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Commentary

The Effectiveness of a Centralized Influenza Vaccine

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DESCRIPTION

During the 2015-16 flu season, the CDC estimates that influenza vaccination prevented 1.9 million influenza illnesses and 67,000 influenza-related hospitalizations. In that same year, however, there were 40 million influenza illnesses and 970,000 influenza-related hospitalizations. In other words, our current influenza vaccine programmes and technologies reduce influenza infections by 4.75% and hospitalizations by 6.9%, respectively. Society is becoming more aware of the "flu shot's" flaws and more sceptical of the vaccine. Antigenic mismatches, limited stocks, and, most recently, the CDC advised against using FluMist due to reports of complete ineffectiveness. There is no doubt that more effective vaccine technologies are required.

A new strain of influenza emerged in Mexico in 2008 and spread to Texas and California later that year. At the time, the vaccine was completely ineffective against this novel "Swine Flu" virus. The vaccine and circulating influenza hemagglutinins differed by 20.5% in amino acid sequence4. By the end of the pandemic, 24% of the world's population had been infected with Swine flu in 2009. In the United States alone, there were 68 million influenza infections and 275,304 influenza-related hospitalizations. The 2009 swine flu pandemic served as a wake-up call about our vulnerability to infectious diseases like influenza. Despite significant investments in global monitoring, antiviral drug development, and advanced vaccine technology, the pandemic was unstoppable.

In addition to the 1918 H1N1 pandemic, the 1957-1958 Asian Flu pandemic was caused by the H2N2 influenza virus. The H3N2 influenza virus caused another global pandemic, the Hong Kong Flu of 1968-1969. In 1997, there were 18 cases of H5N transmission from birds to humans. Between 2003 and 2016, the World Health Organization (WHO) received reports of 856 human cases of avian H5N1 influenza and 452 deaths. Scientists recently demonstrated that H5N1 can be adapted to transmit between ferrets via aerosols. These findings highlight H5N1's ability to mutate into a highly transmissible human-to-human strain with a high mortality rate. H7N9, H7N2, and H9N2 viruses have also been found to infect humans sporadically, usually as a result of close contact with infected animals.

Vaccination against seasonal influenza is critical to lowering the infection burden. However, according to a recent study on influenza vaccine efficacy, our current trivalent inactivated (FluZone) and live-attenuated cold-adapted (FluMist) vaccines are only 59% effective, with variable results across age groups. Furthermore, predicting which influenza strains will be circulating in the coming years is extremely difficult. The use of high-dose vaccines for the elderly and the inclusion of an additional B virus in the Quadrivalent influenza vaccine formulation are two recent advances in influenza vaccine technology. These advancements will contribute to the overall efficacy of the influenza vaccine as well as the likelihood of influenza B virus vaccine coverage. However, the possibility of a vaccine mismatch and failure remains.

A perfect influenza vaccine would be cheap, provide long-lasting immunity, require few immunizations, and work against all strains of the virus. Several approaches have been investigated by researchers in order to improve on our current vaccine technology. The M2 matrix protein's ectodomain is highly conserved among influenza viruses, making it an appealing target for developing a cross-reactive vaccine antigen. While this method has shown some promise, it appears that total protection is limited. Other researchers have focused on directing immunity toward the hemagglutinin stalk region. Because the stalk region is more conserved than the globular head, highly effective cross-reactive neutralising antibodies directed at this region are thought to provide universal protection against heterologous influenza challenge.

This approach has been shown to be effective in challenge studies, but data is limited to only one or two heterologous influenza challenge strains. Another approach is to use influenza's conserved internal genes as vaccine antigens. Recent research has shown that bacterially expressed or MVA expressed proteins like NP, M1, and PB1 are protective against an influenza virus challenge. Consensus genes were first developed

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as broadly reactive HIV vaccine antigens, and they have been shown to provide higher levels of cross-protective immunity than wildtype antigens. As a result, scientists have used this method to study the influenza Hemagglutinin (HA) gene. A vaccine that is genetically identical to the challenge virus will always induce the highest levels of immunity. In the case of vaccine mismatch, however, the consensus vaccine genes tend to exhibit higher levels of cross-protective immunity. While all of these approaches provide some level of protection against heterologous challenge, there is inconsistency in vaccine doses, challenge viruses, and varying challenge doses that makes comparing vaccine platforms impossible. Our method involves a dose-dependent vaccine study, multiple heterologous influenza strains for each subtype, and a highly stringent 10-100 MLD influenza virus challenge.

They used the centralised gene vaccine approach in this study on four human-relevant influenza virus HA genes, H1, H2, H3, and H5. The centralized genes were inserted into replication-defective Adenovirus (Ad) viral vector systems and tested in combination (multivalent) against a diverse panel of H1, H3, and H5 influenza isolates. Furthermore, we compared our Ad-vectored centralised vaccines to the standard FluZone and FluMist vaccine platforms. We discovered that *in vitro* and *in vivo* studies show that Ad-vectored centralised vaccines can provide high levels of protection against a diverse range of influenza strains at very low doses.