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New Influenza Vaccines Approved for 2013-2014 Season

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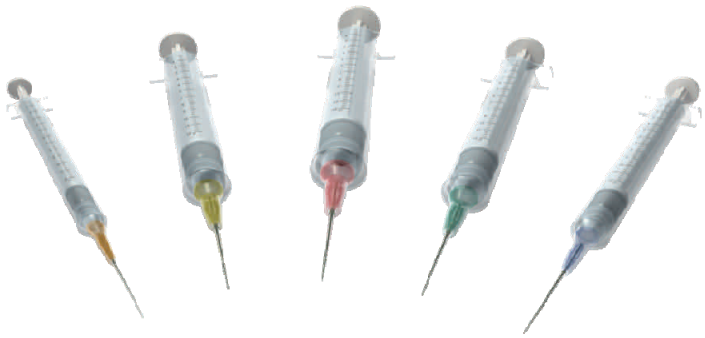
Each year in the United States the influenza virus causes a contagious respiratory illness ("the flu") with significant morbidity and mortality. People who become infected often have symptoms of fever, cough, sore throat, and/or malaise. Hospitalization is sometimes required, typically in patients who are older, very young, or have underlying medical conditions. Treatment options consist of antivirals that reduce the severity and length of symptoms caused by the virus. The best way to prevent influenza is vaccination. At the beginning of the 2012-2013 influenza season there were 9 influenza vaccines approved for use. Eight of them were trivalent inactivated (TIV) injectables and one was a live attenuated (LAIV) intranasal spray.[1]



Vaccine for those with egg allergies: Traditionally, flu vaccines were prepared by means of inoculation of the influenza virus into a chicken egg vehicle. Although rare, severe allergic and anaphylactic reactions can occur when these vaccines are used in patients with egg allergies. It is important to note that a mild egg allergy is no longer considered an absolute contraindication to immunization with TIVs prepared using egg vehicles. The Advisory Committee on Immunization Practices (ACIP) recommends administration of these TIVs in patients with a mild allergy to eggs (hives only) under appropriate precautions, including a post-administration observation of 30 minutes by a medical professional familiar with the potential manifestations of egg allergy who is trained to manage an anaphylactic reaction and has immediate access to emergency resuscitative equipment.[1] Currently, no studies have been conducted with the live attenuated influenza vaccine in patients reporting egg allergy, and it should not be used in patients with any egg allergy.[2] Patients who report reactions to eggs with symptoms of angioedema, respiratory distress, lightheadedness, or recurrent emesis; or who have required emergency medical intervention within minutes to hours of egg exposure, are more likely to have serious reactions upon reexposure to egg proteins. Severe egg allergy was thus a contraindication to the administration of all of the influenza vaccines approved in the U.S. at the onset of this past season.[1-2]

However, during the 2012-2013 flu season, Flucelvax® and Flublok® were both approved by the FDA as vaccines that are safe to use in patients with egg allergies. Each of these vaccines is prepared using a unique alternative to the inoculation of chicken eggs and contain no egg proteins.

Flublok® is prepared utilizing vector transfer to produce recombinant hemagglutinin (HA) proteins from three influenza viruses in an insect cell-line derived from cells of the fall armyworm, *Spodoptera frugiperda.*[3] Vector transfer of recombinant proteins from a virus and not the virus itself has been used to produce vaccines for prevention of other diseases, but is novel to approved influenza vaccines. Efficacy of Flublok® was demonstrated in a placebo controlled clinical trial conducted in the United States during the 2007-2008 influenza season with 4668 subjects between the age of 18 to 49. Subjects were randomized in a 1:1 ratio

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Table 1: Comparison influenza vaccine products that can be used in patients with severe egg allergy

	Manufacturing process	Influenza Strains Contained '12-13	Age (yrs)	Warnings/Precautions
Flucelvax®	Propagated from Madin Darby Canine Kidney cells	A/Brisbane/10/2010 (H1N1) A/Victoria/361/2011 IVR-165 (H3N2) B/Wisconsin/1/2010	18 - 49	Guillain-Barre Syndrome Latex allergy
Flublok®	Derived from Sf9 cells of the fall armyworm, *Spodoptera frugiperda*, and grown in serum free medium composed of chemically defined lipids, vitamins, amino acids, and mineral salts	A/California/7/2009 (H1N1) A/Victoria/361/2011 (H3N2) B/Wisconsin/1/2010	18 - 49	Guillain-Barre Syndrome

