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The Influenza Vaccine: Renewal Necessity and Pursuit of Lasting Immunity

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ABSTRACT

Influenza remains a significant global health concern, prompting continual efforts to enhance vaccine efficacy and broaden protection against diverse strains. Traditional influenza vaccines primarily target strain-specific surface antigens, necessitating annual updates to match strains. Recently, use of adjuvants such as MF59 and AS03 have shown promise in augmenting immune responses, potentially reducing the need for frequent vaccine reformulation. This review explores the recent approaches in influenza vaccine development, focusing on the pursuit of a universal vaccine. Additionally, this review discusses the role of adjuvants in enhancing vaccine immunogenicity.

Introduction

Influenza remains a significant global health concern. Every year, as the viral season rolls around, this seemingly mundane illness exacts a heavy toll, claiming hundreds of thousands of lives globally. This disease made its debut during the pandemic of 1918. Back then, it was called the Spanish Flu—even though it is most likely that it had originated in the United States. This lethal disease took the lives of over 50 million people worldwide—and this was only the first wave of a disease that would be known to make its rounds every year. The World Health Organization estimates that the flu causes between 290,000 and 650,000 deaths by itself annually worldwide.

The annual renewal of the influenza vaccine is necessitated by the continuous alterations in the influenza virus. Because this virus is constantly changing, the immune memory cells from previous year's vaccine will not be able to recognize and destroy the new virus strain that may appear next year. Therefore, developing a universal vaccine for this virus would be revolutionary in terms of finding a long-lasting solution to what feels like inevitable demise every year.

Current Protection and Treatment Strategies

Currently, it is recommended that anyone over the age of 6 months old in the United States should receive the flu vaccine. The exception to this is anyone with a compromised immune system and anyone allergic to the contents of the vaccine. There are several options of the vaccine available to the public—each recommended for a certain age group: The egg-based vaccine is the standard vaccine that has been approved for ages 2 through 49 (CDC 2023). These vaccines contain candidate virus grown in eggs (manufactured influenza viruses that have been prepared with the required immunogenicity needed to provoke an immune response). There is also the live attenuated influenza nasal spray (LAIV), a spray that is made with a live CVV—also recommended for ages 2 through 49. For people over the age of 50, the CDC recommends the fluzone high-dose quadrivalent; an egg-based vaccine that contains four times the antigen as opposed to the standard dose, the fluad quadrivalent;

an inactivated egg-based vaccine that contains the adjuvant MF59, and the Flublok Quadrivalent; a recombinant vaccine (a vaccine manufactured using a small portion of DNA from the virus) that contains three times the antigen of the standard dose (Wong et al., 2013). All of the options listed are trivalent or quadrivalent—they protect from two influenza A (H1N1 and H3N2) strains and two influenza B (Victoria and Yamagata) strains (CDC 2024). Influenza vaccines have been approved for ages 65 and above so it is generally safe, however there is still the possibility of some mild side effects such as a low-grade fever, muscle aches, or pain at the injury site, but these usually resolve by themselves after a few days (Zhu et al., 2021).

How Do Vaccines Work?

Vaccination is an efficient and effective way to protect the body from invading pathogens. There are some virus induced illnesses out there that a vaccine may not completely protect against, but the vaccine can greatly reduce the severity of the illness. Vaccines are designed to expose the body's immune system to traces (one or few proteins) of disease producing pathogens and train them to recognize and neutralize the pathogen, in this case viruses, when they actually attack the body. Vaccines contain weakened (attenuated) forms of pathogens or certain isolated proteins which will not physically harm the body but their very presence is enough to trigger an immune response and generate a long term memory (World Health Organization 2020).

The viral protein that a person is introduced to when they are vaccinated is called an antigen. The introduction of the antigen will trigger an immune response in the body which will result in the activation of T and B cells. B cells transform into plasma cells which then proceed to create antibodies, which can specifically bind to the antigens (proteins on the surface of the virus) and neutralize the virus. These antibodies will accumulate in the bloodstream to be activated in the future if the pathogen were to enter the body later on. T cells make direct contact with infected cells and destroy them. They are also involved in the production of memory cells and activating the B cells to produce antibodies (UChicago Medicine 2020).

Many vaccines require more than one dose to achieve maximum protection. There are two types of vaccines. They are; live-attenuated vaccines and inactivated vaccines. Live, attenuated vaccines are derived from weakened forms of the virus or bacteria as discussed earlier. For most, it is recommended that the person receives two doses because in some cases, the immune system is not adequately stimulated with the first dose alone. Two doses are recommended to achieve maximum T and b cell stimulation to generate long-term protective immunity. . These kinds of vaccines are used for diseases such as rotavirus, chickenpox, and smallpox. A potential side-effect of these kinds of vaccines is that, if the receiver has a compromised immune system, it is possible for the bacteria to multiply and result in the formation of a life-threatening infection (Wodi et al., 2021).

