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Scientists develop 20-subtype mRNA flu vaccine to protect against future flu pandemics

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An experimental mRNA-based vaccine against all 20 known subtypes of influenza virus has provided broad protection from otherwise lethal flu

strains in initial tests, and thus might serve one day as a general preventative measure against future flu pandemics, according to researchers from the Perelman School of Medicine at the University of Pennsylvania.

The "multivalent" vaccine, which the researchers describe in a paper published today in *Science*, uses the same messenger ribonucleic acid (mRNA) technology employed in the Pfizer and Moderna SARS-CoV-2 vaccines. This mRNA technology that enabled those COVID-19 vaccines was pioneered at Penn. Tests in animal models showed that the vaccine dramatically reduced signs of illness and protected from death, even when the animals were exposed to flu strains different from those used in making the vaccine.

"The idea here is to have a vaccine that will give people a baseline level of immune memory to diverse flu strains, so that there will be far less disease and death when the next flu pandemic occurs," said study senior author Scott Hensley, Ph.D., a professor in of Microbiology at in the Perelman School of Medicine.

Hensley and his laboratory collaborated in the study with the laboratory of mRNA vaccine pioneer Drew Weissman, MD, Ph.D., the Roberts Family Professor in Vaccine Research and Director of Vaccine Research at Penn Medicine.

Influenza viruses periodically cause pandemics with enormous death tolls. The best known of these was the 1918-19 "Spanish flu" pandemic, which killed at least tens of millions of people worldwide. Flu viruses can circulate in birds, pigs, and other animals, and pandemics can start when one of these strains jumps to humans and acquires mutations that adapt it better for spreading among humans. Current flu vaccines are merely "seasonal" vaccines that protect against recently circulating strains, but would not be expected to protect against new, pandemic

strains.

The strategy employed by the Penn Medicine researchers is to vaccinate using immunogens—a type of antigen that stimulates immune responses—from all known influenza subtypes in order to elicit broad protection. The vaccine is not expected to provide "sterilizing" immunity that completely prevents viral infections. Instead, the new study shows that the vaccine elicits a memory immune response that can be quickly recalled and adapted to new pandemic viral strains, significantly reducing severe illness and death from infections.

"It would be comparable to first-generation SARS-CoV-2 mRNA vaccines, which were targeted to the original Wuhan strain of the coronavirus," Hensley said. "Against later variants such as omicron, these original vaccines did not fully block viral infections, but they continue to provide durable protection against severe disease and death."

The experimental vaccine, when injected and taken up by the cells of recipients, starts producing copies of a key flu virus protein, the hemagglutinin protein, for all twenty influenza hemagglutinin subtypes—H1 through H18 for influenza A viruses, and two more for influenza B viruses.

"For a conventional vaccine, immunizing against all these subtypes would be a major challenge, but with mRNA technology it's relatively easy," Hensley said.

In mice, the mRNA vaccine elicited high levels of antibodies, which stayed elevated for at least four months, and reacted strongly to all 20 flu subtypes. Moreover, the vaccine seemed relatively unaffected by prior influenza virus exposures, which can skew immune responses to conventional influenza vaccines. The researchers observed that the

antibody response in the mice was strong and broad whether or not the animals had been exposed to flu virus before.

Hensley and his colleagues currently are designing human clinical trials, he said. The researchers envision that, if those trials are successful, the vaccine may be useful for eliciting long-term immune memory against all influenza subtypes in people of all age groups, including young children.

"We think this vaccine could significantly reduce the chances of ever getting a severe flu infection," Hensley said.

In principle, he added, the same multivalent mRNA strategy can be used for other viruses with pandemic potential, including coronaviruses.

More information: Claudia P. Arevalo et al, A multivalent nucleoside-modified mRNA vaccine against all known influenza virus subtypes, *Science* (2022). DOI: 10.1126/science.abm0271. www.science.org/doi/10.1126/science.abm0271

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