

Building a Better Flu Vaccine

A vaccine made by connecting antigens from different flu strains together elicited a more broadly protective immune response than a conventional flu vaccine.

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Seasonal flu vaccines contain hemagglutinin (HA) molecules from various viral strains. But even when the strains in the vaccine exactly match those in circulation, the vaccines have limited efficacy. This is because most vaccinated people end up producing antibodies against only one of the vaccine strains.

This “subtype bias” has two plausible explanations. One is that prior exposure to a particular flu strain primes the immune system to respond to that strain later. Another is that variation in people’s genes for key immune system components affects the vaccine response.

A research team led by Dr. Mark Davis at Stanford University School of Medicine examined the relative contributions of these mechanisms to flu vaccine responses. They aimed to use this information to develop a vaccine that could limit the biased response. Results of their study, which was partly funded by NIH, [appeared in Science](#) on December 20, 2024.

The researchers began by measuring influenza vaccine responses in 39 pairs of identical twins. In most cases, the immune systems of both twins showed the same subtype bias to a seasonal vaccine. Yet they also showed signs of having been exposed to different flu strains in the past.

The team also studied the response to seasonal flu vaccine in 15 infants, aged 6-12 months, who had never been infected with flu before. Most of the infants still developed a subtype-specific antibody response. Together, these findings suggest that individual genetic variation might exert a larger role than prior virus exposure in driving subtype bias, although initial virus exposure also contributes to such bias.

Producing antibodies against a virus requires coordination between two types of immune cells: B cells and T helper (T_H) cells. When a B cell finds a molecule, like HA, that it recognizes, it engulfs it and chops it up into fragments called peptides. The cell then displays those peptides on its surface to activate T_H cell support. The peptides are anchored to the cell surface by molecules called MHC-II. Variations in the genes for MHC-II molecules can affect which peptides are displayed. HA from one flu strain may have more peptides that can be displayed on a B cell than other strains. This could lead some B cells to get more T_H cell support than others, and hence bias antibody production towards that strain.

To try to reduce bias in T_H activation, the team linked together HA molecules from up to four different subtypes before vaccination. That way, a B cell that recognized any one of the individual HAs would engulf all of them. Then, the team reasoned, the different B cells would be able to display the same set of peptides and activate T_H cell support equally well.

As expected, mice vaccinated with a mixture of unlinked antigens developed a clear subtype bias. But mice vaccinated with the linked HAs produced equal amounts of antibodies against all the subtypes tested. Similar results were obtained in organoids grown from human tonsil tissue—a laboratory model that generates an immune response.

The researchers also tried coupling an avian flu HA with the seasonal flu HA. This construct elicited a stronger immune response in the tonsil organoids than the avian flu HA did on its own.

The results suggest that coupling HA molecules from various flu strains could make flu vaccines more effective.

“Overcoming subtype bias this way can lead to a much more effective influenza vaccine, extending even to strains responsible for bird flu,” Davis says. “The bird flu could very likely generate our next viral pandemic.”

This [research summary](#) was published by the National Institutes of Health on January 14, 2025.