Clinical Policy Bulletin: Influenza Vaccine

Number: 0035

Policy

Aetna considers standard or preservative-free injectable influenza vaccine a medically necessary preventive service for members when influenza immunization is recommended by the member's doctor.

Aetna considers high-dose injectable influenza vaccine (Fluzone High-Dose) a medically necessary preventive service for members age 65 years of age or older when influenza immunization is recommended by the member's doctor.

Aetna considers intradermal influenza vaccine a medically necessary preventive service for members 18 to 64 years of age when influenza immunization is recommended by the member's doctor.

Aetna considers intradermal influenza vaccine experimental and investigational for all other indications because its effectiveness for indications other than the one listed above has not been established.

Aetna considers intranasally administered influenza vaccine a medically necessary alternative to injectable influenza vaccine for immunocompetent healthy persons 2 to 49 years of age when influenza immunization is recommended by the member's doctor.

Aetna considers intranasally administered influenza vaccine experimental and investigational for persons younger than 2 years of age or older than 49 years of age and for other persons considered at increased risk for influenza or its complications. The safety and efficacy of intranasally administered influenza vaccine for persons at high risk for influenza and its complications have not been established. Intranasally administered influenza vaccine is contraindicated in autologous and allogeneic hematopoietic cell transplant recipients, and is considered experimental and investigational in these persons.

See also CPB 0476 - Influenza Rapid Diagnostic Tests.

Background

Influenza viruses ("the flu") infect the respiratory tract. Symptoms include fever, cough, sore throat, runny or stuffy nose, headache, muscle aches, and extreme fatigue. Influenza viruses continually change over time,
and each year the vaccine is updated to include the viruses that are most likely to circulate in the upcoming influenza season.

In the United States (U.S.), flu season usually peaks between late December and early March. The best time to be vaccinated against influenza is from October through mid-November. However, influenza vaccination can be taken at any time during the season. Pneumococcal and influenza vaccinations may be given simultaneously when both are required. Children may be given influenza vaccine at the same time as routine pediatric immunizations; however, vaccines should be given at different sites.

The Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) recommends annual influenza immunization for persons aged 6 months and older beginning with the 2010 to 2011 influenza season. Prior to the expanded recommendations for the 2010 to 2011 influenza season, ACIP's recommendations for seasonal influenza vaccination had focused on vaccination of persons who have a higher risk for influenza complications. These higher risk persons should continue to be a primary focus for vaccination as providers transition to routinely vaccinating all persons 6 months of age and older. Higher risk individuals include:

1. Children aged 6 months up to their 5th birthday; or
2. Children aged 6 months up to their 19th birthday who are receiving long-term aspirin therapy and who therefore might be at risk for experiencing Reye syndrome after influenza virus infection; or
3. Health-care personnel; or
4. Household contacts and caregivers of children younger than 5 years of age and adults 50 years of age or older, with emphasis on vaccinating contacts of children younger than 6 months of age; or
5. Household contacts and caregivers of persons with medical conditions that put them at high risk for severe complications from influenza; or
6. Persons 50 years of age or older; or
7. Persons who are American Indians/Alaska natives; or
8. Persons who are immunosuppressed (including immunosuppression caused by medications or by human immunodeficiency virus); or
9. Persons who are morbidly obese (body-mass index of 40 or greater); or
10. Persons who have any condition that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders); or
11. Persons who have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological or metabolic disorders (including diabetes mellitus); or
12. Residents of nursing homes and other chronic care facilities; or
13. Women who will be pregnant during the influenza season.

Children younger than 6 months of age should not receive influenza vaccination.

It takes 1 to 2 weeks after receiving the vaccination for protective antibodies to form. Influenza vaccines are 70 to 90% effective in preventing influenza among healthy adults. Among elderly persons or people with chronic conditions, the vaccine may be less effective in preventing disease than in preventing serious complications and death.

