Universal Influenza Vaccine: Quest in Sight?

Several efforts to develop a vaccine that might work against all or most flu virus strains fortify hopes for fulfilling this one-time “flight of fancy”

Marlene Cimons

“Over a glass of wine, we infectious diseases specialists and public health officials often have allowed ourselves these flights of fancy about how effective a universal influenza vaccine would be. We imagine how we could control or perhaps eliminate the most feared infectious disease plague on the planet...”

William Schaffner, professor of medicine at Vanderbilt University in Nashville, Tenn., and medical director of the National Foundation for Infectious Diseases, remembers the countless times he and other flu experts mused about the possibilities of a universal vaccine, one that would not need modifying each year. These days, however, thanks to modern molecular technology, this dream no longer appears so improbable. “Now or very soon, these may no longer be flights of fancy,” he says. “There are some very impressive scientific efforts underway to make this real.”

Several groups of scientists report significant gains toward developing an influenza vaccine that could yield lifelong protection to an individual following a single injection, or one every 5 to 10 years. Even that latter approach would be a major advance over the current approach that depends on individuals receiving annual injections of a vaccine whose components need painstaking adjustment each year. Indeed, every year public health officials scramble as they try to predict nine months in advance what the common circulating flu virus strains will be, relying on careful analysis plus hope that they are right.

Ideal Flu Vaccine Would Protect against both Seasonal Outbreaks and Pandemics

“We wouldn’t have to worry about that, and manufacturers would not have to reconstitute the vaccine on an annual basis,” Schaffner says, referring to the annual challenge of reconfiguring the flu vaccine. “Each year we have to vaccinate everybody. If we had a universal or long-lasting vaccine, each year we could go after people who hadn’t been vaccinated before. It could be a year-long, daily vaccination activity, not just focused in the fall anymore.”

The truly game-changing flu vaccine would also protect against influenza pandemics, the even bigger nightmare that public health experts face. Pandemics occur irregularly and unpredictably when a new strain of flu virus appears abruptly—one to which few or none in the population carries immunity. “It would be the single most important thing we can do in public health today,” says Michael Osterholm, professor of public health and director of Center for Infectious Disease Research and Policy at the University of Minnesota in Minneapolis, alluding to such a vaccine. “A severe pandemic... could kill up to 300 million people.”

Three types of seasonal influenza viruses are circulating among humans, and those strains are designated A, B, and C. Type A influenza viruses are further classified into subtypes according to the combinations of their two main surface pro-

SUMMARY

➤ Modern molecular technologies are helping researchers to overcome obstacles in the path to developing a universal influenza virus vaccine.
➤ A major near-term goal of flu vaccine researchers is to learn how to elicit a reliable immune response to many or all varieties of the hemagglutinin, or H, protein on the surface of the virus.
➤ Several research teams found ways to anchor the residual stem after removing part of the H protein—an important technical breakthrough en route to a universal flu vaccine.
➤ Other approaches seek site-specific mutations in one case, or subtype-specific versions of a flu vaccine that would prove superior to the now-standard vaccine, which requires annual reformulation to adjust its efficacy and coverage.
teins, hemagglutinin (H) and neuraminidase (N). Among many subtypes of influenza A viruses, influenza A (H1N1) and A (H3N2) subtypes are now the major types circulating among humans. Seasonal flu is riskiest for the very young, the elderly, or the chronically ill. Worldwide, annual epidemics cause an estimated 3 to 5 million cases of serious illness and from 250,000 to 500,000 deaths, according to the World Health Organization.

**Several Distinctive Research Efforts To Develop Versions of a Universal Vaccine**

Such a universal and long-lasting vaccine will be capable of provoking antibody responses against conserved regions of the virus—that is, those common to a broad spectrum of influenza virus strains. Several groups of scientists are trying to do just that, but they differ in their approaches. A major near-term goal of these flu vaccine researchers is to find the means for eliciting a reliable immune response to most or all forms of the hemagglutinin, or H, protein on the surface of the virus. One major challenge is that the amino acid composition of part of this protein, its head, is highly variable, while its stem is not.

Two teams of researchers, in separate efforts, removed its head segment, but found that lopping it off caused the stem to become unstable and fall apart, making it impossible for antibodies to bind to it. However, each team found a way to anchor the stem after beheading the protein.

One approach entailed combining a set of mutations to realign the subunits of the stem at the top, enough to keep its structure for the vaccine, according to Antonietta Impagliazzo of Janssen Pharmaceutical Companies of Johnson & Johnson in Leiden, the Netherlands, Ian Wilson of the Scripps Research Institute in La Jolla, Calif., and their collaborators.

The other approach also involves introducing mutations into the viral H gene to stabilize the stem, which then is bound to a bacteria-based nanoparticle to hold it in the right position, according to Barney Graham, deputy director of the vaccine research center at the National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Md., and his colleagues from there, nearby BioQual, Inc., in Rockville, Md., and Osaka University in Japan.

