

Influenza Vaccine History

This media information sheet provides a brief overview of the history of Influenza vaccine development and recommendations made over time concerning vaccine use.

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The History of the Influenza Vaccine

The history of the development of the influenza vaccine cannot be separated from the changing understanding of the virus itself. The specific viral traits or how the virus enters a host, replicates, and can create completely new forms of itself were not well understood early in the development of influenza vaccines. The development of better lab techniques encouraged improved experiments that led to more information about the virus. Knowledge of the virus structure also grew as vaccine trials failed over time and new solutions were devised to overcome those setbacks. Additionally, with growing information on the virus, a governmental infrastructure was created both nationally and internationally for the monitoring of viral strains, production and testing of vaccines, and the release of recommendations concerning which population groups need to be vaccinated.

Currently, new molecular biology techniques are allowing for the study of the influenza genome and its virulence, specifically why certain viral strains are more lethal and contagious than others. This information sheet will describe the history of the influenza vaccine and the major players in its continued development.

The Influenza Virus: Structure and Perception

The influenza virus has a method of replication that sets it apart from many viruses. The viral genome is composed of eight segments that during the course of viral replication can undergo a process of antigenic shift in which entirely new genomes are assembled by mixing of the segments from two different influenza viruses in various combinations. The new virus could be more or less virulent than the previous strain, depending on the components that make up the new genome. This mechanism facilitates the incredible speed at which the influenza virus can change. In addition, it has the capability of jumping between species and can pick up new mutations from those organisms, adding to its variability.

The ability to create new versions of itself so quickly could be both a benefit and a drawback. The type of strain the population can be exposed from year to year can change drastically. The dominance of several weak strains many seasons in a row contributes to the perception that influenza itself is a benign illness. That mentality can influence whether people get vaccinated or not. The harm in such a belief is that the virus can just as easily mutate unexpectedly into a powerful, lethal strain as was seen in the flu pandemic of 1918.

History of Influenza Vaccine Development

Towards the end and in the aftermath of the First World War, over fifty million people around the world died from a particularly contagious strain of influenza, which became known as the Spanish Flu. The

devastating death toll from the 1918 Spanish Flu, which seemed to target previously healthy young and middle-aged adults, fueled the need for a vaccine that could prevent others from succumbing to the disease. Although there were some vaccines made during that time period claiming to be effective against the sickness, many of them, like the Pfeiffer's vaccine, contained combinations of different bacterial strains which would not produce an immune response to protect against a virus. The vaccines produced, tested, and marketed during that time period reflect the limited agreement in the scientific community of what constitutes a reliable standardized vaccine trial. In addition, the prevalence of bacterial vaccines signified the disagreement over the causal agent of influenza itself.

In response to the need for standardized vaccine production and quality assessment, in January 1919, the American Public Health Association published the "Working Program against Influenza" which set guidelines for testing a vaccine. This publication encouraged authors to be more cautious about conclusions made from their trials and remained the professional standard for several decades.

Vital Breakthroughs

Although there was a great need for an influenza vaccine, intensified by the events of the Great Pandemic, it wasn't until years later that laboratory research began to accumulate substantial knowledge about the virus. Between 1935 and 1960, the influenza virus was the most extensively studied virus infecting humans. The first demonstrably protective vaccine was made by Chenoweth and his colleagues during their study in 1936. This vaccine was made possible through the development of a foundational understanding of the virus and isolation techniques developed during the early 1930's.

One of the first problems faced by scientists was how to grow and maintain the virus. In the middle of the 1930s, the influenza virus could only be studied by observing infected animals. Using this method, the virus could only be cultivated by passing it from one animal to another. This was a slow process, requiring approximately three weeks and was used often into the 1940s, first in ferrets then in mice. In 1940 Frank MacFarlane Burnet showed that the virus could also be grown on the embryos of chicken eggs and that virus cultivated in this allantoic fluid grew in high concentrations. The virus could also be isolated by inoculation into the amniotic cavity of the egg, making animal use unnecessary from then on.

Another issue was diagnosing patients within a reasonable time frame. To shorten the time needed to declare that an individual had been infected with the influenza virus, new serological tests were developed in 1936 that didn't require the use of live animals, shortening the time needed to conduct the test from three weeks to ten to fourteen days. Then, in 1942, it was observed that the presence of influenza virus could cause red blood cells to clump together, yet serum that contained flu antibodies could inhibit this agglutination. This observation led to the Hemagglutination-inhibition test developed by Hirst, which helped identify influenza virus within hours, providing researchers with the ability to measure antibodies against influenza on a massive scale.

