

## Influenza

Influenza is a highly infectious viral illness. The name “influenza” originated in 15th century Italy, from an epidemic attributed to “influence of the stars.” The first pandemic, or worldwide epidemic, that clearly fits the description of influenza was in 1580. At least four pandemics of influenza occurred in the 19th century, and three occurred in the 20th century. The pandemic of “Spanish” influenza in 1918–1919 caused an estimated 21 million deaths worldwide.

Smith, Andrews, and Laidlaw isolated influenza A virus in ferrets in 1933, and Francis isolated influenza B virus in 1936. In 1936, Burnet discovered that influenza virus could be grown in embryonated hens’ eggs. This led to the study of the characteristics of the virus and the development of inactivated vaccines. The protective efficacy of these inactivated vaccines was determined in the 1950s. The first live attenuated influenza vaccine was licensed in 2003.

## Influenza Virus

Influenza is a single-stranded, helically shaped, RNA virus of the orthomyxovirus family. Basic antigen types A, B, and C are determined by the nuclear material. Type A influenza has subtypes that are determined by the surface antigens hemagglutinin (H) and neuraminidase (N). Three types of hemagglutinin in humans (H1, H2, and H3) have a role in virus attachment to cells. Two types of neuraminidase (N1 and N2) have a role in virus penetration into cells.

Influenza A causes moderate to severe illness and affects all age groups. The virus infects humans and other animals. Influenza A viruses are perpetuated in nature by wild birds, predominantly waterfowl. Most of these viruses are not pathogenic to their natural hosts and do not change or evolve. Influenza B generally causes milder disease than type A and primarily affects children. Influenza B is more stable than influenza A, with less antigenic drift and consequent immunologic stability. It affects only humans. Influenza C is rarely reported as a cause of human illness, probably because most cases are subclinical. It has not been associated with epidemic disease.

The nomenclature to describe the type of influenza virus is expressed in this order: 1) virus type, 2) geographic site where it was first isolated, 3) strain number, 4) year of isolation, and 5) virus subtype.

## Antigenic Changes

Hemagglutinin and neuraminidase periodically change, apparently due to sequential evolution within immune or partially immune populations. Antigenic mutants emerge

### Influenza

- Highly infectious viral illness
- First pandemic in 1580
- At least 4 pandemics in 19th century
- Estimated 21 million deaths worldwide in pandemic of 1918-1919
- Virus first isolated in 1933

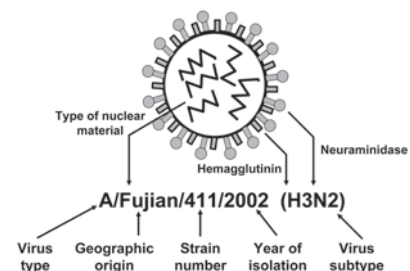
### Influenza Virus

- Single-stranded RNA virus
- Orthomyxoviridae family
- 3 types: A, B, C
- Subtypes of type A determined by hemagglutinin and neuraminidase

### Influenza Virus Strains

- **Type A** - moderate to severe illness  
- all age groups  
- humans and other animals
- **Type B** - milder disease  
- primarily affects children  
- humans only
- **Type C** - rarely reported in humans  
- no epidemics

### Influenza Virus



# Influenza

## Influenza Antigenic Changes

- Hemagglutinin and neuraminidase antigens change with time
- Changes occur as a result of point mutations in the virus gene, or due to exchange of a gene segment with another subtype of influenza virus
- Impact of antigenic changes depend on extent of change (more change usually means larger impact)

## Influenza Antigenic Changes

- **Antigenic Shift**
  - major change, new subtype
  - caused by exchange of gene segments
  - may result in pandemic
- **Example of antigenic shift**
  - H2N2 virus circulated in 1957-1967
  - H3N2 virus appeared in 1968 and completely replaced H2N2 virus

## Influenza Antigenic Changes

- **Antigenic Drift**
  - minor change, same subtype
  - caused by point mutations in gene
  - may result in epidemic
- **Example of antigenic drift**
  - in 2002-2003, A/Panama/2007/99 (H3N2) virus was dominant
  - A/Fujian/411/2002 (H3N2) appeared in late 2003 and caused widespread illness in 2003-2004

## Influenza Type A Antigenic Shifts

<u>Year</u>	<u>Subtype</u>	<u>Severity of Pandemic</u>
1889	H3N2	Moderate
1918	H1N1	Severe
1957	H2N2	Severe
1968	H3N2	Moderate
1977	H1N1	Mild

and are selected as the predominant virus to the extent that they differ from the antecedent virus, which is suppressed by specific antibody arising in the population as a result of infection. This cycle repeats continuously. In interpandemic periods, mutants arise by serial point mutations in the RNA coding for hemagglutinin. At irregular intervals of 10 to 40 years, viruses showing major antigenic differences from prevalent subtypes appear and, because the population does not have protective antibody against these new antigens, cause pandemic disease in all age groups.

Antigenic shift is a major change in one or both surface antigens (H or N) that occurs at varying intervals. Antigenic shifts are probably due to genetic recombination (an exchange of a gene segment) between influenza A viruses, usually those that affect humans and birds. An antigenic shift may result in a worldwide pandemic if the virus is efficiently transmitted from person to person. The last major antigenic shift occurred in 1968 when H3N2 (Hong Kong) influenza appeared. It completely replaced the type A strain (H2N2, or Asian influenza) that had circulated throughout the world for the prior 10 years. There is concern among some influenza experts that the increasingly wide geographic distribution of a highly pathogenic avian virus (H5N1) could increase the chance of another antigenic shift. Although H5N1 virus is known to infect humans who are in contact with infected poultry, the virus is not efficiently transmitted from one human to another. Efficient person-to-person transmission is a necessary characteristic of an influenza virus with pandemic potential.

Antigenic drift is a minor change in surface antigens that results from point mutations in a gene segment. Antigenic drift may result in an epidemic, since the protection that remains from past exposures to similar viruses is incomplete. Drift occurs in all three types of influenza virus (A,B,C). For instance, during most of the 1997–1998 influenza season, A/Wuhan/359/95 (H3N2) was the predominant influenza strain isolated in the United States. A/Wuhan was a drifted distant relative of the 1968 Hong Kong H3N2 strain. In the last half of the 1997–1998 influenza season, a drifted variant of A/Wuhan appeared. This virus, named A/Sydney/5/97, was different enough from A/Wuhan (which had been included in the 1997–1998 vaccine) that the vaccine did not provide much protection. Both A/Wuhan and A/Sydney circulated late in the 1997–1998 influenza season. A/Sydney became the predominant strain during the 1998–1999 influenza season and was included in the 1998–1999 vaccine.

