The efficacy of influenza (flu) vaccines has been greatly improved over the past several decades, but the flu virus still severely sickens hundreds of thousands of individuals each year. Is it possible that scientists have discovered a way to change that?

By Ronale Tucker Rhodes, MS

The Influenza Virus Challenge
The influenza virus is indeed a challenge. Although the first recorded influenza pandemic occurred in 1580, it wasn’t until the devastation caused by the 1918-1919 “Spanish” influenza pandemic that it was discovered influenza virus types A, B and, in rare instances, C cause the flu.² (It was previously thought that a bacterium called Haemophilus influenzae caused the flu.)³

Since this discovery, much has been learned about flu viruses. They have eight genes, including two that are coded to produce the proteins hemagglutinin (H) and neuraminidase (N) that allow the virus to enter a host cell and spread from cell to cell. There are 16 H subtypes and nine N subtypes, making 144 possible HN combinations. But only three — H1N1, H2N2 and H3N2 — observed to date are fully adapted for infecting humans. Other combinations such as the H5N1 bird flu virus have only occasionally infected small numbers of humans.⁴ Also, two antigenically distinct lineages of influenza B viruses have circulated globally since 1985.⁵
Flu viruses change and mutate each year in one of two ways. The first is “antigenic drift,” which is when small changes in the genes of influenza viruses happen continually over time as the virus replicates. The small changes usually produce viruses that are closely related to one another and usually share the same antigenic properties, which means an immune system exposed to a similar virus will usually recognize it and respond. Eventually, however, these small genetic changes accumulate over time and result in viruses that are antigenically different, which means the body’s immune system may not recognize them. A second type of change is caused by “antigenic shift,” an abrupt, major change in the influenza A viruses that result in a new influenza A subtype with an H and/or HN combination that has emerged from an animal population. This subtype is so different from the same subtype in humans that most people won’t have immunity to it. (The 2009 H1N1 swine flu virus was a result of a shift.) Antigenic drift happens all the time, whereas antigenic shift happens only occasionally. And, importantly, while both changes can occur in influenza A viruses, only antigenic drift occurs in influenza B viruses.

Interestingly enough, it is believed that the specific strain that wreaked havoc worldwide in 1918-1919, which was estimated to have infected 50 percent of the world’s population, created the viral dynasty that continues to infect people today. “The 1918-1919 influenza pandemic was a defining event in the history of public health,” said Anthony S. Fauci, MD, director of the National Institute of Allergy and Infectious Diseases. “The legacy of that pandemic lives on in many ways, including the fact that the descendants of the 1918 virus have continued to circulate for nine decades.”

**Flu Vaccine Effectiveness**

In 1938, the first inactivated influenza vaccine to protect against flu viruses was developed by Jonas Salk and Thomas Francis to protect U.S. military forces during World War II. Unfortunately, because the first vaccines developed weren’t as purified as today’s vaccines, they often caused side effects such as fever, aches and fatigue. And, since those are also the symptoms of flu, people mistakenly thought they were getting the virus from the vaccine, a common misperception still believed by some today.

Much has been done to improve flu vaccines’ effectiveness. For years, a troublesome issue surrounding influenza vaccines has been the strains’ potential protective benefit. To address this issue, the U.S. Food and Drug Administration (FDA) and World Health Organization (WHO) have continued to struggle to predict the correct virus strains to include in the vaccines.

In some years, influenza vaccines protect only 50 percent to 70 percent of people who receive them. According to the Centers for Disease Control and Prevention’s midseason vaccine effectiveness (VE) estimates, the 2015-2016 VE for protecting against having to go to the doctor because of flu illness is 59 percent. Specifically, it is 51 percent VE against the H1N1 viruses responsible for most flu illness this season, 76 percent VE against all influenza B viruses and 79 percent VE against the B/Yamagata lineage of B viruses.

Predicting which strains of the virus to include in the influenza vaccines is difficult at best, not only because the virus mutates from year to year, but the number of influenza subtypes A and B that can be selected for inclusion is limited. Prior to 2012 only trivalent influenza vaccines (TIVs) were manufactured. TIVs help protect against the two A virus strains most common in humans and the B strain expected to be predominant in a given
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A final issue with current influenza vaccines is the widespread avoidance of them. On average, the number of people who get a flu shot each year hovers below the 50 percent range. The reasons vary, but mainly it’s due to misconceptions that the flu shot causes the flu, that the flu shot causes unwanted side effects, that it doesn’t work and, for many, it’s a fear of needles.

As such, despite the strides made in improving influenza vaccines, WHO estimates between three million and five million cases of severe illness and between 250,000 and 500,000 deaths occur each year in the world due to influenza.

A More Effective Vaccine on the Horizon

A universal influenza vaccine, which scientists say will soon be a reality, could be a game changer. Many different groups of scientists are working to develop one. One key centers upon developing a vaccine that protects against the part of the virus that doesn’t mutate as much: the stem. William Schaffner, MD, chairman of preventive medicine at Vanderbilt University Medical Center in Nashville, Tenn., describes the influenza virus as a sphere with “a bunch of lollipops on stems sticking out of it.” The “sucker” part of the lollipop changes from year to year, but the stem parts do not, said Dr. Schaffner. Therefore, the universal vaccine would attack the stem portions of the virus, theoretically protecting against all strains. “A universal vaccine is the Holy Grail, and the prospects of what this could do for medicine is staggering,” he added. However, scientists have had trouble achieving an immune response with the stem rather than the ever-changing head.

