the immune response to a new vaccine could be less protective.

This story may be complicated by an additional factor, which is that the vaccine could be inducing a weak immune response in many who receive it.

"We see that both vaccinated and unvaccinated people were infected with similar flu viruses and that the vaccine didn't elicit a strong immune response from most people in our study," said Yonatan Grad, MD, PhD, assistant professor of immunology and infectious diseases at the Harvard T.H. Chan School of Public Health and co-author of the study.

Researchers often test the relationship between different flu strains, or how well infection or vaccination to one strain protects you from infection with another, in lab animals like ferrets. In 2012-13, ferrets immunized with the egg-adapted strain had an antibody response that reacted poorly with that season's circulating H3N2 strains. Thus, officials believed egg adaptations were the culprit that year.

But when Cobey, Grad and their colleagues analyzed blood samples from people who got vaccinated that year, they saw no differences in antibody responses to the vaccine or circulating strains. It seems that their immune systems didn't bother to recognize the differences from the egg mutations because they already recognized so many other sites on the vaccine strain.

"Imagine influenza viruses are like different makes and models of cars," said Grad. "The ferrets, which hadn't seen influenza before, learned to tell the difference between closely related strains-like telling the difference between a Honda Civic and a Toyota Camry. But people didn't distinguish between them and instead just saw cars."

That's not to say egg adaptations don't always matter. In a separate study from 2017, Cobey and a team led by researchers from the University of Pennsylvania found that egg adaptations did cause mismatches in the most common vaccine given in 2016-17, another rough season dominated by H3N2.

Egg adaptations may be a factor during this year's record-breaking flu season as well. H3N2 is again the predominant strain making people sick, and the most common vaccine is the same one from last year with its potentially problematic egg adaptations.

There is an alternative, however. New vaccines grown without eggs, either in insect cells or dog kidney cells, are much less prone to developing mutations that can make them less protective against the flu. Until now they have been more expensive, but the researchers hope continuing research will help shift the focus to these more effective vaccines.

"There hasn't been enough consumer and medical demand to shift to more effective vaccines," Cobey said. "Until recently, there also hadn't been as much research on the complexity and variation in the immune response to influenza."

"We need to do more basic research on how to induce responses to the right sites on the virus, and this will require us to understand original antigenic sin better," she said. "We also need to understand why the vaccine appears to be bad at eliciting responses in some people some of the time. Is there really no response, or are we just not looking in the right places?"

More information: "Poor immunogenicity, not vaccine strain egg adaptation, may explain the low H3N2 influenza vaccine effectiveness in 2012-13,"*Clinical Infectious Diseases* (2018).

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