Since the late 19th century, four occurrences of antigenic shifts have led to major pandemics (1889–1891, 1918–1920, 1957–1958, and 1968–1969). A pandemic starts from a single focus and spreads along routes of travel. Typically, there are

high attack rates involving all age groups, and mortality is usually markedly increased. Severity is generally not greater in the individual patient (except for the 1918–1919 strain), but because large numbers of persons are infected, the number, if not the proportion, of severe and fatal cases will be large. Onset may occur in any season of the year. Secondary and tertiary waves may occur every period of 1–2 years, usually in the winter.

Typically in an epidemic, influenza attack rates are lower than in pandemics. There is usually a rise in excess mortality. The major impact is observed in morbidity, with high attack rates and excess rates of hospitalization, especially for adults with respiratory disease. Absenteeism from work and school is high, and visits to healthcare providers increase. In the Northern Hemisphere, epidemics usually occur in late fall and continue through early spring. In the Southern Hemisphere, epidemics usually occur 6 months before or after those in the Northern Hemisphere.

Sporadic outbreaks can occasionally be localized to families, schools, and isolated communities.

## Pathogenesis

Following respiratory transmission, the virus attaches to and penetrates respiratory epithelial cells in the trachea and bronchi. Viral replication occurs, which results in the destruction of the host cell. Viremia has rarely been documented. Virus is shed in respiratory secretions for 5–10 days.

## Clinical Features

The incubation period for influenza is usually 2 days, but can vary from 1 to 4 days. The severity of influenza illness depends on the prior immunologic experience with antigenically related virus variants. In general, only about 50% of infected persons will develop the classic clinical symptoms of influenza.

“Classic” influenza disease is characterized by the abrupt onset of fever, myalgia, sore throat, nonproductive cough, and headache. The fever is usually 101°–102°F, and accompanied by prostration. The onset of fever is often so abrupt that the exact hour is recalled by the patient. Myalgias mainly affect the back muscles. Cough is believed to be a result of tracheal epithelial destruction. Additional symptoms may include rhinorrhea (runny nose), headache, substernal chest burning and ocular symptoms (e.g., eye pain and sensitivity to light).

Systemic symptoms and fever usually last from 2 to 3 days, rarely more than 5 days. They may be decreased by such

### Influenza Pathogenesis

- Respiratory transmission of virus
- Replication in respiratory epithelium with subsequent destruction of cells
- Viremia rarely documented
- Viral shedding in respiratory secretions for 5-10 days

### Influenza Clinical Features

- Incubation period 2 days (range 1-4 days)
- Severity of illness depends on prior experience with related variants
- Abrupt onset of fever, myalgia, sore throat, nonproductive cough, headache

## Influenza Complications

- **Pneumonia**
  - secondary bacterial
  - primary influenza viral
- **Reye syndrome**
- **Myocarditis**
- **Death 0.5-1 per 1,000 cases**

## Impact of Influenza

- ~36,000 excess deaths per year
- >90% of deaths among persons  $\geq 65$  years of age
- Higher mortality during seasons when influenza type A (H3N2) viruses predominate

## Impact of Influenza

- Highest rates of complications and hospitalization among young children and person  $\geq 65$  years
- Average of >200,000 influenza-related excess hospitalizations
- 57% of hospitalizations among persons <65 years of age
- Greater number of hospitalizations during type A (H3N2) epidemics

medications as aspirin or acetaminophen. Aspirin should not be used for infants, children, or teenagers because they may be at risk for contracting Reye syndrome following an influenza infection. Recovery is usually rapid, but some patients may have lingering depression and asthenia (lack of strength or energy) for several weeks.

## Complications

The most frequent complication of influenza is pneumonia, most commonly secondary bacterial pneumonia (e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Staphylococcus aureus*). Primary influenza viral pneumonia is an uncommon complication with a high fatality rate. Reye syndrome is a complication that occurs almost exclusively in children taking aspirin, primarily in association with influenza B (or varicella zoster), and presents with severe vomiting and confusion, which may progress to coma due to swelling of the brain.

Other complications include myocarditis (inflammation of the heart) and worsening of chronic bronchitis and other chronic pulmonary diseases. Death is reported in 0.5–1 per 1,000 cases. The majority of deaths occur among persons 65 years of age and older.

## Impact of Influenza

An increase in mortality typically accompanies an influenza epidemic. Increased mortality results not only from influenza and pneumonia but also from cardiopulmonary and other chronic diseases that can be exacerbated by influenza.

In a recent study of influenza epidemics, approximately 19,000 influenza-associated pulmonary and circulatory deaths per influenza season occurred during 1976–1990, compared with approximately 36,000 deaths during 1990–1999. Persons 65 years of age and older account for more than 90% of deaths attributed to pneumonia and influenza. In the United States, the number of influenza-associated deaths might be increasing, in part because the number of older persons is increasing. In addition, influenza seasons in which influenza A (H3N2) viruses predominate are associated with higher mortality.

The risk for complications and hospitalizations from influenza are higher among persons 65 years of age and older, young children, and persons of any age with certain underlying medical conditions. An average of more than 200,000 hospitalizations per year are related to influenza, more than 57% of which are among persons younger than 65 years. A greater number of hospitalizations occur during years that influenza A (H3N2) is predominant. In nursing homes, attack rates may be as high as 60%, with fatality rates as



high as 30%. The cost of a severe epidemic has been estimated to be \$12 billion.

Among children 0–4 years of age, hospitalization rates have varied from 100 per 100,000 healthy children to as high as 500 per 100,000 for children with underlying medical conditions. Hospitalization rates for children 24 months of age and younger are comparable to rates for persons 65 and older. Children 24–59 months of age are at less risk of hospitalization from influenza than are younger children, but are at increased risk for influenza-associated clinic and emergency department visits.

