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 world-wide epidemic, that clearly fits the description of influenza was in 1580. At least four pandemics of influenza occurred in the 19th century, and 3 occured in the 20th century. The pandemic of "Spanish flu" 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. Evidence of the protective efficacy of inactivated vaccines was produced 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, such as pigs and birds. **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 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. 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.

Influenza

- Highly infectious viral illness
- Epidemics reported since at least 1510
- At least 4 pandemics in 19th century
- Estimated 21 million deaths worldwide in pandemic of 1918-1919
- Virus first isolated in 1933

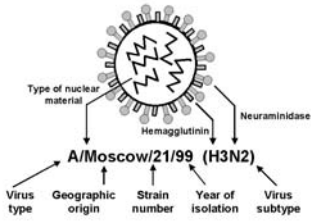
Influenza Virus

- Single-stranded RNA virus
- Family Orthomyxoviridae
- 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 epidemics
  - humans only
  - primarily affects children
- Type C- rarely reported in humans
  - no epidemics

Influenza Virus



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 1997, A/Wuhan/359/95 (H3N2) virus was dominant
  - A/Sydney/5/97 (H3N2) appeared in late 1997 and became the dominant virus in 1998

Influenza Type A Antigenic Shifts

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

Antigenic shift is a major change in one or both surface antigens (H and/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.

Antigenic drift is a minor change in surface antigens that result from point mutations in a gene segment. Antigenic drift may result in epidemics, since incomplete protection remains from past exposures to similar viruses. 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.

In the past 100 years, there have been 4 antigenic shifts that 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 (except for the 1918-1919 strain), but because large numbers of people 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 **epidemics**, 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, with an increase in visits to healthcare providers. 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 localize to families, schools, and isolated communities.

PATHOGENESIS

Following respiratory transmission, the virus attaches to and pene-

trates 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 to 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 around 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, and nonproductive cough. 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 temperature usually last from 2 to 3 days, rarely more than 5 days. They may be decreased by such 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 may have lingering depression and asthenia (lack of strength or energy) for several weeks.

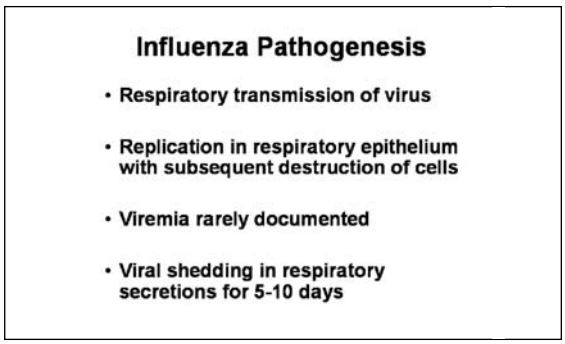
COMPLICATIONS

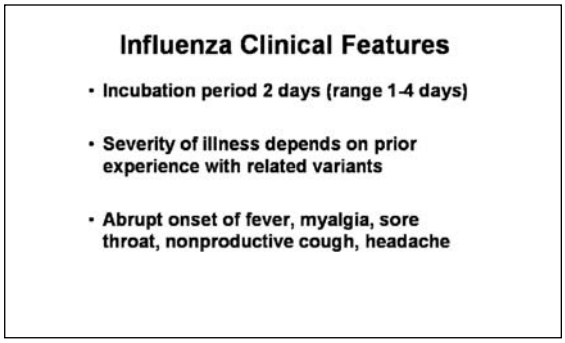
The most frequent complication of influenza is pneumonia, most commonly **secondary bacterial pneumonia** (*e.g.*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Staphylococcus aureus*). **Primary influenza viral pneumonia** is an uncommon complication with a high fatality rate. **Reye syndrome** 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.

