Scientists in the US have shown how optimising vaccinations could help plug the gaps and boost the immune system's ability to neutralise viruses as they evolve.

# Optimising influenza vaccines to harness pre-existing immunity

Understanding how immune cells respond to natural infection compared with vaccination demonstrates how vaccines could broader immunity.

Researchers in the US have demonstrated why our immune response can struggle to fully neutralise mutated forms of the influenza virus. The study provides insight into how vaccines could be further honed to target specific viral components that our natural immunity might miss.

The question of how well our immune system can fight off repeated infections from viruses is critical, particularly as the world struggles to cope with a viral pandemic. When the immune system encounters a virus for the first time, it generates memory B cells that recognise protein segments that are part of the virus. Antibodies released by the memory B cells then bind to these epitopes and work to neutralise the virus. If the immune system encounters the virus again, the existing memory B cells are activated to release the same antibodies and quell infection.

"Unfortunately, our memory B cells don't always recognise epitopes that have mutated or drifted over time, leaving us susceptible to infection by different versions of the same virus," says Jenna Guthmiller at the University of Chicago, who was part of the research team, along with Haley Dugan and Patrick Wilson. "This is why influenza vaccines must change every year: to ensure they provide protection as viral epitopes evolve."

One outstanding question is whether different routes of initial exposure—natural infection versus vaccination—prompt a different level of recall by memory B cells and affect how protective the resulting immunity is. The researchers investigated this by comparing antibodies produced by memory B cells taken from people who had naturally been exposed to two influenza subtypes and from healthy people who had received an influenza vaccine.

"We found that the specificities of recalled memory B cells are drastically different depending on their original exposure route," says Dugan. Most antibodies derived from the infection-route B cells recognised conserved epitopes from past strains but would not neutralise current influenza viruses. Newer epitopes that had drifted were often missed by these antibodies. In contrast, antibodies derived from vaccinated individuals targeted both conserved epitopes from previous strains and epitopes which had changed through drift or mutation.

"While vaccination-induced antibodies were largely cross-reactive to past strains, they were still capable of neutralising the virus," notes Dugan. "This suggests the vaccinated response is better at recalling protective antibodies against both drifted and conserved epitopes."

"By developing vaccines focused on specific viral proteins that our immune systems might miss, we can optimise protective antibody responses," says Wilson.

Dugan, H.L., Guthmiller, J.J., Arevalo, P., Huang, M., Chen, Y-Q., Neu, K.E., Henry, C., Zheng, N-Y., Lan, L., Y-L., Tepora, M.E., Stovicek, O., Bitar, D., Palm, A-K.E., Stamper, C.T., Changrob, S., Utset, H.A., Coughlan, L., Krammer, F., Cobey, S., Wilson, P.C. Preexisting immunity shapes distinct antibody landscapes after influenza virus infection and vaccination in humans. *Science Translational Medicine* **12** eabd3601 (2020).

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