Children less than 9 years of age who have not been vaccinated previously should receive 2 doses of live attenuated (if age appropriate) or trivalent inactivated influenza vaccine (TIV). Children who received only 1 dose of a seasonal influenza vaccine in the first influenza season that they received the vaccine should receive 2 doses, rather than 1, in the following influenza season. In addition, for the 2010 to 2011 influenza season, children 6 months to 9 years of age who did not receive at least 1 dose of an influenza A (H1N1) 2009 monovalent vaccine should receive 2 doses of a 2010 to 2011 seasonal influenza vaccine, regardless
of previous influenza vaccination history. For all children, the second dose of a recommended 2-dose series should be administered 4 weeks or more after the initial dose (ACIP, 2010).

Only the subvirion or purified surface-antigen vaccines, i.e., those termed "split-virus" vaccines, should be administered to children younger than 13 years of age. The whole-virus vaccines are associated with higher rates of adverse effects in young children.

Split-virus vaccine is recommended for children younger than 12 years of age; the recommended vaccine dose is 0.25 ml for children aged 6 to 35 months and 0.5 ml for children aged greater than 3 years. Children less than 9 years of age who have not been vaccinated previously should receive 2 doses of vaccine at least 1 month apart. A 0.5-ml dose of whole or split-virus vaccine is recommended for adolescents and adults.

Influenza vaccine should not be administered to persons with anaphylactic hypersensitivity to eggs or egg products.

The FDA has approved a nasal-spray influenza vaccine (FluMist) jointly developed by MedImmune Vaccines Inc. and Wyeth Vaccines. The nasal-spray influenza vaccine is a made from a cold-adapted live attenuated virus that is sprayed as an aerosol from a syringe into both nostrils. The FDA originally approved the nasal-spray influenza vaccine only for healthy people ages 5 to 49 years of age, a group for whom influenza vaccination is considered elective. On September 19, 2007, the FDA approved expanding the population for use of the nasal influenza vaccine FluMist to include children between the ages of 2 and 5 years. The FDA currently recommends that individuals considered at high risk for severe cases of the illness -- including those older than age 50, infants ages 6 to 23 months, and patients with chronic conditions such as asthma or diabetes -- continue to receive the injectable version of the vaccine.

The Advisory Committee on Immunization Practices (ACIP) (CDC, 2003) has concluded that nasal-spray influenza vaccine is an acceptable option for persons at average risk for influenza. The ACIP has stated that persons at high risk of influenza should not be immunized with the nasal-spray influenza vaccine. Clinical studies are currently underway to assess the safety and effectiveness of this live attenuated virus vaccine in persons at increased risk of influenza.

Administration of vaccine via aerosol avoids local soreness from injection. Nasal-spray influenza vaccine, however, is derived from a live attenuated virus and is associated with an increased incidence of upper respiratory symptoms (sore throat, rhinitis, cough) following administration (MedImmune, 2003).

Preservative-free influenza vaccine (e.g., FluZone, Aventis Pasteur, Inc. Swiftwater, PA; Afluria, CSL Biotherapies, King of Prussia, PA) does not contain the thimerosal, a mercury-containing preservative. Standard thimerosal-preserved influenza vaccines contain trace amounts of mercury (AAP, 2003). The American Academy of Pediatrics, the American Academy of Family Physicians, the Advisory Committee on Immunization Practices and the U.S. Public Health Service has issued a joint statement advising the removal of thimerosal-containing vaccines from vaccines routinely recommended for infants (AAP, 2000). The joint statement explains that "[w]hile there was no evidence of any harm caused by low levels of thimerosal in vaccines and the risk was only theoretical, this goal was established as a precautionary measure. There is public concern about the health effects of mercury exposure of any sort, and the elimination of mercury from vaccines was judged a feasible means of reducing an infant’s total exposure to mercury in a world where other environmental sources of exposure are more difficult or impossible to eliminate (e.g., certain foods)." Other persons who are sensitive to thimerosal should avoid vaccines containing this preservative. Furthermore, the U.S. Public Health Service recommended efforts be made to eliminate or reduce the thimerosal content in vaccines as part of an over-all strategy to reduce mercury exposures from all sources and ACIP and other federal agencies and professional medical organizations continue to support efforts to provide thimerosal preservative-free vaccine options (ACIP, 2008).
Influenza Vaccine

The American College of Obstetricians and Gynecologists and the American Academy of Family Physicians recommend routine vaccination of all pregnant women. No preference is indicated for use of TIV that does not contain thimerosal as a preservative for any group recommended for vaccination, including pregnant women. Live, attenuated influenza vaccine (LAIV) is not licensed for use in pregnant women (ACIP, 2008).

