Prior flu exposure dictates your future immunity, allowing for new, rationally developed regiments

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A team of scientists, led by researchers at The Wistar Institute, has determined that it might be possible to stimulate the immune system against multiple strains of influenza virus by sequentially vaccinating individuals with distinct influenza strains isolated over the last century.

Their results also suggest that world health experts might need to re-evaluate standard tests used for surveillance of novel influenza strains. Their findings are published in the *Journal of Experimental Medicine*, available online now.

According to the Wistar researchers, their analysis could lead to an alternative approach to creating a "universal" flu vaccine—a vaccine that would provide resistance to seasonal and pandemic influenza strains over many years, negating the need for an annual flu shot.

"Influenza vaccines are very safe and provide good protection. However, we need to continuously update seasonal flu vaccines because influenza viral proteins change over time," said Scott Hensley, Ph.D., an assistant professor at The Wistar Institute and corresponding author on the study. "Since influenza viruses are constantly changing, we all have unique pre-exposure histories that depend on when we were born and the specific types of viruses that circulated during our childhood."

Vaccines work by stimulating the immune system to produce antibody

proteins against particles (called antigens) from an infectious agent, such as bacteria or a virus. The immune system saves the cells that produce effective antibodies, which then provide immunity against future attacks by the same or similar infectious agents. Despite the availability of a vaccine, seasonal influenza typically kills 36,000 Americans, alone, and nearly a half million individuals around the world, in total.

Most current efforts to create universal vaccines hinge on the idea of generating antibodies against a portion of the virus that is relatively unchanged year-to-year.

"Our studies demonstrate that individuals that are infected sequentially with dramatically different influenza strains mount antibody responses against a conserved region of influenza virus," Hensley said. "Since we now know that pre-exposure events can influence vaccine responsiveness in a predictable way, we can begin to design vaccine regiments that preferentially elicit antibody responses against conserved regions of influenza virus."

The researchers began their current work by studying human antibody responses against the 2009 pandemic H1N1 virus. The 2009 strain is antigenically distinct from recently circulating seasonal H1N1 strains, and a distant relative of the virus that caused the devastating "Spanish Flu" of the early 20th century. The most effective antibodies are those that bind to a particular portion (or "epitope") of hemagglutinin (HA), a protein produced by the influenza virus.

According to Hensley, however, their chief insight occurred when his team hit the "sort" button on a spreadsheet document, thereby arranging all samples by age of the donor. Different aged people, they found, mount vastly different antibody responses to pandemic H1N1, depending on whether or not they were exposed to a seasonal H1N1 years earlier. "We can now accurately predict how individuals will

respond to the pandemic H1N1 strain based on the year that they were born," Hensley said.

Their investigation also suggests that ferrets with no prior influenza exposure might not be the most reliable predictor of human immune responses. Anti-sera—or blood containing antibodies—created in these "naïve" ferrets are commonly used for influenza surveillance. The researchers found that naïve ferrets mount a response to an epitope in a decidedly different portion of HA than do most humans, but subsequently infecting these ferrets with other historical influenza strains can shift the antibody response toward the epitope that human antibodies recognize. This shift might also be replicable in humans through multiple infections or vaccinations, the researchers believe.

According to Hensley, one strategy would be to sequentially vaccinate children with antigenically distinct viral strains. "Babies are born with an immunological blank slate," Hensley said. "We may be able to strategically vaccinate our children with antigenically diverse influenza strains to elicit antibodies against conserved viral epitopes."

Provided by The Wistar Institute