An influenza pandemic could affect up to 200 million people and result in up to 400,000 deaths. The 1918–1919 influenza pandemic is believed to have resulted in the death of at least 500,000 Americans in less than a year. Planning for pandemic influenza is a critical component of public health preparedness activities and should be conducted by all local and state public health agencies. The federal pandemic plan is available on the Department of Health and Human Services website at <http://www.hhs.gov/pandemicflu/plan/>

## Laboratory Diagnosis

The diagnosis of influenza is usually suspected on the basis of characteristic clinical findings, particularly if influenza has been reported in the community.

Virus can be isolated from throat and nasopharyngeal swabs obtained within 3 days of onset of illness. Culture is performed by inoculation of the amniotic or allantoic sac of chick embryos or certain cell cultures that support viral replication. A minimum of 48 hours is required to demonstrate virus, and 1 to 2 additional days to identify the virus type. As a result, culture is helpful in defining the etiology of local epidemics, but not in individual case management.

Serologic confirmation of influenza requires demonstration of a significant rise in influenza IgG. The acute-phase specimen should be taken less than 5 days from onset, and a convalescent specimen taken 10–21 days (preferably 21 days) following onset. Complement fixation (CF) and hemagglutination inhibition (HI) are the serologic tests most commonly used. The key test is HI, which depends on the ability of the virus to agglutinate human or chicken erythrocytes and inhibition of this process by specific antibody. Diagnosis requires at least a fourfold rise in antibody titer. Rapid diagnostic testing for influenza antigen permits those in office and clinic settings to assess the need for antiviral use in a more timely manner.

### Hospitalization Rates for Influenza By Age and Risk Group\*

Age Group	Rate** (high-risk)	Rate** (not high-risk)
0-11 mos	1900	496-1038
1-2 yrs	800	186
3-4 yrs	320	86
5-14 yrs	92	41
15-44 yrs	56-110	23-25
45-64 yrs	392-635	13-23
≥65 yrs	399-518	125-228

\* Data from several studies 1972 - 1995  
\*\* Hospitalizations per 100,000 population

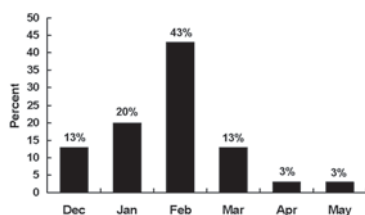
### Influenza Diagnosis

- Clinical and epidemiological characteristics
- Isolation of influenza virus from clinical specimen (e.g., nasopharynx, throat, sputum)
- Significant rise in influenza IgG by serologic assay
- Direct antigen testing for type A virus

## Influenza Epidemiology

- **Reservoir** Human, animals (type A only)
- **Transmission** Respiratory  
Probably airborne
- **Temporal pattern** Peak December – March in temperate climate  
May occur earlier or later
- **Communicability** 1 day before to 5 days after onset (adults)

**Month of Peak Influenza Activity  
United States, 1976-2006**



MMWR 2006;55:22

Details about the laboratory diagnosis of influenza are available on the CDC influenza website at <http://www.cdc.gov/flu/professionals/diagnosis/index.htm>

## Epidemiology

### Occurrence

Influenza occurs throughout the world.

### Reservoir

Humans are the only known reservoir of influenza types B and C. Influenza A may infect both humans and animals. There is no chronic carrier state.

### Transmission

Influenza is primarily transmitted from person to person via large virus-laden droplets (particles more than 5 microns in diameter) that are generated when infected persons cough or sneeze. These large droplets can then settle on the mucosal surfaces of the upper respiratory tracts of susceptible persons who are near (within 3 feet) infected persons. Transmission may also occur through direct contact or indirect contact with respiratory secretions such as when touching surfaces contaminated with influenza virus and then touching the eyes, nose or mouth.

### Temporal Pattern

Influenza activity peaks from December to March in temperate climates, but may occur earlier or later. During 1976–2006, peak influenza activity in the United States occurred most frequently in January (20% of seasons) and February (43% of seasons). However, peak influenza activity occurred in March, April, or May in 19% of seasons. Influenza occurs throughout the year in tropical areas.

### Communicability

Adults can transmit influenza from the day before symptom onset to approximately 5 days after symptoms begin. Children can transmit influenza to others for 10 or more days.

### Secular Trends in the United States

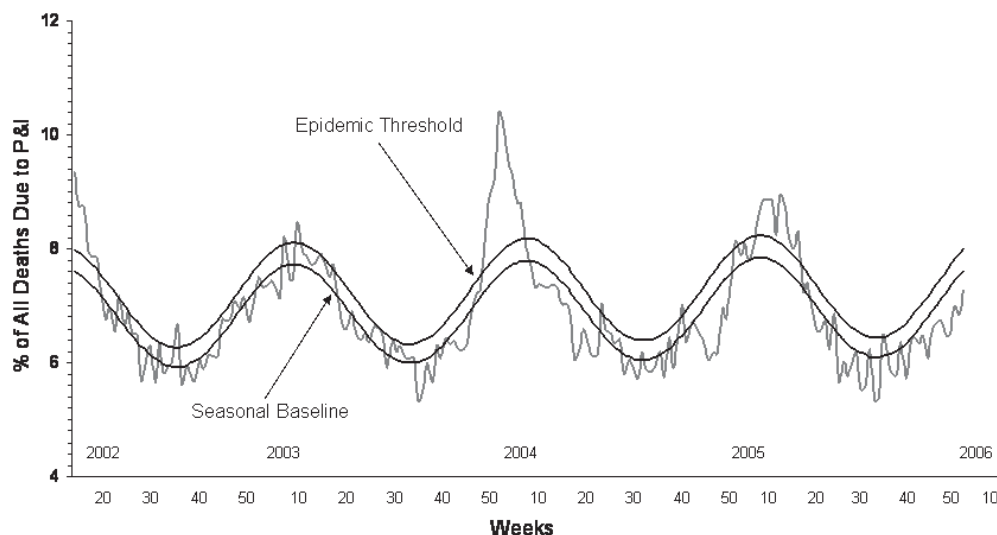
There is a documented association between influenza and increased morbidity in high-risk adult populations. Hospitalization for adults with high-risk medical conditions increases two- to fivefold during major epidemics.

The impact of influenza in the United States is quantified by measuring pneumonia and influenza (P and I) deaths.