(Continued from page 1

to receive either a single dose of Flublok® or a placebo. Vaccine efficacy against antigenically matched culture confirmed cases could not be determined reliably because 96% of the influenza isolates obtained did not represent strains that were represented in the vaccine.[3] An expletory analysis of Flublok® against all strains regardless of antigenic match was determined to have an efficacy of 44.8%.[3]

Flucelvax® is prepared using Madin-Darby Canine Kidney (MDCK) cells as a host for the growing influenza virus. MDCK cells were chosen specifically because they are used in influenza research, have a broad susceptibility to the influenza virus, are capable of producing high yields, and are adaptable to serum free growth conditions.[4-5] Concern was raised about the possibility of MDCK cells being tumorigenic; however, these concerns were ruled mostly theoretical, and the product was deemed safe because the vaccine is inactivated and goes through multiple levels of purification. Approval was based on data from a clinical trial conducted in the United States and Europe involving 11,404 people 18 years to 49 years old.[4] Patients were randomized in a 1:1:1 ratio to receive Flucelvax®, Agriflu® (an egg-based seasonal influenza vaccine also produced by Novartis) or a placebo. Results from the trial showed that Flucelvax® was 83.8% effective in preventing influenza compared with placebo.[4]

In clinical trials, the most commonly reported adverse events associated with both vaccinations were injection site pain and redness, headache, and malaise.[3-4] The symptoms were always mild and always resolved within a couple of days. With Flucelvax®, there was one adverse event of hypersensitivity and one case of erythema multiforme but both conditions responded to treatment and neither was severe enough to require hospitalization.[4] With Flublok®, a single case of pleuropericarditis with effusions that required hospitalization and drainage was reported in the clinical trials.[3] Further studies for both vaccinations are being conducted in the pediatric population.

New Quadrivalent Influenza vaccines: Also in 2012, the FDA approved two new quadrivalent influenza vaccines. One is an inactivated vaccine called Fluarix®.[6] The other is replacing the previous formulation of the trivalent LAIV Flumist®, and will carry the name Flumist Quadrivalent®.[1] The quadrivalent vaccine was developed because it is difficult to predict which strain of influenza type B will circulate. It is estimated that from the 2004 through the 2010 -11 seasons, influenza B has accounted for 22 to 44 percent of the reported influenza deaths in children up to 18 years of age and 34% overall.[7] The hope is to prevent this problem by including the following antigens in the vaccine: two influenza A viruses (H1N1 and H3N2) and two influenza B viruses. Analyses suggest that if a quadrivalent vaccine had been available a decade earlier in the United States there may have been 2.1 million fewer cases of influenza, 20,000 fewer hospitalizations, and 1,200 fewer deaths.[7]

Fluarix® is approved for active immunization in people 3 years of age and over. The dosing and administration of the Fluarix® vaccine depends on the patient's age and past vaccination status. Patients who are age 3 to 8 and have not been previously vaccinated with influenza vaccine should receive two 0.5 mL doses at least four weeks apart. If they have received a vaccination in the past they can receive one or two doses.[6] Patients 9 years and older, regardless of past vaccination history should receive only one dose.[6] This vaccine carries the same contraindications as previous influenza vaccinations and should not be used in patients with a history of severe allergic reactions to any component of the vaccine and including egg protein.

It is anticipated that the quadrivalent formulation of the LAIV, Flumist® will replace the trivalent formulation for the 2013-2014 season. It continues to carry the same indication and recommended dosage as the trivalent formulation for use in healthy, non-pregnant persons aged 2 through 49 years. Persons who care for severely immunosuppressed persons who require a protective environment should not receive FluMist® given the theoretical risk of transmission of the live, attenuated vaccine virus.[8] FluMist® currently has no clinical data for use in patients with egg allergy, mild or severe, and it should not be used.

<Click for References>

Pertussis Vaccine Resistance Emerging in the U.S.