Nichol and colleagues (2007) examined the effectiveness of influenza vaccine in seniors over the long-term. Data were pooled from 18 cohorts of community-dwelling elderly members of 1 U.S. health maintenance organization (HMO) for 1990 to 1991 through 1999 to 2000 and of 2 other HMOs for 1996 to 1997 through 1999 to 2000. Logistic regression was used to estimate the effectiveness of the vaccine for the prevention of hospitalization for pneumonia or influenza and death after adjustment for important co-variates. Additional analyses explored for evidence of bias and the potential effect of residual confounding. There were 713,872 person-seasons of observation. Most high-risk medical conditions that were measured were more prevalent among vaccinated than among unvaccinated persons. Vaccination was associated with a 27% reduction in the risk of hospitalization for pneumonia or influenza (adjusted odds ratio, 0.73; 95% confidence interval [CI]: 0.68 to 0.77) and a 48% reduction in the risk of death (adjusted odds ratio, 0.52; 95% CI: 0.50 to 0.55). Estimates were generally stable across age and risk subgroups. In the sensitivity analyses, these researchers modeled the effect of a hypothetical unmeasured confounder that would have caused over-estimation of vaccine effectiveness in the main analysis; vaccination was still associated with statistically significant -- though lower -- reductions in the risks of both hospitalization and death. The authors concluded that during 10 seasons, influenza vaccination was associated with significant reductions in the risk of hospitalization for pneumonia or influenza and in the risk of death among community-dwelling elderly persons. They noted that vaccine delivery to this high-priority group should be improved.

In an editorial that accompanied the afore-mentioned study, Treanor (2007) stated that these findings support the current policy of vaccinating the elderly but also demonstrate that the inactivated influenza vaccine is by itself a relatively mediocre means for controlling flu in this population. Until more immunogenic vaccines are developed, routine vaccination of children as well as health care workers could limit transmission and play an important role in controlling the development of influenza in the elderly.

A high dose seasonal influenza vaccine specifically intended for people aged 65 and older was approved by the FDA on December 23, 2009. Fluzone High-Dose (Sanofi Pasteur Inc.) was approved via the FDA’s accelerated approval pathway. It contains 4 times the total amount of virus hemagglutinin (180 mcg) found in other seasonal vaccines. The higher-dose formulation is based on the theory that immune functions weaken with age and that the elderly are especially vulnerable to complications from seasonal influenza. In clinical studies, Fluzone High-Dose demonstrated an enhanced immune response compared with Fluzone in individuals aged 65 and older. Common side effects were more frequent with the high-dose than with regular-dose formulations, but the rate of serious adverse events was no higher. Since the product received accelerated approval, the manufacturer must conduct further studies to verify the higher efficacy of the vaccine among older people (FDA, 2009). The Centers for Disease Control and Prevention (CDC) and its Advisory Committee on Immunization Practices (ACIP) have not expressed a preference for any flu vaccine indicated for people 65 and older (CDC, 2014).

There is evidence to suggest that influenza vaccination improves the clinical course of coronary artery disease (CAD) and reduces the frequency of coronary ischemic events. In a randomized, double-blind, placebo-controlled trial, Ciszewski et al (2008) assessed the effect of influenza vaccination on the coronary events in patients with confirmed CAD. This study included 658 optimally treated CAD patients (477 men, mean age of 59.9 +/- 10.3 years). A total of 325 patients received the influenza vaccine, and 333 patients received a placebo. Median follow-up was 298 days (inter-quartile range of 263 to 317). Primary end-point was cardiovascular death. Its estimated 12-month cumulative event rate was 0.63% in the vaccine versus 0.76% in controls (HR 1.06; 95% CI: 0.15 to 7.56, p = 0.95). There were 2 secondary composite endpoints: (i) the MACE (cardiovascular death, myocardial infarction, coronary re-vascularization) tended to
occur less frequently in the vaccine group versus placebo with the event rate 3.00 % and 5.87 %, respectively (HR 0.54; 95 % CI: 0.24 to 1.21, p = 0.13), (ii) coronary ischemic event (MACE or hospitalization for myocardial ischemia) estimated 12-month event rate was significantly lower in the vaccine group 6.02 % versus 9.97 % in controls (HR 0.54; 95 % CI: 0.29 to 0.99, p = 0.047). The authors concluded that in optimally treated CAD patients, influenza vaccination improves the clinical course of CAD and reduces the frequency of coronary ischemic events. They stated that large-scale studies are needed to evaluate the effect of influenza vaccination on cardiovascular mortality.