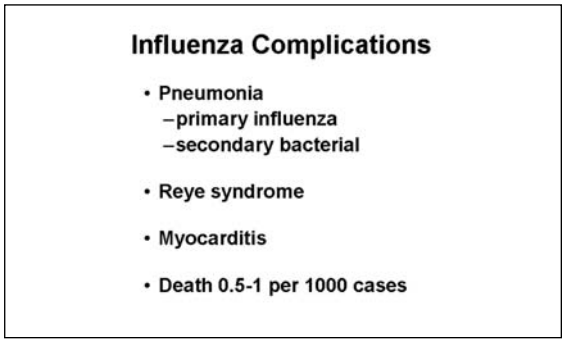
Other complications include **myocarditis** (inflammation of the heart), and **worsening of chronic bronchitis** and other chronic pulmonary diseases. **Death** is reported in 0.5-1 per 1000 cases. The majority of deaths occur in persons ≥65 years of age.

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.







Impact of Influenza

- ~36,000 excess deaths per year
- >90% of deaths among persons ≥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 ≥65 years
- Average of 114,000 influenza-related excess hospitalizations per year since 1969
- 57% of all hospitalizations among persons <65 years of age
- Greater number of hospitalizations during type A (H3N2) epidemics

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 risk in influenza IgG by serologic assay
- Direct antigen testing for type A virus

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 and older, young children, and persons of any age with certain underlying medical conditions. An average of 114,000 hospitalizations per year are related to influenza, more than 50% of which are among persons aged 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 percent, with fatality rates as high as 30 percent. The cost of a severe epidemic has been estimated to be 12 billion dollars.

Among children aged 0-4 years, hospitalization rates have ranged 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 12 months of age and younger are comparable to rates among persons 65 and older.

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.

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 amniotic or allantoic sac of chick embryos or certain cell cultures that support viral replication. A minimum of 48 hours are 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 specimen should be taken less than 5 days from onset and a convalescent specimen taken 10-21 days, or, (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 4-fold 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.

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 transmitted via aerosolized or droplet transmission from the respiratory tract of infected persons. A less important mode of transmission of droplets is by direct contact.

TEMPORAL PATTERN

Influenza activity peaks from December to March in temperate climates, but may occur earlier or later. During 1976-2002, peak influenza activity in the United States occurred most frequently in January (23% of seasons) and February (42% of seasons). However, peak influenza activity occurred in March, April, or May in 20% of seasons. Influenza occurs throughout the year in tropical areas.

COMMUNICABILITY

Maximum communicability occurs 1-2 days before onset to 4-5 days thereafter.

SECULAR TRENDS IN THE UNITED STATES

There is a documented association between influenza and increased morbidity in "high-risk" adults. Hospitalization for adults with high-risk medical conditions increases 2-fold to 5-fold during major epidemics.

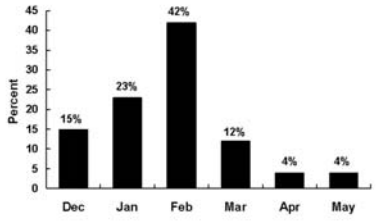
The impact of influenza in the United States is quantified by measuring pneumonia and influenza (P and I) deaths. Death certificate data are collected from 122 U.S. cities with populations of ≥100,000 (approximately 70,000,000). P and I deaths include all deaths for which pneumonia is listed as a primary 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 stan-

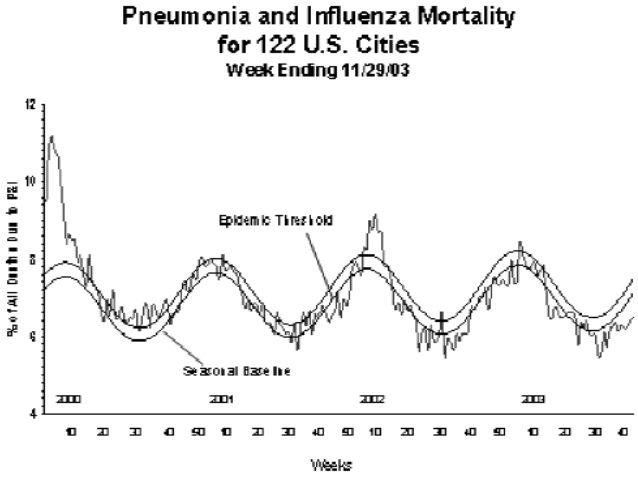
Influenza Epidemiology

• Reservoir	Human, animals (type A only)
• Transmission	Respiratory Probably airborne
• Temporal pattern	Peak December - March in temperate area May occur earlier or later
• Communicability	Maximum 1-2 days before to 4-5 days after onset

Month of Peak Influenza Activity – United States, 1976-2002



dard deviations above the values projected on the basis of a periodic regression model applied to 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.