In contrast, inactivated vaccines contain killed off forms of the bacteria or virus. Influenza is an example of a virus that requires an inactivated vaccine. One plus from this is that these versions of the bacteria/viruses can not cause disease, unlike the live, attenuated vaccines. However, inactivated virus are less potent than live virus in inducing adequate levels of antibodies in the bloodstream. . Because of this, inactivated vaccines require multiple doses over a period of time to prolong its effects as opposed to a live, attenuated vaccine. The first dose doesn't immediately produce strong immunity, but instead "primes" the immune system—or prepares it to respond to the coming doses (Wodi et al., 2021). The body's immune response to the antigen develops during the second and/or third doses. However, use of adjuvants enables induction of a potent immune response without the need for repeated doses.

Adjuvants

Adjuvants are substances added to vaccines to enhance the body's immune response to the antigen (the part of the vaccine that triggers an immune response (CDC 2022). By using adjuvants, vaccine developers aim to increase the effectiveness and longevity of the immune response generated by the vaccine. Some common adjuvants used in vaccines include aluminum salts (e.g., aluminum hydroxide, aluminum phosphate), which have been used for decades and are found in many vaccines, and more recently developed adjuvants such as MF59 and AS03. MF59 adjuvant was developed by the pharmaceutical company Novartis has been used in several vaccines, including influenza vaccines. MF59 can prolong the duration of the immune response by facilitating the gradual release of the antigen, allowing for a sustained immune reaction and the generation of memory immune cells

Predicting Seasonal Flu Strains

Every year, scientists are tasked with predicting the likely viral strains for that season to create the annual vaccine. A "strain" is a genetically distinct variant of a virus. Mutations in the virus can lead to alterations in the characteristics of the variants. There are four strains of the flu— they are: Influenza A, B, C, and D. Influenza A and B are the most common strains of the virus. Both strains are pretty similar with one of the only differences being that Influenza A can be spread amongst animals as well as humans while Influenza B can only be contracted by humans (CDC 2023).

One approach scientists have experimented with is training the body to produce antibodies that will target antigens that do not change as much between the different strains of the virus every year. They will achieve this by predicting which strains will be prevalent in the following years and pose a threat to us. Researchers target regions of viral proteins, such as Hemagglutinin (HA)—-a glycoprotein that plays a crucial role in the infection process. It binds to receptors on red blood cells and initiates the transmission of the virus. Once binded to a host cell receptor, the virus then infects the cell which allows it to replicate itself (Nobusawa 1997). This makes the HA protein an important target for the body's antibodies which will bind themselves to host cells to prevent the HA protein from gaining entry to these cells. The HA protein seems to be consistent amongst the various strains of the virus. Although the 'head' of the protein tends to change as the virus evolves, the 'stem' of the protein evolves at a slow rate as opposed to that of the head (Tedjasaputra 2023). This means that this part of the HA protein is similar between the strains of the virus, and a target for scientists seeking an answer for a universal flu vaccine. Research teams are working to recognize antibodies that will target these parts of the strains to create a universal vaccine that produces these antibodies to fight against and prevent this virus from resurfacing again.

Clinical Trials by NIAID's Vaccine Research Center

Early-Stage Trial

Using the strategy discussed previously, the NIAID's VRC developed the H1ssF vaccine to enter into a clinical trial. This vaccine is an experiment *non-RNA* vaccine that displays the stem of hemagluttin. The objective of this trial was to see if this vaccine would administer an immune response and asses the safety of the doses.The trial would house up to 52 participants ages ranging from 18-70 years old (NIAD 2023). Volunteers were given either a 20-microgram dose or two 60-microgram doses (injected into the upper arm) which were followed up with a booster injection regardless of which dose they received (NIAD 2023). Their temperature and symptoms were consistently assesed over the span of a year. As expected, antibodies were synthesized that targetted the head of the HA protein to induce immunity and no severe side-effects followed the initial administering of the vaccine (Deatrick 2023).

Phase 1 Clinical Trial

Following the success of the preceding trial, a mRNA vaccine (H1ssF-3928 mRNA-LNP) was launched into production. This vaccine, similar to the H1ssF, is a nanoparticle as well, however, unlike H1ssF, it uses mRNA as a platform to display the stem of the HA protein (Walter 2023) This trial was conducted by members of Duke University and housed 50 participants of ages ranging form 18-49. Much like the previous clinical trial, the objective of this trial was also to assess the security and efficacy of the vaccine in study. Volunteers either received a 10, 25, or 50 microgram dose of the vaccine to draw conclusions of what optimal dosage may be depending on the symptoms the participants exhibited (Walter 2023). Overall, the vaccine was deemed safe as typical reactions to the vaccine included mild headaches and little discomfort at the injection site.

Conclusion

The annual renewal of the flu vaccine is necessitated by the influenza virus's ability to evolve rapidly and evade pre-existing immunity. However, ongoing research endeavors offer hope for developing more enduring solutions, such as universal vaccines and advanced delivery systems. By harnessing cutting-edge technologies and interdisciplinary approaches, scientists aim to mitigate the need for yearly vaccine updates, ultimately bolstering global efforts to combat influenza and safeguard public health.

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