A Cochrane review concluded that despite the significant effects noted in available randomized controlled clinical trials, that there are not enough data to evaluate the effect of influenza vaccination on coronary heart disease (Keller et al, 2008).

Maternal influenza immunization is a strategy with substantial benefits for both mothers and infants. Zaman et al (2008) evaluated the clinical effectiveness of inactivated influenza vaccine administered during pregnancy in Bangladesh. In this randomized study, a total of 340 mothers were assigned to receive either inactivated influenza vaccine (influenza-vaccine group) or the 23-valent pneumococcal polysaccharide vaccine (control group). Mothers were interviewed weekly to assess illnesses until 24 weeks after birth. Subjects with febrile respiratory illness were assessed clinically, and ill infants were tested for influenza antigens. These researchers estimated the incidence of illness, incidence rate ratios, and vaccine effectiveness. Mothers and infants were observed from August 2004 through December 2005. Among infants of mothers who received influenza vaccine, there were fewer cases of laboratory-confirmed influenza than among infants in the control group (6 cases and 16 cases, respectively), with a vaccine effectiveness of 63 % (95 % CI: 5 to 85). Respiratory illness with fever occurred in 110 infants in the influenza-vaccine group and 153 infants in the control group, with a vaccine effectiveness of 29 % (95 % CI: 7 to 46). Among the mothers, there was a reduction in the rate of respiratory illness with fever of 36 % (95 % CI: 4 to 57). The authors concluded that inactivated influenza vaccine reduced proven influenza illness by 63 % in infants up to 6 months of age and averted about one-third of all febrile respiratory illnesses in mothers and young infants.

According to the CDC, H1N1 (swine flu) is an influenza virus that was first detected in people in the U.S. in April 2009. It spreads from person-to-person in much the same way that regular seasonal influenza viruses spread (i.e., through coughing or sneezing by people with influenza). This virus was originally referred to as “swine flu” because laboratory testing showed that many of the genes in this new virus were very similar to influenza viruses that normally occur in pigs (swine) in North America. However, studies have shown that this new virus is very different from what normally circulates in North American pigs. It has two genes from flu viruses that normally circulate in pigs in Europe and Asia as well as genes from bird (avian) flu and human influenza strains. It is referred to as a “quadruple reassortant" virus. Symptoms are similar to seasonal influenza (e.g., fever and chills, cough, sore throat, muscle aches, headache, and extreme fatigue). The CDC, however, reported that there is little 2009 H1N1 virus currently circulating in the U.S. and the Department of Health and Human Services has declared the end of the H1N1 influenza public health emergency as of June 23, 2010. With 2009 H1N1, approximately 90 % of estimated hospitalizations and 87 % of estimated deaths from April 2009 through January 16, 2010 occurred in people younger than age 65 years. In contrast, with seasonal influenza, about 60 % of seasonal flu-related hospitalizations and 90 % of flu-related deaths occur in people aged 65 years and older. These data confirm that the 2009 H1N1 impacted younger adults and children more than older adults compared to seasonal flu. However, people in all age groups can develop severe illness from either seasonal flu or from 2009 H1N1.

Guidelines for preventing infections in hematopoietic cell transplant (HCT) recipients by the Center for International Blood and Marrow Transplant Research, National Marrow Donor Program, European Group for Blood and Marrow Transplantation, American Society for Blood and Marrow Transplantation, Canadian Blood and Marrow Transplant Group, Infectious Diseases Society of America, Society for Healthcare
Epidemiology of America, Association of Medical Microbiology and Infectious Disease, and the CDC (Ljungman et al, 2009) indicated that intranasal influenza vaccine (live) should not be given to HCT recipients since an effective, inactivated alternative exist.