Until now. Two U.S. teams of scientists have found success with formulating a vaccine that created antibodies from the stem. The vaccines were successful among mice, ferrets and monkeys and protected against flu strains like H5N1 avian flu and H1N1 swine flu. “The [experimental] designs were different, but the end results were very similar and highly complementary,” said Ian Wilson, co-author of the paper reporting on one of the studies and a structural and computational biologist at the Scripps Research Institute in San Diego. “It’s a promising first step, and it’s very exciting to see this research come to fruition.”

Both teams, which worked independently, tried to remove the variable head region and keep the stem as the base of their vaccines. Unfortunately, without the head, the stems fall apart so that antibodies aren’t able to bind to it. So, to anchor the headless stem, they introduced a combination of mutations to stabilize the core of the hemagglutinin stem. One team bound a bacteria-derived nanoparticle to the stem, which pulled the subunits of the protein together to hold it in the right position. The other team applied a combination of mutations that realigned the subunits of the stem at the top. Both proved to make the stem a functional structure for the vaccine. They then vaccinated mice with the vaccine, and found that both vaccines provided full protection against H5N1, a lethal influenza strain distantly related to H1N1. The mice that didn’t receive the vaccine died, but the vaccinated mice all survived. One vaccine also showed partial protection in ferrets, and the other vaccine showed partial protection in monkeys. The unvaccinated ferrets all died, but only two of the six vaccinated ferrets fell ill and died. None of the unvaccinated monkeys died, but the vaccinated monkeys had significantly lower fevers than the unvaccinated ones.

The vaccines now need to be tested in clinical trials to see how well they work in humans. “We still need to perform human trials and also want to develop a vaccine that protects against all the types of influenza that cause human pandemics, so we don’t have to worry about viruses like the bird flu that spread from animals to people,” said Wilson. “The current flu vaccine only protects against two subtypes of influenza A (H1 and H3) and two lineages of influenza B. Although we are targeting the HA stem to stimulate production of broadly neutralizing antibodies,
there are still some differences between types of influenza. This makes it harder to develop a one-shot vaccine, but we’re working on new mini-HA designs.”

Another group of researchers has discovered a new class of antibodies that they say may provide the basis for a universal flu vaccine. The researchers at McMaster University and the Icahn School of Medicine at Mount Sinai in New York compared an isolated strain-specific flu antibody (the type that current vaccines generate) with an isolated broadly neutralizing flu antibody (the type generated by universal vaccines). Initially, they found the universal vaccine type of antibody to be much less effective at neutralizing influenza than the strain-specific antibodies. However, when they isolated the universal-type antibodies in their natural setting from human blood, both types of antibodies were found to be comparable in effectiveness.

They also found that the subtype of antibodies located in the lungs and upper respiratory system are especially effective at neutralizing influenza. According to Matthew Miller, senior author of the study and assistant professor in McMaster’s Department of Biochemistry and Biomedical Sciences at the Michael G. DeGroote School of Medicine, this finding provides guidance about whether an inactivated versus live-attenuated vaccine would be best for delivering a universal flu vaccine. Currently, the flu vaccine is an inactivated vaccine consisting of virus particles that are grown under controlled conditions and then killed, unlike an attenuated virus that is kept alive but has reduced virulence. With an attenuated vaccine, the virus is able to replicate in the upper-respiratory tract but isn’t capable of infecting the lung, and when the live virus replicates harmlessly, an immune response is generated.

“Unlike seasonal vaccines, which must be given annually, this type of vaccine would only be given once, and would have the ability to protect against all strains of flu, even when the virus mutates,” said Miller. “This would prevent the occurrence of flu pandemics and poor vaccine efficacy in the case of mismatches.” Miller and the other researchers are hopeful that their universal vaccine will be available in four to six years.15

FDA is also testing a potential vaccine. After studying related universal influenza vaccines, FDA scientists chose to study one developed by scientists at Okairos in Rome, Italy, because it is based on a virus to which humans have no prior exposure, thus avoiding any issue about prior immunity. Like some other universal vaccine candidates, this one triggered immune responses against conserved antigens (viral protein targets that mutate only slowly), which are similar among many strains of influenza viruses and, therefore, can generate immune responses that cross-react among virus strains.

The vaccine is made by genetically modifying a virus called PanAd3, which is isolated from a bonobo (a type of great ape). The modified virus, called a vector, carried two genes for proteins conserved among many different influenza viruses: M1 and NP. The vector can infect cells, causing them to express M1 and NP influenza antigens and, thus, immunize the recipient. However, it can’t replicate itself and spread. FDA scientists tested the PanAd3 vaccine by administering a single dose in the noses of mice, which caused a strong immune response that protected the animals against infection a few weeks later by exposure to a high dose of a very virulent influenza virus called A/FM. The vaccine not only triggered antibody production, but also activated T cells. Importantly, strong T cell immunity was found in the lungs, the site of infection.16

**A Universal Advantage**

Undoubtedly, the public is better protected today from the flu than it was decades ago. But, it’s still not as effective as needed, and too many people suffer from severe illness and, sometimes, die. Hopefully, with teams of scientists pursuing a breakthrough vaccine, the days of the yearly flu shot are numbered. It seems highly probable that a universal vaccine may soon arrive that could be given just once. It would protect against most types of flu, including seasonal varieties and the highly mutated kinds that cause pandemics. And, in contrast to the seasonal flu vaccine that takes six months to manufacture, a universal vaccine could be used immediately “off-the-shelf.”16 Now, that’s a game changer.

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**References**