Death certificate data are collected from 122 U.S. cities with populations of more than 100,000 (total of approximately 70,000,000). P and I deaths include all deaths for which pneumonia is listed as a primary or underlying cause or for which influenza is listed on the death certificate.

An expected ratio of deaths due to P and I compared with all deaths for a given period of time is determined. The epidemic threshold for influenza seasons is generally estimated at 1.645 standard deviations above observed P and I deaths for the previous 5-year period excluding periods during influenza outbreaks. Influenza epidemic activity is signaled when the ratio of deaths due to P and I exceeds the threshold ratio for 2 consecutive weeks.

**Pneumonia and Influenza Mortality  
for 122 U.S. Cities**  
Week Ending 01/07/2006



## Influenza Vaccine

### Characteristics

Two types of influenza vaccine are available in the United States. Trivalent inactivated influenza vaccine (TIV) has been available since the 1940s. TIV is administered by the intramuscular route and currently contains three inactivated viruses: type A (H1N1), type A (H3N2), and type B. Only split-virus and subunit inactivated vaccines are available in the United States. Vaccine viruses are grown in chicken eggs, and the final product contains residual egg protein. The vaccine is available in both pediatric (0.25-mL dose) and adult (0.5-mL dose) formulations. TIV is available with thimerosal as a preservative (in multidose vials), and in reduced and preservative free formulations.

### Influenza Vaccines

- **Inactivated subunit (TIV)**
  - intramuscular
  - trivalent
- **Live attenuated vaccine (LAIV)**
  - intranasal
  - trivalent

## Transmission of LAIV Virus

- LAIV replicates in the nasopharyngeal mucosa
- Mean shedding of virus 7.6 days – longer in children
- One instance of transmission of vaccine virus documented in a child care setting
- Transmitted virus retained attenuated, cold-adapted, temperature-sensitive characteristics
- No transmission of LAIV reported in the U.S.

## Inactivated Influenza Vaccine Efficacy

- 70%-90% effective among healthy persons <65 years of age
- 30%-40% effective among frail elderly persons
- 50%-60% effective in preventing hospitalization
- 80% effective in preventing death

For the 2007–2008 influenza season four manufacturers provided TIV. Fluzone (sanofi pasteur) was available in multidose vials, in a thimerosal-free pediatric formulation (0.25 mL) in single-dose syringes, and in a thimerosal-free adult formulation in single-dose syringes and vials. Fluzone is the only TIV currently approved for use among children younger than 48 months. Fluvirin (Novartis) was available in multidose vials. Fluvirin is approved only for persons 4 years of age and older. Fluarix (GlaxoSmithKline) was available in a reduced-thimerosal (“preservative free”) single-dose syringe for persons 18 years of age and older. FluLaval (GlaxoSmithKline) was available in a multidose vial for persons 18 years of age and older. Afluria (CSL Biotherapies) produced TIV in a single dose syringe and multidose vial for persons 18 years of age and older. All TIV supplied in multidose vials contain thimerosal as a preservative.

Live attenuated influenza vaccine (LAIV) was approved for use in the United States in 2003. It contains the same three influenza viruses as TIV. The viruses are cold-adapted, and replicate effectively in the mucosa of the nasopharynx. The vaccine viruses are grown in chicken eggs, and the final product contains residual egg protein. The vaccine is provided in a single-dose sprayer unit; half of the dose is sprayed into each nostril. LAIV does not contain thimerosal or any other preservative. LAIV is approved for use only in healthy, nonpregnant persons 2 through 49 years of age.

Vaccinated children can shed vaccine viruses in nasopharyngeal secretions for up to 3 weeks. One instance of transmission of vaccine virus to a contact has been documented. The transmitted virus retained its attenuated, cold-adapted, temperature-sensitive characteristics. The frequency of shedding of vaccine strains by persons 5–49 years of age has not been determined.

## Immunogenicity and Vaccine Efficacy

### TIV

For practical purposes, immunity following inactivated influenza vaccination is less than 1 year because of waning of vaccine-induced antibody and antigenic drift of circulating influenza viruses. Influenza vaccine efficacy varies by the similarity of the vaccine strain(s) to the circulating strain and the age and health status of the recipient. Vaccines are effective in protecting up to 90% of healthy vaccinees younger than 65 years of age from illness when the vaccine strain is similar to the circulating strain. However, the vaccine is only 30%–40% effective in preventing illness among persons 65 years of age and older.

Although the vaccine is not highly effective in preventing



clinical illness among the elderly, it is effective in preventing complications and death. Among elderly persons, the vaccine is 50%–60% effective in preventing hospitalization and 80% effective in preventing death. During a 1982–1983 influenza outbreak in Genesee County, Michigan, unvaccinated nursing home residents were four times more likely to die than were vaccinated residents.

## LAIV

LAIV has been tested in groups of both healthy children and healthy adults. A randomized, double-blind, placebo-controlled trial among healthy children 60–84 months of age assessed the efficacy of the trivalent LAIV against culture-confirmed influenza during two influenza seasons. In year 1, when vaccine and circulating virus strains were well matched, efficacy was 87% against culture-confirmed influenza. In year 2, when the type A component was not well matched between vaccine and circulating virus strains, efficacy was also 87%. Other results from this trial included a 27% reduction in febrile otitis media and a 28% reduction in otitis media with concomitant antibiotic use. Receipt of LAIV also resulted in decreased fever and otitis media in vaccine recipients who developed influenza.

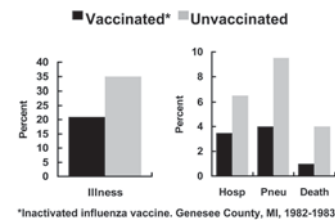
A randomized, double-blind, placebo-controlled trial among 3,920 healthy working adults aged 18–49 years assessed several endpoints and documented reductions in illness, absenteeism, healthcare visits, and medication use during influenza outbreak periods. This study was conducted during the 1997–98 influenza season, when the vaccine and circulating type A strains were not well matched. This study did not include laboratory virus testing of cases. There is no evidence that efficacy of LAIV is greater than that of TIV.