By 1942 there were three additional techniques that were developed to create more concentrated vaccines: centrifugation, freezing and thawing the allantoic fluid in embryonated chicken eggs, and absorption of the virus into red cells at low temperature and their elution at higher temperature. It was during the 1940s that vaccines using these methods became standard, made from relatively pure virus grown on chick embryo allantoic fluid and purified by red blood cell elution and formalin inactivation.

Army Involvement in Vaccine Development

During that same time period, the threat of another world war put pressure on the development of an influenza vaccine. In 1941 the Army Epidemiological Board created a Commission on Influenza and Vaccine Development which led to a program to control influenza during the war and was a focus of American influenza research for twenty years. That commission later became known as the Armed Forces Epidemiological Board (AFEB) in 1949. It was created with the goal to advise the Surgeon General on matters pertaining to preventative medicine, to investigate through lab and epidemiological studies of infectious disease, and to conduct research on infectious diseases that are of particular concern to the Army. The AFEB was a central organization in development of many vaccines and treatments for infectious diseases, though its main focus initially was the discovery of an influenza vaccine.

In 1942 AFEB created a vaccine that had all the latest innovations in vaccine development techniques and was polyvalent, containing both the influenza A and B virus strains. Yet a field trial of the vaccine set in Michigan failed due to the lack of any influenza outbreaks at any of the testing sites. The following year a larger, more inclusive trial involved 12,500 students from universities and medical colleges. The trial itself was innovative, having the vaccines and controls randomized by serial number as well as placebo controlled and double blinded. It is regarded as the prototype of the Salk polio vaccine trial conducted a decade later. The results of the 1943 field trial were positive and the vaccine was used in 1945 to vaccinate all of the soldiers in the Army. It was even shown to be more effective against influenza B than influenza A.

Yet when the vaccine was used again in 1947, it offered no protection and it was discovered then that the vaccine did still offer a good protection against the viruses it contained, leading to the realization that the virus strain encountered during that time was a new strain of influenza. That same year, before the outbreak, George Hirst at the International Health Division published a study of antigen change in two similar influenza A viruses isolated in Alabama in 1941. He discovered that although passage of the virus between eggs did not produce any change in the virus, when it was passed with mice, the virus diverged significantly from the original type. By the late 1940s and early 1950s, studies showed these antigenic differences and helped explain that the failure of the 1947 trial was due to the antigenic differences between viruses that were in the vaccine and the current outbreak strain.

New Knowledge on Antigenic Shift

By the 1950's, there were two major beliefs about the influenza virus. One side believed that the influenza virus was the product of rapid evolutionary change, concluding that a successful influenza vaccine might not be possible. American investigators who had a lot of stake into vaccine development, tended to disagree and worked to create vaccines that incorporated several strains and attempted to construct a virus whose antigenic variation was finite. Thomas Francis, for example, was convinced that all influenza A viruses were made up of the same antigenic components and that it should be possible to create a vaccine that could provide universal protection against influenza.

At the same time the World Health Organization (WHO) had recently created the Influenza Study Center which monitored the movement of influenza epidemics through isolation of the virus around the globe. It attempted to isolate and type all influenza viruses in circulation, a much harder task than anticipated. In April 1957, researchers believed that the Asian flu virus encountered during that time period was the first instance of antigen shift that they had seen. The variations that had been seen previously were

instances of antigenic drift, resulting from point mutations in the genetic code. Antigenic shift, on the other hand, involves drastic changes in the surface antigens, hemagglutinin and neuraminidase which allow the virus to vary greatly from previously seen strains, giving it the capacity to be incredibly infectious to newly susceptible hosts. That particular outbreak was the most serious outbreak since the 1918 influenza pandemic and resulted in eighty million cases and seventy thousand deaths.

The discovery that influenza viruses undergo genetic recombination through the reassortment of RNA genome pieces was built upon understanding of the virus structure. It was known at the time that the virion surface had enzymes that performed two opposing functions, one that helped the virus bind to red blood cells and another that helped it dissociate. R.G. Laver helped determine that there were two different proteins. With his help researchers were capable of discovering 'antigenic hybrids' following mixed infection with viruses of different subtype. Earlier, while working with James Murphy, Kilbourne was able to show that the transfer of viral morphological characteristics by genetic recombination.