Available evidence shows that two doses of influenza vaccine does not improve antibody response in persons with hematologic malignancies. In a randomized controlled study (n = 70), Ljungman and associates (2005) examined if 2 doses of influenza vaccine were more effective than one to elicit an immune response in patients with hematological malignancies. These investigators found that responses were not improved by 2 doses compared with 1 (influenza A virus serotypes H1/N1 18 % versus 22 % and H3/N2 26 % versus 14 %; influenza B 25 % versus 22 %). The results were similar in patients with ongoing and discontinued therapy. Patients treated with monoclonal antibodies for lymphoma had very poor responses. These researchers concluded that 2 doses of influenza vaccine do not improve the antibody response in patients with hematological malignancies.

Frenck and colleagues (2011) examined if reduced doses of trivalent inactivated influenza vaccine (TIV) administered by the intradermal (ID) route generated similar immune responses to standard TIV given intramuscularly (IM) with comparable safety profiles. Recent changes in immunization recommendations have increased the number of people for whom influenza vaccination is recommended. Thus, given this increased need and intermittent vaccine shortages, means to rapidly expand the vaccine supply are needed. Previously healthy subjects 18 to 64 years of age were randomly assigned to 1 of 4 TIV vaccine groups: standard 15 μg HA/strain TIV IM, either 9 μg or 6 μg HA/strain of TIV ID given using a new microinjection system (BD Soluvia™ Microinjection System(1)), or 3 μg HA/strain of TIV ID given by Mantoux technique. All vaccines contained A/New Caledonia (H1N1), A/Wyoming (H3N2) and B/Jiangsu strains of influenza. Sera were obtained 21 days after vaccination and hemagglutination inhibition (HAI) assays were performed and geometric mean titers (GMT) were compared among the groups. Subjects were queried immediately following vaccination regarding injection pain and quality of the experience. Local and systemic reactions were collected for 7 days following vaccination and compared. A total of 10 study sites enrolled 1,592 subjects stratified by age; 18 to 49 years (n = 814) and 50 to 64 years (n = 778). Among all subjects, for each of the 3 vaccine strains, the GMTs at 21 days post-vaccination for both the 9 μg and the 6 μg doses of each strain given ID were non-inferior to GMTs generated after standard 15 μg doses/strain IM. However, for the 3 μg ID dose, only the A/Wyoming antigen produced a GMT that was non-inferior to the standard IM dose. Additionally, in the subgroup of subjects 50 to 64 years of age, the 6 μg dose given ID induced GMTs that were inferior to the standard IM TIV for the A/H1N1 and B strains. No ID dose produced a GMT superior to that seen after standard IM TIV. Local erythema and swelling were significantly more common in the ID groups but the reactions were mild-to-moderate and short-lived. No significant safety issues related to intradermal administration were identified. Participants given TIV ID provided favorable responses to questions about their experiences with ID administration. The authors concluded that for the aggregated cohorts of adults 18 to 64 years of age, reduced doses (6 μg and 9 μg) of TIV delivered ID using a novel microinjection system stimulated comparable HAI antibody responses to standard TIV given IM. The reduced 3 μg dose administered ID by needle and syringe, as well as the 6 μg ID for subjects aged 50 to 64 years of age generated poorer immune responses as compared to the 15 μg IM dose.

On May 11, 2011, the FDA approved Sanofi Pasteur's supplemental Biologics License Application for licensure of Fluzone Intradermal (Influenza Virus Vaccine). Fluzone intradermal vaccine is indicated for active immunization of adults 18 through 64 years of age against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

In 2011, the ACIP provided the following recommendations regarding influenza vaccination of individuals with egg allergies:
I. Individuals who have experienced only hives may receive influenza vaccine with the following additional measures:

A. As studies published to date involved the use of trivalent inactivated influenza vaccine (TIV), TIV rather than LAIV should be used;
B. Vaccine should be administered by a healthcare provider who is familiar with the subject of egg allergy;
C. Vaccine recipients should be observed for at least 30 minutes for signs for a reaction following administration of each vaccine dose.

II. Other measures, such as dividing and administering the vaccine by a 2-step approach and skin testing with vaccine are not necessary.