“Our group’s goal, which is an intermediate goal—before we get to one vaccination for life—is to have a group-specific vaccine that covers either group 1 or group 2 of influenza A,” Graham says, referring to viral groups based on the sequence and characteristics of the viral hemagglutinin protein. (H1, H2, and H5 are examples of group 1 viral subtypes, while H3, H7, and H10 are examples of group 2.) “What we are working on is to find a way to cover all the viruses in a group. It might be possible to cover both groups of A. Even if we could have an H1 construct that would cover current and future H1s, that would be a major advance. It just wouldn’t cover pandemic H5.”

Both these constructs can protect mice against the potentially lethal H5N1 influenza strain, according to Graham. “We made a vaccine against H1 that protected against H5,” he says. “Getting protection against subtypes hasn’t been done before. So this was exciting to see a vaccine against H1 protect against H5. The goal was to have antibodies that were cross neutralizing. We got antibodies that bound to the viruses, but didn’t necessarily neutralize—but still protected. We’re not giving up the goal of having cross neutralization, because that would protect better.”

**Other Strategies for Developing Universal Flu as well as Other Antiviral Vaccines**

Yet another strategy for developing a universal-type vaccine against the influenza virus first applies reverse genetics to this negative-strand RNA virus, according to Peter Palese, who chairs the microbiology department at the Icahn School of Medicine at Mt. Sinai Hospital in New York, N.Y. Site-specific mutations are introduced into the genomes of these viruses, a step that proves critical for studying the structure and function relationships of viral genes and viral pathogenicity as well as in developing novel vaccines. Thus, he and his colleagues took this approach to reconstruct and study the highly virulent but extinct 1918 pandemic influenza virus.

“We are changing the head of the hemagglutinin to one which we have not experienced in terms of human infections,” Palese says. He and his collaborators then designed a vaccine aimed against “a [flu] virus we made in the lab that is an entirely new virus,” he says. “We hope that, by doing that, our immune system will remember the conserved regions—meaning the stalk and the neuraminidase—so that changes in the head won’t matter. The immune system will redirect
Recent Concerns over FluMist: Yet Another Reason for Seeking Universal Vaccine

Having access to a universal or even long-acting influenza vaccine would surely help to overcome other peculiar public health issues that arise through reliance on available flu vaccines. For example, officials at the Centers for Disease Control and Prevention (CDC) in June 2016 recommended against using the live-attenuated influenza vaccine (LAIV) during the 2016–2017 flu season, saying data from the last three years indicate that it works poorly, or not at all.

In August, however, a Canadian study challenged the findings that are the basis for that CDC recommendation, saying the LAIV, which is administered as a nasal spray, is as effective as the standard inactivated flu vaccine, which is administered by injection. The Food and Drug Administration (FDA) has not withdrawn FluMist’s license, and the CDC said that this decision applies only to the current flu season. FDA officials first approved this vaccine in 2003 for use among US adults, and later extended that approval to children aged 2 to 5 in 2007.

According to CDC officials, data from the previous flu season show that efficacy for LAIV for young people from ages 2 through 17 was only 3%—in effect, it provided little, if any, protective benefit. This conclusion is based on an analysis conducted by members of the CDC advisory committee on immunization practices (ACIP). Moreover, this version of the flu vaccine fared equally poorly during the two previous flu seasons, the ACIP said. In contrast, use of the injectable vaccine proved about 63% effective among young people in the same age group.

Meanwhile, an evaluation of a similar version of the nasally administered flu vaccine in Canada shows just the opposite—that it was effective, according to Mark Loeb at McMaster University in Hamilton, Ontario, Eleanor Pullennayegum at the Hospital for Sick Children in Toronto, Ontario, and their collaborators there and elsewhere in Canada. Their study was based on use of that vaccine among children in 52 Hutterite colonies in Alberta and Saskatchewan, Canada. Its use led to levels of protection from flu similar to that of the standard vaccine administered by inoculation. Thus, overall vaccine protection among children in the nasal spray group was 76.9% versus 72.3% for children who received the injectable flu vaccine.

However, a difference between versions of LAIV used in treating the two different groups of children might help to explain this discrepancy. The Canadian group, which conducted its study for three years beginning in 2012, used a trivalent formulation of the nasal spray vaccine, while the children in the US group were treated with a quadrivalent product, which became available in 2013.

“ACIP has no plans to revisit [this] decision regarding the use of LAIV during the 2016–2017 season at this time,” says Kristen Nordlund from CDC. “However, the decision was an interim one meant to apply only to 2016–2017, so the issue will be brought up for deliberation before the 2017–2018 influenza season. And while the quadrivalent nasal spray vaccine is still FDA-approved, CDC and other organizations do not recommend its use because of concerns about how well it works.”

