Bacteria seek to topple the egg as top flu vaccine tool

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Only the fragile chicken egg stands between Americans and a flu pandemic that would claim tens of thousands more lives than are usually lost to the flu each year.

Vaccine production hinges on the availability of hundreds of millions of eggs – and even with the vaccine, flu still claims somewhere around 36,000 lives in the United States during a typical year. Now scientists have taken an important step toward ending the dominance of the oval. In a paper published in the Dec. 6 issue of the journal *Vaccine*, scientists showed that an experimental flu vaccine grown entirely in bacteria – a process that bypasses the egg completely – works well in people, triggering an immune response that would protect them against the flu.

The study of 128 healthy people ages 18 to 49 at the University of Rochester Medical Center was led by John Treanor, M.D., an expert on flu vaccines who has helped lead efforts to create and test new ways to make flu vaccine more quickly and less expensively. The vaccine – which is free of bacteria itself – is made by New Jersey-based VaxInnate Inc., which funded the study.

"There are a number of problems with using eggs to produce flu vaccine," said Treanor. "It's a very specialized product. It's hard to make more eggs in a hurry – you only get them as fast as hens lay them. They're not easy to manipulate, and it can be challenging to get the flu virus to grow within an egg. The flu vaccine system would be more flexible and reliable if we didn't have to rely on them."

Scientists have been exploring a number of alternatives to eggs – creating doses to cover just the U.S. population requires millions of eggs that, if laid end to end, would just about encircle the continental United States.

Bacteria have not been high on the list of options, even though they have the capability of producing vaccine more quickly and less expensively than many other methods. Most efforts to use bacteria have faltered due to basic differences in the way that bacteria process proteins compared to more complex eukaryotic cells, which have a nucleus. Proteins are a crucial component of flu vaccine, and keeping the key proteins folded correctly has been a challenge in bacteria, which lack cellular machinery critical to the process.

"It was long accepted as dogma that you could not make a flu vaccine in bacteria that could stimulate a protective immune response in humans," said Treanor. "But in this vaccine, the surface flu protein hemagglutinin was made by E.coli in such a way that it folded correctly, stimulating an authentic immune response. It's almost surprising that this is possible."

VaxInnate addressed the problem by focusing on just one small key protein of hemagglutinin that can be correctly refolded after synthesis in bacteria. The small protein is enough to spur the immune system because it was attached to an adjuvant – a compound designed to strengthen the vaccine by stimulating a more robust immune response. Adjuvants currently are not part of U.S. flu vaccines, though they are used in other countries and as parts of other vaccines. Usually, adjuvants are simply mixed into a vaccine, but the latest work offers a new method. A bacterial protein called flagellin was actually fused to a molecule that mimics the flu's hemagglutinin protein – a combination designed both to draw the attention of the immune system and immediately amplify it in one step.

The amount of material in the experimental flu shot under study is just a fraction of the amount used in a licensed flu shot. The most successful tests were done with one or two micrograms of vaccine, much smaller than today's licensed 15-microgram shot. About half of participants got a strong immune response at 1 microgram, and about 80 percent got a strong immune response at 2 micrograms.

Provided by University of Rochester Medical Center