III. Egg allergy may be confirmed by a consistent medical history of adverse reactions to eggs and egg-containing foods, plus a skin and/or blood testing for IgE antibodies to egg proteins.

In 2012, the US Food and Drug Administration approved quadrivalent formulations of both the live-attenuated influenza vaccine and the inactivated influenza vaccine; these vaccines contain two strains of influenza A virus and two strains of influenza B virus (Hibberd, 2012). Fluarix Quadrivalent is a vaccine indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. It is approved for use in persons 3 years of age and older. Safety has not been established in pregnant women or nursing mothers. (FDA, 2013).

On January 16, 2013 the FDA approved Flublok in individuals aged 18 through 49 for active immunization against disease caused by influenza virus. Flublok is the first trivalent influenza vaccine made using an insect virus (baculovirus) expression system and recombinant DNA technology. Flublok's manufacturing technology allows for production of large quantities of the influenza virus protein, hemagglutinin (HA), the active ingredient in all inactivated influenza vaccines that is essential for entry of the virus into cells of the body. Flublok contains three, full-length, recombinant HA proteins to help protect against two influenza virus A strains, H1N1 and H3N2, and one influenza virus B strain (FDA, 2013). Fluzone Quadrivalent received FDA approval on June 7, 2013. Fluzone received approval for active immunization of persons 6 months of age and older for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine (FDA, 2013c). Flumist Quadrivalent received FDA approval on February 29, 2013 for active immunization of individuals 2 through 49 years of age for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine (FDA, 2013b).

In a June 19-20, 2013 meeting, ACIP voted and unanimously approved language changes to the vaccine safety update to state that “for individuals who have no known history of exposure to egg but who are suspected of being egg-allergic on the basis of previously performed allergy testing, use of RIV3 or consultation with a physician with expertise in the management of allergic conditions should be obtained prior to vaccination. If the patient only experiences hives after ingestion of egg, administer RIV3 (FluBlok) if the patient is aged 18 to 49 years or administer a inactivated influenza vaccine (IIV) of choice and observe for at least 30 minutes following vaccination. If more severe reactions have been noted with eggs administer RIV3 (FluBlok) or refer to a clinician with expertise in allergic reaction” (Lardy et al, 2013).

The CDC’s ACIP and the American College of Obstetricians and Gynecologists (2014) recommend that all adults receive an annual influenza vaccine. Influenza vaccination is an essential element of pre-conception, pre-natal, and post-partum care because pregnant women are at an increased risk of serious illness due to seasonal and pandemic influenza. Since 2010, influenza vaccination rates among pregnant women have increased but still need significant improvement. It is particularly important that women who are or will be
pregnant during influenza season receive an inactivated influenza vaccine as soon as it is available. It is critically important that all obstetrician-gynecologists and all providers of obstetric care advocate for influenza vaccination, provide the influenza vaccine to their pregnant patients, and receive the influenza vaccine themselves every season. It is imperative that obstetrician-gynecologists, other health care providers, health care organizations, and public health officials continue efforts to improve the rate of influenza vaccination among pregnant women.

Madhi et al (2014) conducted 2 double-blind, randomized, placebo-controlled trials of trivalent IIV (IIV3) in South Africa during 2011 in pregnant women infected with HIV and during 2011 and 2012 in pregnant women who were not infected. The immunogenicity, safety, and efficacy of IIV3 in pregnant women and their infants were evaluated until 24 weeks after birth. Immune responses were measured with a HAI assay, and influenza was diagnosed by means of reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assays of respiratory samples. The study cohorts included 2,116 pregnant women who were not infected with HIV and 194 pregnant women who were infected with HIV. At 1 month after vaccination, seroconversion rates and the proportion of participants with HAI titers of 1:40 or more were higher among IIV3 recipients than among placebo recipients in both cohorts. Newborns of IIV3 recipients also had higher HAI titers than newborns of placebo recipients. The attack rate for RT-PCR-confirmed influenza among both HIV-uninfected placebo recipients and their infants was 3.6 %. The attack rates among HIV-uninfected IIV3 recipients and their infants were 1.8 % and 1.9 %, respectively, and the respective vaccine-efficacy rates were 50.4 % (95 % CI: 14.5 to 71.2) and 48.8 % (95 % CI: 11.6 to 70.4). Among HIV-infected women, the attack rate for placebo recipients was 17.0 % and the rate for IIV3 recipients was 7.0 %; the vaccine-efficacy rate for these IIV3 recipients was 57.7 % (95 % CI: 0.2 to 82.1). The authors concluded that influenza vaccine was immunogenic in HIV-uninfected and HIV-infected pregnant women and provided partial protection against confirmed influenza in both groups of women and in infants who were not exposed to HIV.