## Vaccination Schedule and Use

### TIV

Influenza activity peaks in temperate areas between late December and early March. TIV is most effective when it precedes exposure by no more than 2 to 4 months. It should be offered annually, beginning in September for routine patient visits. The optimal time for vaccination efforts is usually during October and November. In October vaccination in provider-based settings should start or continue for all patients, both high risk and healthy, and extend through November. Vaccination of children aged 6 months through 8 years of age who are receiving vaccine for the first time should also begin in October, if not done earlier, because those children need a second dose 4 to 6 weeks after the initial dose, depending upon whether they are receiving inactivated influenza vaccine or LAIV. Organized vaccination

### Influenza and Complications Among Nursing Home Residents



### LAIV Efficacy in Healthy Children

- 87% effective against culture-confirmed influenza in children 5-7 years old
- 27% reduction in febrile otitis media (OM)
- 28% reduction in OM with accompanying antibiotic use
- Decreased fever and OM in vaccine recipients who developed influenza

### LAIV Efficacy in Healthy Adults

- 20% fewer severe febrile illness episodes
- 24% fewer febrile upper respiratory illness episodes
- 27% fewer lost work days due to febrile upper respiratory illness
- 18%-37% fewer days of healthcare provider visits due to febrile illness
- 41%-45% fewer days of antibiotic use

### Timing of Inactivated Influenza Vaccine Programs

- Actively target vaccine available in September and October to persons at increase risk of influenza complications, children <9 years, and healthcare workers
- Vaccination of all other groups should begin in November
- Continue vaccinating through December and later, as long as vaccine is available

campaigns should be scheduled no earlier than mid-October. Vaccine may be given up to and even after influenza activity is documented in a region. Although most influenza vaccination activities should be completed by December (particularly for high-risk groups), providers should continue to provide vaccine throughout influenza season. One dose of TIV may be administered annually for persons 9 years of age or older. Children 6 months to 9 years of age receiving influenza vaccine for the first time should receive two doses administered at least 1 month apart.

**Inactivated Influenza Vaccine Dosage, by Age Group – United States**

Age Group	Dosage	Number of Doses	Route
6-35 months	0.25 mL	1* or 2	IM
3-8 years	0.50 mL	1* or 2	IM
≥9 years	0.50 mL	1	IM

\*Only one dose is needed if the child received 2 doses of influenza vaccine during the previous influenza season.

Inactivated influenza vaccine should be given by the intramuscular (IM) route. Other methods, such as intradermal, subcutaneous, topical, or mucosal should not be used unless approved by the Food and Drug Administration or recommended by ACIP.

TIV is recommended for all persons 50 years of age or older and all children 6–59 months of age, regardless of the presence of chronic illness. Other groups targeted for TIV include residents of long-term care facilities, pregnant women, and persons 6 months to 18 years of age receiving chronic aspirin therapy (because of the risk of Reye syndrome following influenza infection).

Persons 6 months of age and older with a chronic illness should receive TIV annually. These chronic illnesses include the following:

- pulmonary illnesses, such as emphysema, chronic bronchitis, or asthma
- cardiovascular illnesses, such as congestive heart failure
- metabolic diseases, including diabetes mellitus
- renal dysfunction
- hemoglobinopathy, such as sickle cell disease
- immunosuppression, including human immunodeficiency virus (HIV) infection
- any condition (e.g., cognitive dysfunction, spinal cord injury, seizure disorder, or other neuromuscular disorder) that can compromise respiratory function or the handling of respiratory secretions

Case reports and limited studies suggest that pregnant women may be at increased risk for serious medical complications of influenza as a result of increases in heart

### Inactivated Influenza Vaccine Recommendations

- All persons 50 years of age or older
- Children 6-59 months of age
- Residents of long-term care facilities
- Pregnant women
- Persons 6 months to 18 years receiving chronic aspirin therapy
- Persons >6 months of age with chronic illness

### Inactivated Influenza Vaccine Recommendations

- Persons with the following chronic illnesses should be considered for inactivated influenza vaccine:
  - pulmonary (e.g., asthma, COPD)
  - cardiovascular (e.g., CHF)
  - metabolic (e.g., diabetes)
  - renal dysfunction
  - hemoglobinopathy
  - immunosuppression, including HIV infection
  - any condition that can compromise respiratory function or the handling of respiratory secretions

rate, stroke volume and oxygen consumption; decreases in lung capacity; and changes in immunologic function. A recent study found that the risk of hospitalization for influenza-related complications was more than four times higher for women in the second or third trimester of pregnancy than for nonpregnant women. The risk of complications for these pregnant women was comparable to that for nonpregnant women with high-risk medical conditions, for whom influenza vaccine has been traditionally recommended.

ACIP recommends vaccination of women who will be pregnant during influenza season. Vaccination can occur during any trimester. Influenza season in the United States generally occurs in December through March. Only TIV should be administered to pregnant women.

Available data suggest that persons with HIV infection may have prolonged influenza illnesses and are at increased risk of complications of influenza. Many persons with HIV infection will develop protective antibody titers following inactivated influenza vaccine. In persons who have advanced HIV disease and low CD4+ T-lymphocyte cell counts, TIV vaccine may not induce protective antibody titers. A second dose of vaccine does not improve the immune response in these persons.

Some studies have demonstrated a transient increase in viral titer in the blood of vaccinated persons infected with HIV. There is no evidence of deterioration in CD4 counts or progression of clinical HIV disease. Because influenza can result in serious illness and complications and because influenza vaccination may result in protective antibody titers, ACIP believes that influenza vaccination will benefit many persons with HIV infection. LAIV should not be administered to persons with HIV infection.

Persons who have contact with high-risk persons should receive TIV. These include healthcare workers, employees of long-term care facilities, and household contacts of high-risk persons. These individuals may be younger and healthier and more likely to be protected from illness than are elderly persons. All healthcare providers should receive annual inactivated influenza vaccine. Groups that should be targeted include physicians, nurses, and other personnel in hospitals and outpatient settings who have contact with high-risk patients in all age groups, and providers of home care to high-risk persons (e.g., visiting nurses, volunteers). LAIV may be administered to healthy healthcare workers 49 years of age or younger, except those who have contact with severely immunosuppressed persons who require hospitalization and care in a protective environment (i.e., in isolation because of severe immunosuppression).