In 1959 Dr. Kilbourne was successful at transferring the high yielding properties of standard laboratory strain (PR8) to a wild-type H2N2 virus. In the following pandemic of 1968 he was successful in producing another such high-yielding reassortment X-30. Both times they were rejected as vaccine candidates due to distrust of 'recombinants' at the time. He created a third X-31 reassortant derived from an H3N2 ("Hong Kong" strain) virus provided by the Bureau of Biologics which researchers then employed in correlation studies of a single vaccine batch. These particular studies included animal immunogenicity and toxicity studies, electron microscopic characterization, and volunteer challenge and clinical field trials. The vaccine they produced was immunogenic, non-toxic and protective. Since 1971, all subsequent influenza vaccines have been made by genetic reassortment, becoming the first genetic engineered vaccines.

Governmental Legislation and Monitoring

While Dr. Kilbourne was working on getting his reassortment vaccines accepted, the U.S. government passed the Vaccination Assistance Act in 1962. This act encouraged extensive immunizations by establishing a mechanism by which state and local health departments could receive financial support to assist in managing of immunization programs. This act remains to be the most important means of supporting health department immunization activities with federal funds.

Two years later, in 1964, Advisory Committee on Immunization Practices (ACIP) was started with the designated task to provide the CDC with recommendations on vaccine use. Since then it has released recommendations on which individuals should be vaccinated. In 1972, it was realized that sequential antigenic change patterns require that the formula for flu vaccines be replaced annually. The observation of co-circulation of two type A subtypes in 1977 encouraged the addition of another subtype and the need to replace variants annually as well.

In June 2003, the FDA approved the use of a live attenuated influenza vaccine, which is administered as a nasal-spray and made with live, weakened flu viruses. Most recently, in February 2012, the Food and Drug Administration (FDA) approved the use of a quadravalent influenza vaccine, which like the FluMist (trivalent) vaccine, contains weakened forms of the virus that can be applied through a nasal spray. This new FluMist Quadravalent vaccine increases the likelihood of adequate protection against circulating influenza B strains. The Live attenuated influenza vaccine is shown to produce a similar immunity in

adults to injected killed virus vaccines, and as good if not better immunity in children. It is in particular preferable for use in children because it is administered as a nasal spray, instead of a shot.

How Influenza Vaccines are Chosen Today

Currently, surveillance of influenza activity is conducted by labs around the world sponsored by the World Health Organization (WHO). The WHO each year releases a recommended formula for each region of the world based on the data it has collected on the prevalence of particular strains. The individual governmental organizations tasked with influenza vaccine research ultimately choose which strains to use for that season of influenza. In the United States, both the Centers for Disease Control and Prevention (CDC) and Federal Drug Administration (FDA) collaborate to ensure the safety, effectiveness, and security of vaccines. The Influenza Branch of the CDC is in charge of influenza surveillance while the Immunization Safety Office (ISO) leads most of the agency's vaccine safety and research monitoring.

Each year, three strains are chosen to be included in the vaccine for that season, usually chosen several months before in February. Each year the FDA-approved seasonal influenza vaccine contains two strains of influenza A and one strain of influenza B. There are several manufacturers that produce the inactivated virus vaccine and one manufacturer of the live attenuated vaccine. Along with influenza monitoring and vaccine production, the CDC also has an organization which fulfills the role of overseeing vaccine use.

Current Recommendations on the Vaccine

In 2010, the ACIP recommended annual influenza vaccination to be administered to everyone over the age of 6 months. This is a major change from previous recommendations. Prior to 2008, ACIP had recommended annual flu vaccinations for people older than 50, children between 6 months and 4 years, and 18-49 year olds who were at high risk for influenza complications. In 2008 those recommended for vaccination expanded to include children from 5 to 18 years old, and then in 2010 to include 18-49 year olds who are not at high risk for influenza complications. Thus the list now includes all people over 6 months of age.

This universal inclusion of individuals to be vaccinated makes it unethical to perform efficacy studies with people who are explicitly recommended to receive the vaccine. Thus, randomized studies, in which one group gets a treatment with a vaccine and another gets a placebo and the two groups' outcomes are compared are compared, can no longer be conducted because it would be unethical to withhold vaccination for people who are clearly recommended to have one. Only observational studies can now be conducted to determine vaccine effectiveness.

Useful Resources

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