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Why the Flu Vaccine Is Less Effective in the Elderly

Around this time every year, the flu virus infects up to one-fifth of the U.S. population and kills thousands of people, many of them elderly. A study published by Cell Press on Dec. 15 in *Immunity* now explains why the flu vaccine is less effective at protecting older individuals. More broadly, the findings reveal novel molecular signatures that could be used to predict which individuals are most likely to respond positively to vaccination.

“We provide novel evidence of a potential connection between the baseline state of the immune system in the elderly and reduced responsiveness to vaccination,” said co-senior study authors Shankar Subramaniam, bioengineering professor in the Jacobs School of Engineering at the University of California, San Diego, and Bali Pulendran, professor in the Department of Pathology and Laboratory Medicine at Emory University. “By providing a more complete picture of how the immune system responds to vaccination, our findings may help guide the development of next-generation vaccines that offer long-lasting immunity and better protection of at-risk populations.”

Flu vaccines, which contain proteins found in circulating viral strains, offer protection by eliciting the production of antibodies—proteins that help the immune system identify pathogens and protect against infectious disease. While vaccination is considered the most effective method for preventing influenza, it is less effective in the elderly. But until now, the molecular mechanisms underlying this decrease in vaccine efficacy were unknown.

To address this question, Subramaniam and Pulendran identified molecular signatures of immunity to flu vaccination using systems biology approaches, which involve the computational and mathematical modeling of complex biological systems. They vaccinated 212 subjects, including 54 elderly individuals, across five influenza vaccine seasons, from 2007 to 2011, and analyzed blood samples to identify molecular pathways associated with protective antibody responses elicited by vaccination. They also analyzed previously published data for 218 additional subjects.

Using this approach, the researchers identified molecular signatures present in blood samples collected a few days after vaccination that predicted with 80% accuracy whether the vaccine would elicit immune protection approximately four weeks later. Within one week of flu vaccination, young individuals showed high levels of antibody-producing B cells, whereas the elderly showed high levels of immune cells called monocytes, which elicit inflammatory responses in the body. These age-related differences predicted impaired vaccine-induced immune responses observed in the elderly three weeks later. “Together, these results suggest potential mechanisms by which changes to the innate response in the elderly may result in diminished antibody responses to vaccination,” said Subramaniam, who is associate director of the Institute of Engineering in Medicine at UC San Diego.

Even before vaccination, high baseline levels of B cells, in conjunction with low levels of monocytes and related inflammatory molecules, predicted vaccine-induced immune protection four weeks later. “This supports the concept that inflammatory responses at baseline may be detrimental to the induction of vaccine-induced antibody responses,” said Subramaniam. “While it is early to suggest, supplementary therapeutic approaches, such as reducing the inflammatory response in elderly patients after vaccination, would be valuable avenues to pursue. However, this warrants longer and more detailed investigations.”

For their own part, the researchers plan on applying similar system biology approaches to study other viral infections, such as shingles and yellow fever. “Analyzing these myriad ‘omics’ data in conjunction with physiological measurements is novel and will serve as a paradigm for future studies on influenza and other infections.”

In the meantime, they urge caution against over-generalizing their new findings. “This is obviously a complex problem, and the study reveals responses that are averaged across populations,” said Subramaniam. “As is true in every medical diagnosis, prognosis, and treatment, there is a distribution of responses with a majority conforming to the mean predicted response. So the important thing for the general audience to recognize is that there will be exceptions and variations.”

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