In a systematic review, Prutsky and colleagues (2014) evaluated the evidence on LAIV in children younger than 2 years. These investigators searched Medline, EMBASE, the Cochrane Library, Web of Science, Scopus, PsycInfo and CINAHL through February 2013 for existing systematic reviews, randomized controlled trials (RCTs) and observational studies (for safety). They included studies enrolling healthy children less than 2 years of age who received LAIV, compared with placebo or IIV. Data were extracted independently by 2 investigators. The relative risk (RR) was pooled across studies using the random effects model. These researchers found 7 eligible RCTs and 2 observational studies. Randomized controlled trials included 6,281 children and were at low-to-moderate risk of bias. Live attenuated influenza vaccine reduced the incidence of influenza compared with placebo (RR = 0.36, 95 % CI: 0.23 to 0.58, p < 0.05) with a number needed to vaccinate of 17. Live attenuated influenza vaccine increased the incidence of minor side effects (fever and rhinorrhea); it had a similar effect in preventing influenza (RR = 0.76, 95 % CI: 0.45 to 1.30, p > 0.05) compared with IIV. There was an increase of hospitalization rate (post-hoc analysis) and medical attended wheezing with LAIV. The authors concluded that LAIV is highly effective in children less than 2 years of age compared with placebo and is as effective to IIV. The safety profile of LAIV is reasonable although evidence is sparse. They stated that LAIV may be considered as an option in this age group particularly during seasons with vaccine shortage.

In a Cochrane review, Dharmaraj and Smyth (2014) evaluated the effectiveness of influenza vaccination for people with cystic fibrosis (CF). These investigators searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register which comprises of references identified from comprehensive electronic database searches and hand-searching of relevant journals and abstract books of conference proceedings. They also contacted the companies which market the influenza vaccines used in the trials to obtain further information about RCTs. Date of the most recent search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register: July 8, 2013. All randomized and quasi-randomized trials (published or unpublished) comparing any influenza vaccine with a placebo or with another type of influenza vaccine were selected for analysis. Two authors independently assessed study quality and extracted data.
Additional information was obtained by contacting the investigators when it was indicated. A total of 4 studies enrolling a total of 179 participants with CF (143 (80 %) were children aged 1 to 16 years) were included in this review. There was no study comparing a vaccine to a placebo or a whole virus vaccine to a subunit or split virus vaccine. Two studies compared an intra-nasal applied live vaccine to an intra-muscular inactivated vaccine and the other 2 studies compared a split virus to a subunit vaccine and a virosome to a subunit vaccine (all intra-muscular). The incidence of all reported adverse events was high depending on the type of influenza vaccine. The total adverse event rate ranged from 48 out of 201 participants (24 %) for the intra-nasal live vaccine to 13 out of 30 participants (43 %) for the split virus vaccine. With the limitation of a statistical low power there was no significant difference between the study vaccinations. None of the events was severe. All study influenza vaccinations generated a satisfactory serological antibody response. No study reported other clinically important benefits. The authors concluded that there is currently no evidence from randomized studies that influenza vaccine given to people with CF is of benefit to them. They stated that there remains a need for a well-constructed clinical study, that assesses the effectiveness of influenza vaccination on important clinical outcome measures.

