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Flu vaccine's effectiveness can be improved, new findings suggest

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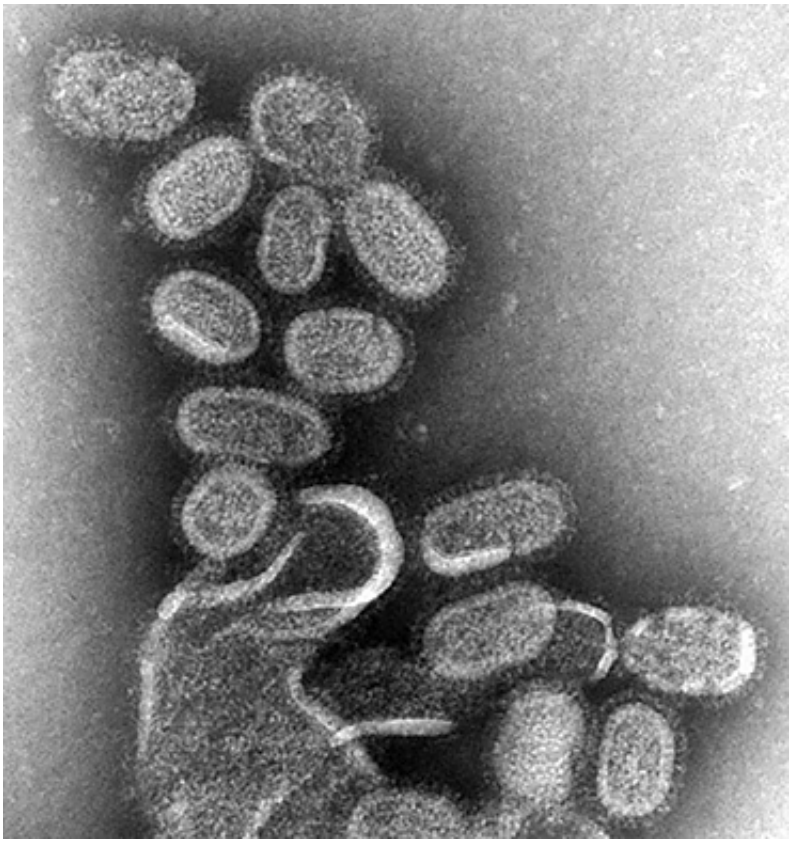

Electron microscopy of influenza virus. Credit: CDC

A team of engineers and scientists at The University of Texas at Austin is reporting new findings on how the influenza vaccine produces antibodies that protect against disease, research that suggests that the conventional flu vaccine can be improved. The findings were reported in

the journal *Nature Medicine* on Nov. 7.

The UT Austin team suggests that quadrivalent influenza vaccines—which are currently recommended by the Centers for Disease Control and Prevention to protect against four virus strains and which may cost more for consumers and health insurers to use—may not offer significant benefits over trivalent influenza vaccines. The team also discovered a new class of antibodies that are effective at offering the body protection from several influenza virus strains.

The four-year project was led by George Georgiou, a professor in the Cockrell School of Engineering and in the College of Natural Sciences. His team includes 34 researchers from various institutions, including the Icahn School of Medicine at Mount Sinai in New York, the National Institutes of Health and Stanford University.

According to the study, these insights were possible because of the team's new technology that is able to directly identify and quantify antibodies—the protein molecules responsible for protecting our bodies from viruses and bacteria—that are present in human blood. Exposure to a pathogen or virus stimulates our immune systems to generate a diverse array of antibodies, collectively known as the antibody repertoire, that then help fend off disease. Although various clinical tests can help determine whether a patient has antibodies that recognize the pathogen (for example, antibodies to HIV-1 in infected individuals), the number, molecular identities and amounts of the different antibodies that recognize the pathogen had not been known.

This breakthrough, which provides a molecular-level analysis of the serum antibody repertoire—called "Ig-Seq"—capitalizes on a series of technical advances in protein and single-cell DNA sequencing pioneered by the UT Austin team. The Ig-Seq technology is the first and only approach able to identify antibodies and to quantify how much of each

type of antibody are present in blood or other bodily fluids. Antibodies that are present in circulation in higher concentrations play a more significant role in preventing disease relative to those present at low levels.

The ability to identify and quantify antibodies is important because it allows scientists to see how the vaccine stimulates the immune system to induce the production of antibodies that may then protect against infection.

"In order to develop a better vaccine, you need to have a more precise, better understanding of the current vaccine's efficacy, and to do that you need to identify the individual antibodies that specifically bind to influenza, understand how they protect from disease and measure how long they can persist in circulation," said Jiwon Lee, a Cockrell School chemical engineering doctoral student and first author on the paper.

The team evaluated the serum antibody repertoire in young adults before and after seasonal flu vaccination. Every year, influenza infections cause more than 5 million cases of severe illness, resulting in approximately half a million deaths globally and posing a threat of another pandemic.

The UT Austin team discovered that after vaccination, only about 40 percent of the influenza-specific antibodies were elicited directly in response to the vaccine. The remaining 60 percent were antibodies that were already present, the result of previous exposure to earlier circulating viruses or vaccines.

The study also reported the discovery of a new class of antibodies that are remarkably proficient in protecting laboratory mice against lethal challenge by influenza yet unexpectedly do not block the virus from infecting cells.

This finding is important because all current metrics of influenza vaccine efficacy depend solely on the ability of serum to block infection and do not take into account the effect of antibodies that can protect against disease via alternate mechanisms.

The researchers also investigated the relative benefits of the longstanding influenza vaccine composed of three different strains of virus (trivalent) compared with the quadrivalent vaccine, which contains four viruses. They found that about 90 percent of the antibodies elicited by one of the viruses in the trivalent vaccine also bind to the fourth virus that is now included in the newer vaccine, raising the question of whether the adaption of the more complex quadrivalent vaccine confers an improved health care benefit.

In a separate collaborative study led by researchers at Harvard University and also published in the same issue of *Nature Medicine*, Georgiou and colleagues reported that because the current flu vaccines are produced in chicken eggs, they partly direct the human immune system to produce antibodies toward the mutated form of the virus adapted for better production in eggs, but not the human strain.

"The implication here is that the production of the vaccine in eggs can detract from its utility in eliciting a protective immune response in humans," Georgiou said.

More information: Jiwon Lee et al. Molecular-level analysis of the serum antibody repertoire in young adults before and after seasonal influenza vaccination, *Nature Medicine* (2016). DOI: 10.1038/nm.4224

Provided by University of Texas at Austin