“It’s a bit complicated, but the bottom line is that when FluMist went from trivalent to quadrivalent, something happened to substantially reduce its effectiveness,” says William Schaffner of Vanderbilt University School of Medicine in Nashville, Tenn. “The ‘something’ remains a scientific mystery.”

This mystery becomes a bit more confusing when one considers a recent recommendation from public health officials in the United Kingdom (UK), according to Peter Palese from Mt. Sinai Hospital in New York, N.Y. “The UK National Health Care system [declared recently] that they only will pay for LAIV, the quadrivalent version,” he says. “Go figure!”

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itself to recognize the stalk and the neuraminidase.”

Thus far, this experimental vaccine “works wonderfully in mice and it works wonderfully in ferrets and guinea pigs, but these are not humans,” Palese continues. The experimental vaccine, although ready to test in humans, awaits major financial backing—an estimated $1 billion—before a clinical trial can be launched, he says. In addition to receiving development money from GlaxoSmithKline in England, additional support is being sought from that company as well as the Bill & Melinda Gates Foundation.

Palese is confident that this kind of vaccine will work and that the reverse genetics approach could also be effective for developing vaccines against other viruses with variable regions.
in their respective genomes, including HIV, hepatitis C (HCV), and rhinoviruses. Moreover, even if the flu vaccine, the first in this anticipated set, proves imperfect, it might well prove useful from a public health standpoint, he says. However, the approach will require considerable improvement before it can be applied to other viruses.

“If I reduce the amount of flu virus 10-fold, we won’t get sick, but that’s not good enough for HIV,” Palese explains. “With HIV, you have to get sterile, or neutralizing, immunity. With hepatitis C virus, a 10-fold reduction might be a viable vaccine, although it might not be enough to avoid the most deadly consequences of the virus, like liver cancer. Rhinoviruses should be similar to flu.”

In yet another strategy, one whose focus is on developing a longer-lasting flu vaccine, researchers at the University of Georgia (UG) and Sanofi Pasteur have developed an experimental vaccine against multiple strains of both seasonal and pandemic flu H1N1 using a technique called computationally optimized broadly reactive antigen, or COBRA, according to Ted Ross, director of the University of Georgia Center for Vaccines and Immunology in Athens. He and his collaborators made nine prototype synthetic compound vaccines whose compositions were based on genetic sequences from multiple influenza virus strains. The same type of COBRA programs also might prove promising in developing vaccines against HIV, dengue, and even Ebola, he notes. “I think it could work in any pathogen with a variety of diversity.”

The initial COBRA flu-targeting vaccines specifically recognize H1N1 viruses isolated within the last 100 years, but many of the experimental vaccines tested in mice produced immunity against flu strains not included in the design, according to Ross. “We’ve demonstrated that we can go back in history and make vaccines that protect against all the variants for the last 100 years,” he says. “That doesn’t mean we can do 100 years in the future, but we still can prevent a lot of disease.” The researchers hope to begin clinical trials of their candidate vaccines near the beginning of 2018.

The UG-Sanofi vaccine is not aimed for being universal against flu, but to be long-lasting while protecting recipients against a variety of flu strains, Ross says. Comparing this approach to the one that Palese and his collaborators are following, Ross invokes a baseball metaphor. “Peter’s approach is a homerun or a strikeout. We’re trying to get on base,” he says.

The UG-Sanofi vaccine is subtype specific, “the next layer down,” from a type-specific product, such as Palese’s, Ross continues. “If we could go 5 or 10 years or even longer, it means you won’t have to change it every season. But you can continuously do surveillance and make adjustments. We don’t know how long it will be. It might be 5 years. It might be 20.”

In yet another effort, researchers at the Dana-Farber Cancer Institute in Boston, Mass., led by Wayne A. Marasco, a cancer immunologist and virologist, report finding a type of antibody that can rapidly adapt to and neutralize a wide array of influenza virus strains—including some that have not yet been encountered. The antibody protein, called 3114 mAb, is a “broadly neutralizing antibody,” that can identify and disable a diverse group of flu strains, according to Marasco and his collaborators. More specifically, it can neutralize the two main types of influenza A virus, group 1 and 2, and protects mice against otherwise lethal doses of flu virus.

**Perspective**

The prospect of a universal flu vaccine, or even a long-lasting one, makes public health experts almost giddy. “Influenza is at the very top of the list of pathogens feared by public health specialists because it has the capacity to create pandemics that run around the world,” Schaffner says. “It staggers the mind how much illness and mortality it creates. If we had an effective universal vaccine, it would take a huge dent out of health care costs, disruption of work, school attendance and social activities. Even if you had to be revaccinated every 5 or 10 years, it could still change the entire way we prevent influenza.”

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**Suggested Reading**