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. Split vaccines are associated with fewer adverse reactions among children, than previously-produced whole virus vaccines. 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) formulations. TIV is available with thimerosal as a preservative, and in reduced and preservative free formulations.

Live attenuated influenza vaccine (LAIV) was approved for use in the United States in 2003. LAIV is administered by the intranasal route and contains the same three influenza viruses as TIV. The live attenuated influenza viruses in LAIV are **temperature sensitive**, so they do not replicate effectively at core body temperature (38°-39° C). The viruses are also **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.

Vaccinated children can shed vaccine viruses in nasopharyngeal secretions for up to 3 weeks. In one study in a daycare setting, 80% of vaccinated children 8-36 months of age shed at least one virus

strain for an average of 7.6 days. In this study, one instance of transmission of vaccine virus to a contact was documented. The transmitted virus retained it's 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 rarely exceeds 1 year. Priming by prior infection with a closely related strain or prior vaccination enhances immunologic response after vaccination.

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 young adult vaccinees from illness when the vaccine strain is similar to the circulating strain. However, the vaccine is only 30%-40% effective in preventing illness among frail elderly persons.

Although the vaccine is not highly effective in prevention of clinical illness among the elderly, it is effective in prevention of 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 vaccinated residents.

LAIV

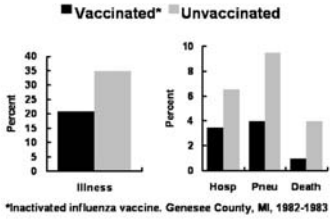
LAIV has been tested in groups of both healthy children and healthy adults. A randomized, double-blind, placebo-controlled trial in healthy children 60-84 months of age assessed the efficacy of the trivalent LAIV against culture confirmed influenza during two influenza seasons. In year one, when vaccine and circulating virus strains were well matched, efficacy was 87% against culture confirmed influenza. In year two, 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.

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

Influenza and Complications Among Nursing Home Residents



*Inactivated influenza vaccine. Genesee County, MI, 1982-1983

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

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. Organized campaigns for high-risk persons who are routinely accessible are optimally undertaken in October and November. The ACIP recommends that high-risk persons, healthcare workers, and children <9 years old being vaccinated for the first time, should begin vaccinations in October. All other groups should begin vaccinations in November. 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 persons), providers should continue to provide vaccine throughout influenza season.

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

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 influenza vaccine during a previous 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 Recommendations

- All persons 50 years of age or older
- 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 should be given by the intramuscular (IM) route. Other methods, such as intradermal, subcutaneous, topical, or mucosal should not be used.

TIV is recommended for **all persons 50 years of age or older**, 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 Reyes syndrome following influenza infection).

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
  - hemoglobinopathies
  - immunosuppression, including HIV infection

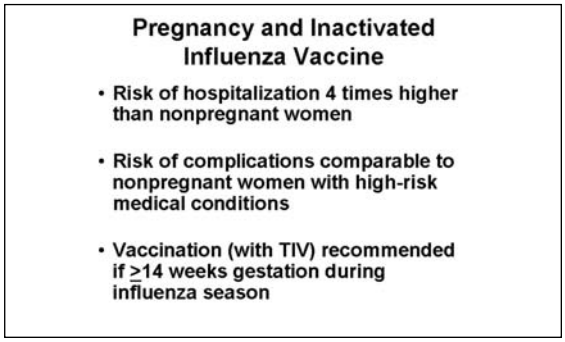
Persons >6 months of age with a chronic illness should receive TIV anually. These chronic illnesses include the following:

- pulmonary illnesses, such as emphysema, chronic bronchitis, or asthma
- cardiovascular illnesses, such as congestive heart failure
- metabolic diseases, including diabetes mellitus
- renal dysfunction
- hemoglobinopathies, such as sickle cell disease
- immunosuppression.

Case reports and limited studies suggest that **pregnant women** may be at increased risk for serious medical complications of

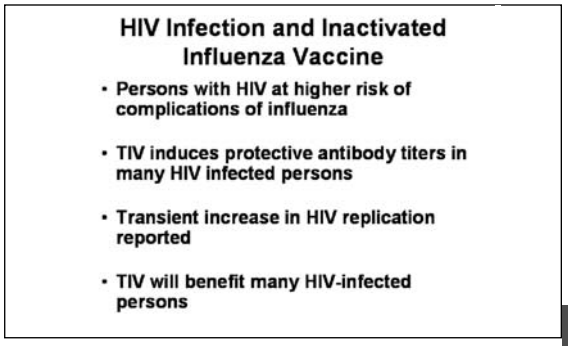
influenza as a result of increases in heart rate, stroke volume and oxygen consumption, decreases in lung capacity, and changes in immunologic function. A recent study found that the risk of hospitalization for influenza-related complications was more than 4 times higher for women in the second or third 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 in at least the 14th week or later of gestation during influenza season. Influenza season in the United States generally occurs in December through March. Therefore, women who become pregnant between March and December are TIV candidates. Pregnant women who have high-risk medical conditions should receive TIV before influenza season regardless of the stage of pregnancy. **Only TIV should be administered to pregnant women.**

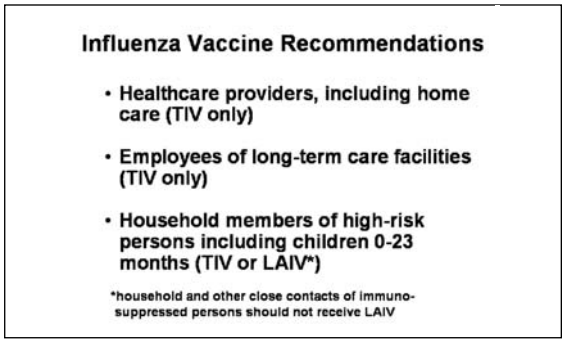


Available data suggest that persons with **HIV infection** may have prolonged influenza illnesses and are at increased risk of complications of influenza. Many persons with HIV infection will develop protective antibody titers following inactivated influenza vaccine. In persons who have advanced HIV 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.

Recent studies have examined the effect of inactivated influenza vaccine on replication of HIV. Some studies have demonstrated a transient increase in viral titer in the blood of vaccinated persons infected with HIV. This phenomenon has also been reported after other vaccines, such as tetanus toxoid and pneumococcal polysaccharide vaccines. Not all studies produced these findings; other investigators using similar methods have not documented increased HIV titers after influenza vaccination. Furthermore, although HIV titers may transiently increase, 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.**



Groups that have contact with high-risk persons should receive TIV. These groups include **healthcare workers, employees of long-term care facilities, and household members of high-risk persons.** These individuals may be younger and healthier, and more likely to be protected from illness than 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 should not be administered to persons with close contact with immunosuppressed persons (*e.g.*, healthcare workers or household contacts).**

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. **Foreign travelers** 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. The most current available vaccine should be used. Any person who wishes to lessen his/her chance of acquiring influenza infection may be vaccinated. These groups may receive TIV, and some may be elegible for LAIV (see below).

Influenza Vaccine Recommendations*

- Providers of essential community services
- Foreign travelers
- Students
- Anyone who wishes to reduce the likelihood of becoming ill from influenza

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

Influenza Vaccination of Children

- Children <24 months at increased risk of hospitalization
- Inactivated influenza vaccination of healthy children 6-23 months is encouraged*
- Vaccination of household contacts and out-of-home caretakers is encouraged

*Beginning in influenza season 2004-2005, routine annual influenza vaccination (TIV) of children 6-23 months of age will be recommended rather than "encouraged"

Beginning in 2002, the ACIP encouraged healthy children aged 6-23 months be vaccinated because they are at increased risk of influenza-related hospitalization. Household contacts and other caregivers of children <24 months of age are also encouraged to receive annual influenza vaccination. Beginning in influenza season 2004-2005, ACIP will recommend (rather than encourage) routine annual influenza vaccination of all children 6-23 months of age. Only TIV should be used for this age group.

LAIV

The optimum timing of LAIV has not been determined. 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 for persons 9-49 years of age. Children 5-8 years of age receiving influenza vaccine for the first time should receive two doses administered 6-10 weeks apart.

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

Age Group	Number of Doses	Route
5-8 years, no previous influenza vaccine	2 (separated by 6-10 weeks)	Intranasal
5-8 years, previous influenza vaccine*	1	Intranasal
9-49 years	1	Intranasal

*LAIV or inactivated vaccine

Live Attenuated Influenza Indications

- Healthy* persons 5 – 49 years of age
  - –Close contacts of persons at high risk for complications of influenza (except immunosuppressed)
  - –Persons who wish to reduce their own risk of influenza

*Persons who do not have medical conditions that increase their risk for complications of influenza

Live attenuated influenza vaccine is approved by the Food and Drug Administration only for use among healthy persons 5-49 years of age. This group, including most persons in close contact with high-risk groups, and those wishing to reduce their risk of influenza, now have the option for choosing either inactivated vaccine or LAIV.

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 individuals. There are no data assessing the risk of transmission of LAIV from vaccine recipients to immunosuppressed contacts. **In the absence of such data, use of inactivated influenza vaccine is preferred for vaccinating household members, healthcare workers, and others who have close contact with immunosuppressed individuals.** This preference is because of the theoretical risk that a live attenuated vaccine virus could be transmitted to the immunosuppressed individual and cause disease. ACIP states no preference between inactivated vaccine and LAIV for vaccination of healthy persons aged 5 to 49 years in close contact with all other high-risk groups.

Vaccination of Healthcare Workers and Close Contacts of Immunosuppressed Persons

- No data regarding transmission from adults vaccinated with LAIV to immunosuppressed persons
- ACIP prefers the use of inactivated influenza vaccine for persons with household or other close contact with immunosuppressed persons, including healthcare workers

The manufacturer's package insert recommends that LAIV not be administered concurrently with other vaccines, because it is not known whether concurrent administration of LAIV with other vaccines affects the safety or efficacy of either LAIV or the simultaneously administered vaccine. In the absence of specific data indicating interference, ACIP recommends that providers follow the simultaneous administration guidelines published in the General Recommendations on Immunization. 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 at the same visit as LAIV. Live vaccines not administered on the same day should be administered at least 4 weeks apart when possible.

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 at the same visit as LAIV
- Live vaccines not administered on the same day should be administered ≥4 weeks apart

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 myalgias are reported in <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 systemic symptoms are no more common than in persons given a placebo injection.

Inactivated Influenza Vaccine Adverse Reactions

• Local reactions	15%-20%
• Fever, malaise	uncommon
• Allergic reactions	rare
• Neurological reactions	very rare

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 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 among persons with severe egg allergy. Persons who have developed hives, had swelling of the lips or tongue, or 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 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 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.

Although influenza vaccination can inhibit the clearance of warfarin and theophylline, studies have failed to show any adverse clinical effects attributable to these drugs among patients receiving influenza vaccine.

LAIV

The safety of the approved LAIV has been assessed in 20 prelicensure clinical trials. More than 6,000 study participants were in the approved age range of 5-49 years. Among healthy children, there were no significant differences between vaccine 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. Data from an unpublished study suggested **a significantly increased risk of asthma or reactive airways disease among children 12-59 months of age** who received LAIV. Because of this, LAIV is not approved for use in children less than 60 months of age, and it should not be used in persons with asthma, reactive airways disease, or other chronic pulmonary diseases.

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 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

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, and generally 3%-10% higher than in 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.

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

There are few data 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 is available, persons at high risk of complications of influenza should not receive LAIV. These persons should continue to receive inactivated influenza vaccine.

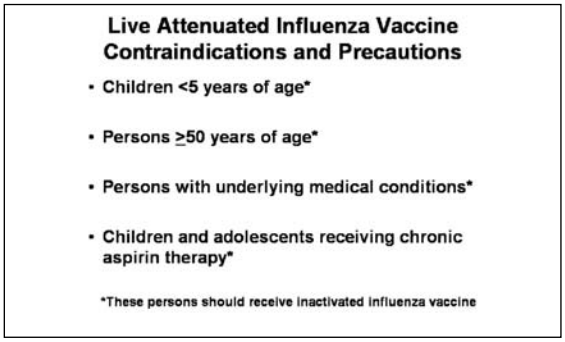
CONTRAINDICATIONS AND PRECAUTIONS TO VACCINATION

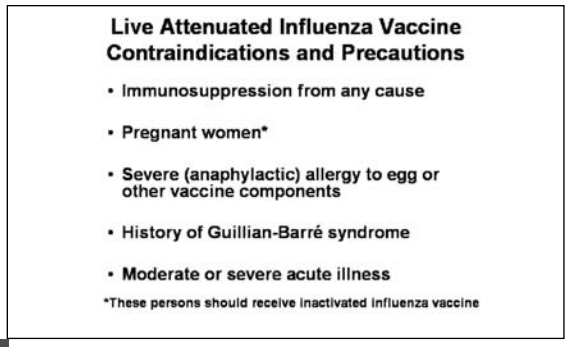
TIV

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. Neither pregnancy nor breastfeeding is a contraindication to inactivated influenza vaccination.

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





LAIV

Persons who should **not** receive LAIV include children less than 5 years of age; persons 50 years of age and older; and persons with chronic medical conditions, including asthma, reactive airways disease or other chronic pulmonary or cardiovascular conditions, metabolic disease such as diabetes, renal disease, or hemoglobinopathies, such as sickle cell disease; and children or adolescents receiving chronic 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.

As with other live virus vaccines, persons who are immunosuppressed because of disease, including HIV, or who are receiving immunosuppressive therapy, should not receive LAIV. 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 nasal congestion is present that 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 antivirals 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

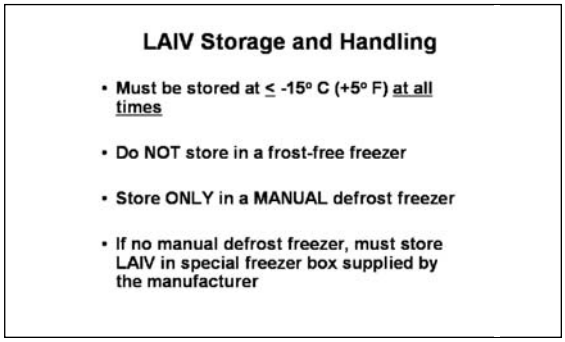
Inactivated influenza vaccine is generally shipped in an insulated container with coolant packs. Although some brands of TIV vaccine can tolerate room temperature for a few days, CDC recommends that the vaccine be stored at refrigerator temperature (2^{o}-8^{o}C [35^{o}-46^{o}F]). **Inactivated influenza vaccine must not be frozen**. Opened multidose vials may be used until the expiration date printed on the package if not visibly contaminated.

LAIV

LAIV must be stored at or below -15^{o}C (+5^{o}F) at all times. The vaccine is shipped from the manufacturer with dry ice, and it should be frozen on arrival at the provider's office. The manufacturer recommends that LAIV not be stored in a frost-free freezer because the temperature in these units may rise above -15^{o} C during the defrost

cycle. LAIV must be stored only in a manual defrost freezer that can reliably maintain -15°C (+5°F). **If a manual defrost freezer is not available, LAIV must be stored in a special manufacturer-supplied freezer box.** The freezer box is made of special insulating material that will protect LAIV from the temperature of defrost cycles in a self-defrosting freezer. Contact the manufacturer for more information about the availability and use of a freezer box.

In general, LAIV should be kept frozen until immediately before it is used, at which time it should be thawed by holding the sprayer in the palm of a hand. The sprayer should not be rolled between the palms because this could dislodge the dose divider clip or plunger. LAIV may also be thawed in a refrigerator. However, it can be stored at refrigerator temperature (2°-8°C) for no more than 24 hours prior to use. Any LAIV that is kept at refrigerator temperature more than 24 hours must be discarded.



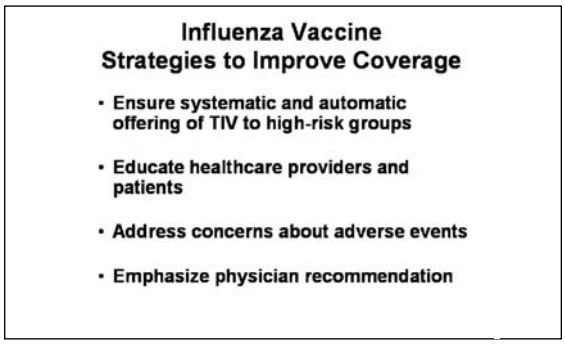
YEAR 2010 OBJECTIVES AND COVERAGE LEVELS

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 2001, 64% of persons 65 years of age and older reported influenza vaccine in the previous year. Vaccination levels were lower in black and Hispanic persons than among non-Hispanic white persons.

STRATEGIES FOR IMPROVING INFLUENZA VACCINE COVERAGE

Up to 75% of persons at high risk for influenza or who die from pneumonia and influenza may have received care in a physician's office during the previous year. One study indicated that all persons who died from pneumonia or influenza and did not reside in a nursing home, had at least one medical visit during the previous year.

An average of less than 20% of persons in high-risk groups receive influenza vaccine each year. More effective strategies for delivering vaccine to high-risk persons, their healthcare providers, and household contacts are needed. Persons for whom the vaccine is recommended can be identified and immunized in a variety of settings.



OUTPATIENT CLINICS AND PHYSICIANS' OFFICES

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.

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.

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.

VISITING NURSES AND OTHERS PROVIDING HOME CARE TO HIGH-RISK PERSONS

Persons providing home care should identify high-risk patients and administer TIV in the home, if necessary.

FACILITIES PROVIDING SERVICES TO PERSONS AGED ≥ 50 YEARS

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

HEALTHCARE FOR TRAVELERS

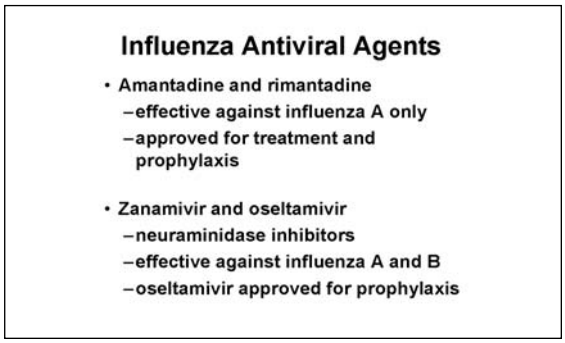
Indications for influenza vaccine should be reviewed prior to travel and vaccine offered, if appropriate.

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. Amantadine and rimantadine are effective against type A influenza only, and are approved by the Food and Drug Administration for both influenza A prophylaxis and treatment in persons 1 year of age and older.

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 2 days. 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 2 days. Oseltamivir is approved for prophylaxis of influenza infection among persons ≥13 years. Zanamivir is not approved for prophylaxis.



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.

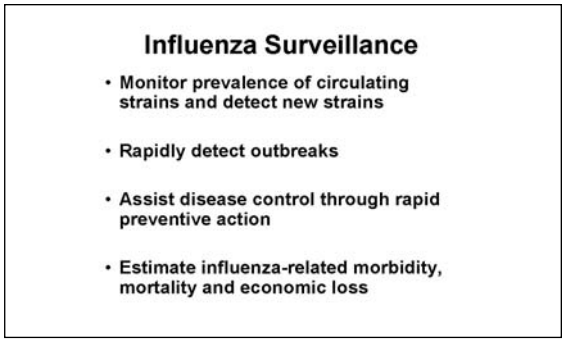
NOSOCOMIAL INFLUENZA CONTROL

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 not immunized or immunized too recently to have protective antibody levels. Antivirals 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 (1) monitor the prevalence of circulating strains and to detect new strains necessary for vaccine formulation; (2) estimate influenza-related impact on morbidity, mortality, and economic loss; (3) rapidly detect outbreaks; and (4) 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: (1) no cases, (2) sporadic, (3) regional (cases occurring in counties collectively contributing less than 50% of a state's population), (4) widespread (cases occurring in counties collectively contributing 50% or more of a state's population).

SENTINEL FAMILY PHYSICIAN NETWORK

Physicians nationwide provide weekly telephone information about the number of cases and hospitalizations that have occurred in their practices; a subgroup of physicians collect nasopharyngeal specimens from selected cases for submission to the Centers for Disease Control and Prevention (CDC) for culture confirmation.

LABORATORY SURVEILLANCE

More than 100 World Health Organization (WHO) Collaborating Laboratories in the U.S. regularly submit reports on the number of specimens tested and the number and type of influenza viruses isolated for each week from early October through mid-May to the WHO Collaborating Center for Influenza at CDC.

SELECTED REFERENCES

American Academy of Pediatrics. Influenza. In Pickering L, ed. *Red Book: 2003 Report of the Committee on Infectious Diseases.* 26th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2003:382-91.

Belshe RB, Mendelman PM, Treanor J, et al. Efficacy of live attenuated, cold-adapted trivalent, intranasal influenza virus vaccine in children. *N Engl J Med* 1998;338:1405-12.

CDC. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2003;52(No. RR-8):1-34. Note: ACIP recommendations for influenza vaccine are revised annually.

CDC. Immunization of health-care workers. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Hospital Infection Control Practices Advisory Committee (HICPAC). *MMWR* 1997;46(RR-18):1-42.

CDC. Using live attenuated influenza vaccine for prevention and control of influenza. *MMWR* 2003;52(No. RR-13):1-8.

Fedson DS, Houck P, Bratzler D. Hospital-based influenza and pneumococcal vaccination: Sutton's law applied to prevention. *Infect Control Hosp Epidemiol* 2000;21:692-699.

Glezen WP, Couch RB. Influenza viruses. In: Evans AS, Kaslow RA, eds. *Viral Infections of Humans. Epidemiology and Control.* 4th edition. New York, NY: Plenum Medical Book Company; 1997:473-505.

McBean AM, Babish JD, Warren JL. The impact and cost of influenza in the elderly. *Arch Intern Med* 1993;153:2105-11.

Murphy KR, Strunk RC. Safe administration of influenza vaccine in asthmatic children hypersensitive to egg protein. *J Pediatr* 1985;106:931-933.

Neuzil KM, Zhu Y, Griffin MR, et al. Burden of interpandemic influenza in children younger than 5 years: a 25 year prospective study. *J Infect Dis* 2002;185:147-52.

Nichol KL, Lind A, Margolis KL, et al. The effectiveness of vaccination against influenza in healthy, working adults. *N Eng J Med* 1995;333:889-93.

Saxen H, Virtanen M. Randomized, placebo-controlled double blind study on the efficacy of influenza immunization on absenteeism of healthcare workers. *Pediatr Infect Dis J* 1999;18:779-83.

Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *J Am Med Assoc* 2003;289:179-86