## **Pregnancy and Inactivated Influenza Vaccine**

- Risk of hospitalization 4 times higher than nonpregnant women
- Risk of complications comparable to nonpregnant women with high-risk medical conditions
- Vaccination (with TIV) recommended if pregnant during influenza season
- Vaccination can occur during any trimester

## **HIV Infection and Inactivated Influenza Vaccine**

- Persons with HIV at increased risk of complications of influenza
- TIV induces protective antibody titers in many HIV infected persons
- Transient increase in HIV replication reported
- TIV will benefit many HIV-infected persons

# Influenza

## Influenza Vaccine Recommendations

- Healthcare providers, including home care\*
- Employees of long-term care facilities
- Household contacts of high-risk persons

\*LAIV should not be administered to healthcare workers who have contact with severely immunosuppressed persons who require hospitalization and care in a protective environment

## Influenza Vaccine Recommendations\*

- Providers of essential community services
- Students
- Persons traveling outside the U.S.
- Anyone who wishes to reduce the likelihood of becoming ill from influenza

\*these groups may receive TIV, and some may be eligible for LAIV

Persons who provide essential community services and students or others in institutional settings (e.g., schools and colleges) may be considered for vaccination to minimize disruption of routine activities during outbreaks. Persons traveling outside the United States should consider influenza vaccination. The risk of exposure to influenza during foreign travel varies, depending on season of travel, the mode of travel (e.g., increased risk during cruises), and destination. Influenza can occur throughout the year in the tropics. In the Southern Hemisphere, influenza activity peaks in April–September. If not vaccinated the previous fall/winter, persons (especially those in high-risk groups) preparing to travel to the tropics at any time of the year or to the Southern Hemisphere during April–September should be considered for influenza vaccination before travel. Any person who wishes to lessen his/her chance of acquiring influenza infection may be vaccinated.

In 2005, the ACIP recommended routine vaccination of all children 6 through 59 months of age because of the increased risk of influenza-related hospitalization and physician visits in this age group. Household contacts and other caregivers of children younger than 59 months of age are also encouraged to receive annual influenza vaccination.

## LAIV

LAIV is approved for healthy, nonpregnant persons 2 through 49 years of age. The vaccine can be administered to eligible persons as soon as it becomes available in the late summer or fall. Vaccination can continue throughout influenza season. One dose of LAIV may be administered by the intranasal route to persons 9–49 years of age. Children 2–8 years of age receiving influenza vaccine for the first time should receive two doses administered at least 4 weeks apart.

Live Attenuated Influenza Vaccine Dosage, by Age Group – United States

Age Group	Number of Doses	Route
2-8 years, no previous influenza vaccine	2 (separated by 4 weeks)	Intranasal
5-8 years, previous influenza vaccine*	1	Intranasal
9-49 years	1	Intranasal

\*LAIV or inactivated vaccine

Close contacts of persons at high risk for complications from influenza should receive influenza vaccine. This reduces the risk of transmission of wild-type influenza viruses to high-risk persons. Contacts of persons at high risk of complications of influenza may receive LAIV if they are otherwise eligible



(i.e., 2–49 years of age, healthy and not pregnant). Persons in close contact with severely immunosuppressed persons who are hospitalized and receiving care in a protected environment should not receive LAIV.

Inactivated vaccines do not interfere with the immune response to live vaccines. Inactivated vaccines, such as tetanus and diphtheria toxoids, can be administered either simultaneously or at any time before or after LAIV. Other live vaccines can be administered on the same day as LAIV. Live vaccines not administered on the same day should be administered at least 4 weeks apart when possible.

## Adverse Reactions Following Vaccination

### TIV

Local reactions are the most common adverse reactions following vaccination with TIV. Local reactions include soreness, erythema, and induration at the site of injection. These reactions are transient, generally lasting 1 to 2 days. Local reactions are reported in 15%–20% of vaccinees.

Nonspecific systemic symptoms, including fever, chills, malaise, and myalgia, are reported in fewer than 1% of TIV recipients. These symptoms usually occur in those with no previous exposure to the viral antigens in the vaccine. They usually occur within 6–12 hours of TIV vaccination and last 1–2 days. Recent reports indicate that these systemic symptoms are no more common than in persons given a placebo injection.

Rarely, immediate hypersensitivity, presumably allergic, reactions (such as hives, angioedema, allergic asthma, or systemic anaphylaxis) occur after vaccination with TIV. These reactions probably result from hypersensitivity to a vaccine component. The majority are most likely related to residual egg protein. Although current influenza vaccines contain only a small quantity of egg protein, this protein may induce immediate allergic reactions in persons with severe egg allergy. Persons who have developed hives, had swelling of the lips or tongue, or have experienced acute respiratory distress or collapse after eating eggs should consult a physician for appropriate evaluation to assist in determining whether influenza vaccination may proceed or should be deferred. Persons with documented immunoglobulin E (IgE)-mediated hypersensitivity to eggs—including those who have had occupational asthma or other allergic responses from exposure to egg protein—may also be at increased risk for reactions from influenza vaccines, and similar consultation should be considered. Protocols have been published for influenza vaccination of patients who

### Simultaneous Administration of LAIV and Other Vaccines

- Inactivated vaccines can be administered either simultaneously or at any time before or after LAIV
- Other live vaccines can be administered on the same day as LAIV
- Live vaccines not administered on the same day should be administered  $\geq 4$  weeks apart

### Inactivated Influenza Vaccine Adverse Reactions

Local reactions	15%-20%
Fever, malaise	not common
Allergic reactions	rare
Neurological reactions	very rare



have egg allergies and medical conditions that place them at increased risk for influenza infection or its complications.

The potential exists for hypersensitivity reactions to any vaccine component. Although exposure to vaccines containing thimerosal can lead to induction of hypersensitivity, most patients do not develop reactions to thimerosal administered as a component of vaccines, even when patch or intradermal tests for thimerosal indicate hypersensitivity. When it has been reported, hypersensitivity to thimerosal has usually consisted of local delayed-type hypersensitivity reactions.

Unlike the 1976 swine influenza vaccine, subsequent inactivated vaccines prepared from other virus strains have not been clearly associated with an increased frequency of Guillain-Barré syndrome (GBS). However, obtaining a precise estimate of a small increase in risk is difficult for a rare condition such as GBS, which has an annual background incidence of only one to two cases per 100,000 adult population. Among persons who received the swine influenza vaccine in 1976, the rate of GBS exceeded the background rate by less than one case per 100,000 vaccinations. Even if GBS were a true adverse reaction in subsequent years, the estimated risk for GBS was much lower than one per 100,000. Further, the risk is substantially less than that for severe influenza or its complications, which could be prevented by vaccination, especially for persons aged 65 years or older and those with a medical indication for influenza vaccine.