**CPT Codes / HCPCS Codes / ICD-9 Codes**

**CPT codes covered if selection criteria are met:**

90630  Influenza virus vaccine, quadrivalent (IIV4), split virus, preservative free, for intradermal use

90653  Influenza vaccine, inactivated, subunit, adjuvanted, for intramuscular use

90654  Influenza virus vaccine, trivalent (IIV3), split virus, preservative-free, for intradermal use

90655  Influenza virus vaccine, split virus, preservative free, when administered to children 6-35 months of age, for intramuscular use

90657  Influenza virus vaccine, split virus, when administered to children 6-35 months of age, for intramuscular use

90658  Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use

90660  Influenza virus vaccine, live, for intranasal use

90661  Influenza virus vaccine, derived from cell cultures, subunit, preservative and antibiotic free, for intramuscular use

90662  Influenza virus vaccine, split virus, preservative free, enhanced immunogenicity via increased antigen content, for intramuscular use

90672  Influenza virus vaccine, quadrivalent, live, for intranasal use

90673  Influenza virus vaccine, trivalent, derived from recombinant DNA (RIV3), hemagglutinin (HA) protein only, preservative and antibiotic free, for intramuscular use

90685 - 90688  Influenza virus vaccine, quadrivalent, split virus
Other CPT codes related to the CPB:

87275  Infectious agent antigen detection by immunoflourescent technique; influenza B virus
87276  influenza A virus
87400  Infectious agent antigen detection by enzyme immunoassay technique, qualitative or semi quantitative, multiple step method; influenza A or B, each
90460  Immunization administration through 18 years of age via any route of administration with counseling by physician or other qualified health care professional; first or only component of each vaccine or toxoid administered
90461  Immunization administration through 18 years of age via any route of administration, with counseling by physician or other qualified health care professional; each additional vaccine or toxoid component (list separately in addition to code for primary procedure)
90471  Immunization administration (includes percutaneous, intradermal, subcutaneous, intramuscular injections); one vaccine (single or combination vaccine/toxoid)
+ 90472   each additional vaccine (single or combination vaccine/toxoid) (List separately in addition to code for primary procedure)
90473  Immunization administration by intranasal or oral route: one vaccine (single or combination vaccine/toxoid)
+ 90474   each additional vaccine (single or combination vaccine/toxoid) (List separately in addition to code for primary procedure)
90664  Influenza virus vaccine. pandemic formulation, live, for intranasal use
90666  Influenza virus vaccine, pandemic formulation, split virus, preservative free, for intramuscular use
90667  Influenza virus vaccine, pandemic formulation, split virus, adjuvanted, for intramuscular use
90668  Influenza virus vaccine, pandemic formulation, split virus, for intramuscular use

HCPCS codes covered if selection criteria are met:

G0008  Administration of influenza virus vaccine
J3530  Nasal vaccine inhalation
Q2034  Influenza virus vaccine, split virus, for intramuscular use (agriflu)
Q2035  Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (Afluria)
Q2036  Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (Flulaval)
Q2037  Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (Fluvirin)

Q2038  Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (Fluzone)

Q2039  Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (not otherwise specified)

ICD-9 codes covered if selection criteria are met:

V04.81  Need for prophylactic vaccination and inoculation against influenza

Other ICD-9 codes related to the CPB:

042  Human immunodeficiency virus [HIV] disease

250.00 - 250.93  Diabetes mellitus

270.0 - 279.9  Other metabolic and immunity disorders

280.0 - 289.9  Diseases of the blood and blood-forming organs

331.81  Reye's syndrome

393 - 429.9  Chronic rheumatic heart disease, hypertensive disease, ischemic heart disease, diseases of pulmonary circulation, and other forms of heart disease

487.0 - 487.8  Influenza

490 - 496  Chronic obstructive pulmonary disease and allied conditions

510.0 - 519.9  Other disease of respiratory system

590.00 - 599.9  Other diseases of urinary system

640.00 - 648.94  Complications mainly related to pregnancy

745.0 - 747.9  Bulbus cordis anomalies and anomalies of cardiac septal closure, other congenital anomalies of heart, and other congenital anomalies of circulatory system

753.0 - 753.9  Congenital anomalies of urinary system

V01.0 - V01.9  Contact with or exposure to communicable diseases

V15.03  Personal history of allergy to eggs

V20.0 - V20.2  Health supervision of infant or child

V22.0 - V23.9  Supervision of normal pregnancy and high-risk pregnancy

V58.66  Long-term (current) use of aspirin

V60.6  Person living in residential institution
The above policy is based on the following references:


