Study finds factors that may influence influenza vaccine effectiveness

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Credit: National Cancer Institute

The long-held approach to predicting seasonal influenza vaccine effectiveness may need to be revisited, new research suggests. Currently, seasonal flu vaccines are designed to induce high levels of protective antibodies against hemagglutinin (HA), a protein found on the surface of the influenza virus that enables the virus to enter a human cell and initiate infection. New research conducted by scientists at the National

Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, found that higher levels of antibody against a different flu surface protein—neuraminidase (NA)—were the better predictor of protection against flu infection and its unpleasant side effects. Neuraminidase, which is not currently the main target antigen in traditional flu vaccines, enables newly formed flu viruses to exit the host cell and cause further viral replication in the body.

The findings, from a clinical trial in which healthy volunteers were willingly exposed to naturally occurring 2009 H1N1 influenza type A virus, appear online today in the open-access journal *mBio*.

"Each year between 3,000 and 49,000 people in the United States die as the result of seasonal influenza and its complications," said NIAID Director Anthony S. Fauci., M.D. "Annual vaccination against seasonal flu continues to be the most effective way to protect against infection, and this new study provides some interesting clues about how we might improve the level of protection that flu vaccines provide."

Higher levels of HA antibodies in a person's body have long been associated with greater protection against influenza infection. As a result, HA antibody levels have traditionally been used to guide vaccine strain selection and to infer how effective that vaccine might be against circulating viruses until field studies are available. However, variations in seasonal influenza vaccine effectiveness over the past decade have raised questions about their protective ability and whether other factors, such as antibodies to the NA protein on the flu virus, should be considered in designing the annual flu vaccine to improve its performance.

"The idea behind this study was to re-evaluate the bar that was previously established for evaluating a person's immune response to influenza vaccines," said the study's principal investigator Matthew J.

Memoli, M.D., director of the Clinical Studies Unit in NIAID's Laboratory of Infectious Diseases. "We wanted to test the conventional wisdom and see if people with high levels of HA antibodies were less likely to develop mild-to-moderate influenza compared with those with lower HA antibody levels."

To do this, the research team enrolled 65 healthy volunteers aged 18 to 50 years in the human challenge study—a type of research study in which individuals are exposed to disease-causing pathogens under carefully controlled conditions. The flu challenge study, which began in September 2013, was conducted at the NIH Clinical Center in Bethesda, Maryland, in the specially designed Clinical Studies Unit, which has distinct isolation and infection control features.

Dr. Memoli and his colleagues measured levels of existing anti-HA and anti-NA antibodies in the participants' blood. Based on those results, the volunteers were placed into two groups: those with high levels of anti-HA antibodies (25 participants) and those with low levels of anti-HA antibodies (40 participants). Each of the volunteers was then administered an intranasal dose (1 milliliter) of 2009 H1N1 influenza virus; the volunteers were required to stay in the study unit for nine days where they were monitored by medical staff 24 hours daily. After the nine-day testing period, participants were discharged after completing two days of negative flu tests. After that time, they had four follow-up visits with the study team over eight weeks.

As expected, the researchers found that the group of participants who had high levels of anti-HA antibodies when enrolled in the trial experienced a significantly lower incidence of mild-to-moderate influenza disease and some reduction in its duration compared with participants with low HA antibody levels. However, the NIAID researchers also found that these participants were just as likely to experience some flu symptoms as those with low levels of HA

antibodies. If these results are consistent with naturally occurring flu infection, it suggests that while high HA antibody levels may limit viral shedding, and thus the spread of virus from person to person, these levels may not prevent the development of flu symptoms. This would help to explain why some people who receive the seasonal flu vaccine might still report flu symptoms.

Surprisingly, the researchers found that participants with high levels of NA antibodies experienced a more robust protective effect from the vaccine than did those in the high HA group. Specifically, the NIAID team found that the individuals with high NA antibody levels experienced less severe disease, a shorter duration of viral shedding and symptoms, and fewer and less severe symptoms compared with those with high HA levels when challenged with the 2009 H1N1 virus. HA and NA antibody levels considered together may be a better predictor of whether someone develops mild-to-moderate influenza disease—and the severity of their symptoms—than either factor alone, but this study suggests that NA antibodies are the stronger factor for determining disease severity, the authors conclude.

Based on these findings, the authors suggest that the role of NA immunity should be considered when studying influenza susceptibility and that NA antigens should be considered in the design of future flu vaccine platforms.

More information: MJ Memoli et al. Evaluation of Antihemagglutinin and Antineuraminidase Antibodies as Correlates of Protection in an Influenza A/H1N1 Virus Healthy Human Challenge Model. *mBio* DOI: 10.1128/mBio.00417-16 (2016).

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