Although the incidence of GBS in the general population is very low, persons with a history of GBS have a substantially greater likelihood of subsequently developing GBS than do persons without such a history, irrespective of vaccination. As a result, the likelihood of coincidentally developing GBS after influenza vaccination is expected to be greater among persons with a history of GBS than among persons with no history of GBS. Whether influenza vaccination might be causally associated with this risk for recurrence is not known. It seems prudent for persons known to have developed GBS within 6 weeks of a previous influenza vaccination to avoid subsequent influenza vaccination. For most persons with a history of GBS who are at high risk for severe complications from influenza, the established benefits of influenza vaccination justify yearly vaccination.

## **LAIV**

Among healthy children, there have been no significant differences between LAIV and placebo recipients in the proportion with upper respiratory symptoms such as runny nose and nasal congestion, fever, or other systemic symptoms.

These symptoms were reported in 10%–40% of both vaccine and placebo recipients. Healthy children 2–4 years of age who received LAIV during clinical trials appeared to have an increased risk of wheezing.

Among healthy adults, a significantly increased rate of cough, runny nose, nasal congestion, sore throat, and chills was reported among vaccine recipients. These symptoms were reported in 10%–40% of vaccine recipients, a rate 3%–10% higher than reported for placebo recipients. There was no increase in the occurrence of fever among vaccine recipients. No serious adverse reactions have been identified in LAIV recipients, either children or adults.

No instances of Guillain-Barré syndrome have been reported among LAIV recipients. However the number of persons vaccinated to date is too small to identify such a rare vaccine adverse reaction.

Few data are available concerning the safety of LAIV among persons at high risk for development of complications of influenza, such as immunosuppressed persons or those with chronic pulmonary or cardiac disease. Until additional data are available, persons at high risk of complications of influenza should not receive LAIV. These persons should continue to receive inactivated influenza vaccine.

## Contraindications and Precautions to Vaccination

### TIV

Persons with a severe allergic reaction to a prior dose of inactivated influenza vaccine, or to a vaccine component (e.g., eggs) should not receive TIV. Persons with a moderate or severe acute illness normally should not be vaccinated until their symptoms have decreased. Pregnancy, breastfeeding, and immunosuppression are not contraindications to inactivated influenza vaccination.

### LAIV

Persons who should not receive LAIV include children younger than 2 years of age; persons 50 years of age and older; persons with chronic medical conditions, including asthma, a recent wheezing episode, reactive airways disease or other chronic pulmonary or cardiovascular conditions, metabolic disease such as diabetes, renal disease, or hemoglobinopathy, such as sickle cell disease; and children or adolescents receiving long-term therapy with aspirin or other salicylates, because of the association of Reye syndrome with wild-type influenza infection. Persons in these groups should receive inactivated influenza vaccine.

### Live Attenuated Influenza Vaccine Adverse Reactions

- **Children**
  - no significant increase in URI symptoms, fever, or other systemic symptoms
  - significantly increased risk of asthma or reactive airways disease in children 12–59 months of age
- **Adults**
  - significantly increased rate of cough, runny nose, nasal congestion, sore throat, and chills reported among vaccine recipients
  - no increase in the occurrence of fever
- **No serious adverse reactions identified**

### Inactivated Influenza Vaccine Contraindications and Precautions

- **Severe allergic reaction to a vaccine component (e.g., egg) or following a prior dose of vaccine**
- **Moderate or severe acute illness**

### Live Attenuated Influenza Vaccine Contraindications and Precautions

- **Children <2 years of age\***
- **Persons ≥50 years of age\***
- **Persons with chronic medical conditions\***
- **Children and adolescents receiving long-term aspirin therapy\***

\*These persons should receive inactivated influenza vaccine

## Live Attenuated Influenza Vaccine Contraindications and Precautions

- Immunosuppression from any cause
- Pregnant women\*
- Severe (anaphylactic) allergy to egg or other vaccine components
- History of Guillian-Barré syndrome
- Moderate or severe acute illness

\*These persons should receive inactivated influenza vaccine

As with other live-virus vaccines, LAIV should not be given to persons who are immunosuppressed because of disease, including HIV, or who are receiving immunosuppressive therapy. Pregnant women should not receive LAIV. Immunosuppressed persons and pregnant women should receive inactivated influenza vaccine. Since LAIV contains residual egg protein, it should not be administered to persons with a history of severe allergy to egg or any other vaccine component. The manufacturer recommends that LAIV not be administered to a person with a history of Guillain-Barré syndrome.

As with all vaccines, LAIV should be deferred for persons with a moderate or severe acute illness. If clinical judgment indicates that nasal congestion might impede delivery of the vaccine to the nasopharyngeal mucosa, deferral of administration should be considered until the condition has improved.

The effect on safety and efficacy of LAIV coadministration with influenza antiviral medications has not been studied. However, because influenza antiviral agents reduce replication of influenza viruses, LAIV should not be administered until 48 hours after cessation of influenza antiviral therapy, and influenza antiviral medications should not be administered for 2 weeks after receipt of LAIV.

## Vaccine Storage and Handling

### TIV

Inactivated influenza vaccine is generally shipped in an insulated container with coolant packs. Although some brands of TIV vaccine can tolerate room temperature for a few days, CDC recommends that the vaccine be stored at refrigerator temperature (35°–46°F [2°–8°C]). Inactivated influenza vaccine must not be frozen. Opened multidose vials may be used until the expiration date printed on the package if no visible contamination is present.

### LAIV

LAIV should be stored at refrigerator temperature (35°–40° F [2°–8°C]). LAIV inadvertently exposed to freezing temperature should be placed at refrigerator temperature and used as soon as possible.

LAIV is intended for intranasal administration only and should never be administered by injection. LAIV must be thawed before administration. If the vaccine is not thawed in a refrigerator, this can be accomplished by holding an individual sprayer in the palm of the hand until thawed and then administering the vaccine immediately. LAIV is

supplied in a prefilled single-use sprayer containing 0.2 mL of vaccine. Approximately 0.1 mL (i.e., half of the total sprayer contents) is sprayed into the first nostril while the recipient is in the upright position. An attached dose-divider clip is removed from the sprayer to administer the second half of the dose into the other nostril. If the vaccine recipient sneezes after administration, the dose should not be repeated.