Michael Golding, PharmD Candidate; Katherine Tromp, PharmD

Pertussis, an illness characterized by a whooping cough, is caused by the bacteria *Bordetella Pertussis*. The disease frequently affects young children and infants. In the pre-vaccine era, pertussis was very common and a major cause of childhood mortality in the United States. Since the institution of routine childhood vaccinations, the incidence of pertussis has reduced from 150 reported cases per 100,000 persons in 1940, to a low of 0.5 per 100,000 in 1976.[1] Since the 1980's, the incidence of the disease has gradually increased to 13.3 cases per 100,000 in 2012, the highest total since 1955.[2]

One explanation for the increasing prevalence of pertussis is the adaptation of the bacteria due to vaccine selection pressure. A mutated, pertactin-negative *B. pertussis* strain has been reported in other countries such as France, Finland, and Japan.[3] Pertactin is one of many antigenic components used in the current pertussis vaccine. Pertactin is a protein that helps *B. pertussis* attach to the lining of the airways. Pertactin-negative *B. pertussis* strains have been found to have similar lethality and transmissibility compared to traditional strains. A letter published in the New England Journal of Medicine in February shows the first known occurrence of pertactin-negative *B. pertussis* strains in the United States.[4] In the letter, researchers analyzed the pertactin genes in 12 isolates of *B. pertussis* cultured from children hospitalized in Philadelphia during 2011 and 2012. By the use of Western blotting, they found that 11 of the 12 isolates did not contain the pertactin protein. Pulsed-field gel electrophoresis showed multiple mutations to the gene encoding pertactin, resulting in non-expression of the protein. It was concluded that further research is needed in different geographical regions throughout the United States to determine if their findings are local, or if a more widespread shift in *B. pertussis* strains has occurred.

It is important to note that of the 12 *B. pertussis* isolates in the report, only two were collected from patients greater than 6 months of age; therefore many of the subjects were unvaccinated or under-vaccinated. Because of this, it is unknown if pertactin-negative *B. pertussis* is more likely to cause disease in individuals who are fully vaccinated. Although the report confirms that pertactin-negative *B. pertussis* variants are now in the United States, it remains to be seen whether this is a major cause of the increasing incidence of infection.

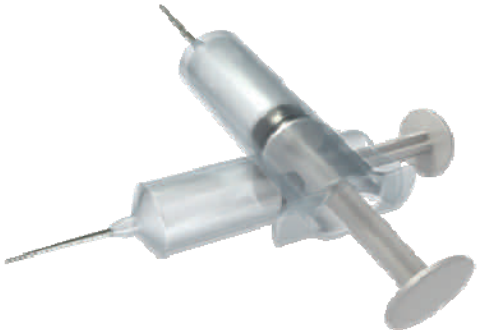
The Center for Disease Control (CDC) has acknowledged these findings. They report that other factors such as increased reporting, awareness, recognition by clinicians, better lab diagnostic testing, and the vaccine formulation change from whole cell to acellular in the 1990's are mainly responsible for the increasing incidence. The CDC also reports that the pertussis vaccine remains effective against the pertactin-negative variants because it contains other components that produce an immune response. In addition to pertactin, the current acellular pertussis vaccines also contain combinations of inactivated pertussis toxin (PT), filamentous hemagglutinin, and fimbriae, each of which can produce an immune response.[3] They conclude that the vaccine continues to be a safe and effective tool in the prevention of pertussis infections.

<Click here for references>

Updated Recommendations for Tdap Vaccination in Pregnancy

Edward McLean, PharmD Candidate; Marcus Campbell, PharmD

According to the data from the Center for Disease Control (CDC) on communicable diseases, the incidence of pertussis cases has been increasing over the past several years, most notably among the infant population.[1] In order to combat this rising trend, The Advisory Committee on Immunization Practices (ACIP) revised and produced new guidelines for Tetanus, Diphtheria, and Pertussis (Tdap) vaccinations in women who are pregnant. ACIP recommendations are based on scientific data which supports the contention that maternal antibodies produced after Tdap administration will protect infants post-partum until the time they are able to receive the proper immunizations.[2]



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ACIP Recommendations for Pregnant Women[2]:

Tdap immunization programs should be initiated and implemented by health care specialists who provide prenatal care to pregnant women. Tdap immunization should be administered during every pregnancy, regardless of prior vaccination history.

Guidance for Use: Ideally, the Tdap immunization should be administered between 27-36 weeks gestation. However, it may be given at any point during gestation. Postpartum administration should occur immediately in those patients not receiving the vaccination during their pregnancy.

Wound management for pregnant women: Toxoid containing vaccine might be recommended for wound management in pregnant patients who have been without a Td booster for five years.

Pregnant women with unknown or incomplete tetanus vaccination: Three dose series containing tetanus and reduced diphtheria toxoids is recommended for pregnant women with an unknown or incomplete tetanus vaccination history. Tdap should replace one of the Td doses, optimally occurring during the 27-36th week of gestation.

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