## **Year 2010 Objectives and Coverage Levels**

Year 2010 objectives are to increase influenza vaccination levels to 60% or higher among high-risk populations (90% in residents of chronic care facilities) and to reduce epidemic-related pneumonia and influenza-related deaths among persons 65 years of age and older. In 2003, 66% of persons 65 years of age and older reported receiving influenza vaccine in the previous year. Vaccination levels were lower among black and Hispanic persons than among non-Hispanic white persons.

## **Strategies for Improving Influenza Vaccine Coverage**

On average, fewer than 20% of persons in high-risk groups receive influenza vaccine each year. This points to the need for more effective strategies for delivering vaccine to high-risk persons, their healthcare providers, and household contacts. Persons for whom the vaccine is recommended can be identified and immunized in a variety of settings. In physicians' offices and outpatient clinics, persons who should receive inactivated influenza vaccine should be identified and their charts marked. TIV use should be promoted, encouraged and recommended beginning in October and continuing through the influenza season. Those without regularly scheduled visits should receive reminders.

In nursing homes and other residential long-term care facilities, immunization with TIV should be routinely provided to all residents at one period of time immediately preceding the influenza season; consent should be obtained at the time of admission.

In acute care hospitals and continuing care centers, persons for whom vaccine is recommended who are hospitalized from October through March should be vaccinated prior to discharge. In outpatient facilities providing continuing care to high-risk patients (e.g., hemodialysis centers, hospital specialty-care clinics, outpatient rehabilitation programs), all patients should be offered TIV shortly before the onset of the influenza season.

### **Influenza Vaccine Strategies to Improve Coverage**

- Ensure systematic and automatic offering of TIV to high-risk groups
- Educate healthcare providers and patients
- Address concerns about adverse events
- Emphasize physician recommendation

Visiting nurses and others providing home care to high-risk persons should identify high-risk patients and administer TIV in the home, if necessary.

In facilities providing services to persons 50 years of age and older (e.g., retirement communities, recreation centers), inactivated influenza vaccine should be offered to all unvaccinated residents or attendees on site. Education and publicity programs should also be conducted in conjunction with other interventions.

For travelers, indications for influenza vaccine should be reviewed prior to travel and vaccine offered, if appropriate.

Administrators of all of the above facilities and organizations should arrange for influenza vaccine to be offered to all personnel before the influenza season. Additionally, household members of high-risk persons and others with whom they will be in contact should receive written information about why they should receive the vaccine and where to obtain it.

## Antiviral Agents for Influenza

In the United States, four antiviral agents are approved for preventing or treating influenza: amantadine, rimantadine, zanamivir, and oseltamivir.

Testing of influenza A isolates from the United States and Canada has demonstrated that many of these viruses are resistant to amantadine and rimantadine. The ACIP recommends that neither amantadine nor rimantadine be used for the treatment or chemoprophylaxis of influenza A in the United States until susceptibility to these antiviral drugs has been re-established.

Zanamivir and oseltamivir are members of a new class of drugs called neuraminidase inhibitors and are active against both influenza type A and type B. Zanamivir is provided as a dry powder that is administered by inhalation. It is approved for treatment of uncomplicated acute influenza A or B in persons 7 years of age and older who have been symptomatic for no more than 48 hours. Oseltamivir is provided as an oral capsule. It is approved for the treatment of uncomplicated influenza A or B in persons 1 year of age and older who have been symptomatic for no more than 48 hours. Zanamivir is approved for prophylaxis of influenza in persons 5 years and older. Oseltamivir is approved for prophylaxis of influenza infection among persons 1 year of age and older.

### Influenza Antiviral Agents\*

- Amantadine and rimantadine
  - Not recommended because of documented resistance in U.S. influenza isolates
- Zanamivir and oseltamivir
  - neuraminidase inhibitors
  - effective against influenza A and B
  - oseltamivir approved for prophylaxis

\*see influenza ACIP statement or CDC influenza website for details



Antiviral agents for influenza are an adjunct to vaccine and are not a substitute for vaccine. Vaccination remains the principal means for preventing influenza-related morbidity and mortality. Additional information on the use of influenza antiviral drugs can be found in the current ACIP statement on influenza vaccine and on the CDC influenza website at <http://www.cdc.gov/flu>.

## **Nosocomial Influenza Control**

Many patients in general hospitals, and especially in referral centers, are likely to be at high risk for complications of influenza. Hospitalized susceptible patients may acquire influenza from patients, hospital employees, or visitors. The preferred method of control is to administer inactivated influenza vaccine to high-risk patients and medical personnel prior to the outbreak.

During community influenza A activity, the use of antiviral prophylaxis may be considered for high-risk patients who were not immunized or were immunized too recently to have protective antibody levels. Antiviral agents may also be considered for unimmunized hospital personnel. Other measures include restricting visitors with respiratory illness, cohorting patients with influenza for 5 days following onset of illness, and postponing elective admission of patients with uncomplicated illness.

## **Influenza Surveillance**

Influenza surveillance is intended to monitor the prevalence of circulating strains and detect new strains necessary for vaccine formulation; estimate influenza-related impact on morbidity, mortality, and economic loss; rapidly detect outbreaks; and assist disease control through rapid preventive action (e.g., chemoprophylaxis of unvaccinated high-risk patients).

CDC receives weekly surveillance reports from the states showing the extent of influenza activity. Reports are classified into four categories: no cases, sporadic, regional (cases occurring in counties collectively contributing less than 50% of a state's population), widespread (cases occurring in counties collectively contributing 50% or more of a state's population).

Weekly surveillance reports are available at <http://www.cdc.gov/flu/weekly/fluactivity.htm>

### **Influenza Surveillance**

- Monitor prevalence of circulating strains and detect new strains
- Estimate influenza-related morbidity, mortality and economic loss
- Rapidly detect outbreaks
- Assist disease control through rapid preventive action

## Selected References

A special issue of *Emerging Infectious Diseases* (January 2006) focused on influenza. The issue is available on the CDC website at <http://www.cdc.gov/ncidod/EID/index.htm>

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