Complete Summary

GUIDELINE TITLE

Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008.

BIBLIOGRAPHIC SOURCE(S)

Fiore AE, Shay DK, Broder K, Iskander JK, Uyeki TM, Mootrey G, Bresee JS, Cox NS, Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices (ACIP). Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008. MMWR Recomm Rep 2008 Aug 8;57(RR-7):1-60. [502 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Fiore AE, Shay DK, Haber P, Iskander JK, Uyeki TM, Mootrey G, Bresee JS, Cox NJ, Advisory Committee on Immunization Practices (ACIP), Centers for Disease. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2007. MMWR Recomm Rep 2007 Jul 13;56(RR-6):1-54. PubMed

**** REGULATORY ALERT ****

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- April 2, 2008, Relenza (zanamivir): GlaxoSmithKline informed healthcare professionals of changes to the warnings and precautions sections of prescribing information for Relenza. There have been reports (mostly from Japan) of delirium and abnormal behavior leading to injury in patients with influenza who are receiving neuraminidase inhibitors, including Relenza.
- March 4, 2008, Tamiflu (oseltamivir phosphate): Roche and the U.S. Food and Drug Administration (FDA) informed healthcare professionals of neuropsychiatric events associated with the use of Tamiflu, in patients with influenza. Roche has updated the PRECAUTIONS section of the package insert to include the new information and guidance under the Neuropsychiatric Events heading.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Influenza

GUIDELINE CATEGORY

Management
Prevention
Treatment

CLINICAL SPECIALTY

Allergy and Immunology
Family Practice
Geriatrics
Infectious Diseases
Internal Medicine
Pediatrics
Pharmacology
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Emergency Medical Technicians/Paramedics
Health Care Providers
Hospitals
Nurses
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

To update the 2007 recommendations by the Advisory Committee on Immunization Practices (ACIP) regarding the use of influenza vaccine and antiviral agents

TARGET POPULATION

- Children aged 6 months to 18 years
- Persons who are at increased risk for severe complications from influenza, or at higher risk for influenza-associated clinic, emergency department, or hospital visits, including:
    - All children aged 6 to 59 months (i.e., 6 months to 4 years)
    - All persons aged $\geq$50 years
    - Children and adolescents (aged 6 months to 18 years) who are receiving long-term aspirin therapy and who, therefore, might be at risk for experiencing Reye syndrome after influenza virus infection
    - Women who will be pregnant during the influenza season
    - Adults and children who have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological, or metabolic disorders (including diabetes mellitus)
    - Adults and children who have immunosuppression (including immunosuppression caused by medication or by human immunodeficiency virus [HIV])
    - Adults and children who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration
    - Residents of nursing homes and other chronic-care facilities
- Persons who live with or care for persons at high risk
    - Health care providers (HCP)
    - Healthy household contacts (including children) and caregivers of children aged $\leq$59 months (i.e., <5 years) and adults aged $\geq$50 years
    - Healthy household contacts (including children) and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza
- All persons who wish to reduce the likelihood of becoming ill with influenza or transmitting influenza to others

INTERVENTIONS AND PRACTICES CONSIDERED

1. Influenza vaccination
    - Inactivated (i.e., killed-virus) trivalent influenza vaccine (TIV)
    - Live attenuated influenza vaccine (LAIV)
        - Both the inactivated and live, attenuated vaccines prepared for the 2008-2009 season will include:
            - A/Brisbane/59/2007 (H1N1)-like antigen
            - A/Brisbane/10/2007 (H3N2)-like antigen
            - B/Florida/4/2006-like antigen

2. Antiviral agents for influenza

- Zanamivir
- Oseltamivir

Note: Use of amantadine and rimantadine are not recommended.

MAJOR OUTCOMES CONSIDERED

- Influenza-related morbidity and mortality rates
- Influenza-related hospitalization rates
- Vaccine efficacy and effectiveness
- Cost effectiveness of influenza vaccination
- Vaccine coverage levels
- Side effects and adverse reactions of influenza vaccination and antiviral agents

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Center for Disease Control and Prevention's (CDC's) Advisory Committee on Immunization Practices (ACIP) provides annual recommendations for the prevention and control of influenza. The ACIP Influenza Vaccine Working Group meets monthly throughout the year to discuss newly published studies, review current guidelines, and consider potential revisions to the recommendations. As they review the annual recommendations for ACIP consideration of the full committee, members of the Working Group consider a variety of issues, including burden of influenza illness, vaccine effectiveness, safety and coverage in groups recommended for vaccination, feasibility, cost-effectiveness, and anticipated vaccine supply. Working Group members also request periodic updates on vaccine and antiviral production, supply, safety and efficacy from vaccinologists, epidemiologists and manufacturers. State and local immunization program representatives are consulted. Influenza surveillance and antiviral resistance data were obtained from CDC's Influenza Division. The Vaccines and Related Biological Products Advisory Committee provides advice on vaccine strain selection to the Food and Drug Administration (FDA), which selects the viral strains to be used in the annual trivalent influenza vaccines.

Published, peer-reviewed studies are the primary source of data used by ACIP in making these recommendations for the prevention and control of influenza, but unpublished data that are relevant to issues under discussion also might be considered. Among studies discussed or cited, those of greatest scientific quality and those that measured influenza-specific outcomes are the most influential. For example, population-based estimates that use outcomes associated with laboratory-confirmed influenza virus infection outcomes contribute the most specific data for estimates of influenza burden. The best evidence for vaccine or antiviral efficacy and effectiveness comes from randomized controlled trials that assess laboratory-confirmed influenza infections as an outcome measure and consider factors such as timing and intensity of influenza circulation and degree of match between vaccine strains and wild circulating strains. Randomized, placebo-controlled trials cannot be performed in populations for which vaccination already is recommended, but observational studies that assess outcomes associated with laboratory-confirmed influenza infection can provide important vaccine or antiviral effectiveness data. Randomized, placebo-controlled clinical trials are the best source of vaccine and antiviral safety data for common adverse events; however, such studies do not have the power to identify rare but potentially serious adverse events. The frequency of rare adverse events that might be associated with vaccination or antiviral treatment is best assessed by retrospective reviews of computerized medical records from large linked clinical databases, and by reviewing medical charts of persons who are identified as having a potential adverse event after vaccination. Vaccine coverage data from a nationally representative, randomly selected population that includes verification of vaccination through health-care record review is superior to coverage data derived from limited populations or without verification of vaccination but is rarely available for older children or adults. Finally, studies that assess vaccination program practices that improve vaccination coverage are most influential in formulating recommendations if the study design includes a nonintervention comparison group. In cited studies that included statistical comparisons, a difference was considered to be statistically significant if the p-value was <0.05 or

the 95% confidence interval (CI) around an estimate of effect allowed rejection of the null hypothesis (i.e., no effect).

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Cost-Effectiveness of Influenza Vaccine

Economic studies of influenza vaccination are difficult to compare because they have used different measures of both costs and benefits (e.g., cost-only, cost-effectiveness, cost-benefit, or cost-utility). However, most studies find that vaccination reduces or minimizes health care, societal, and individual costs, or the productivity losses and absenteeism associated with influenza illness. One national study estimated the annual economic burden of seasonal influenza in the United States (using 2003 population and dollars) to be $87.1 billion, including $10.4 billion in direct medical costs.

Studies of influenza vaccination in the United States among persons aged $\geq$65 years have documented substantial reductions in hospitalizations and deaths and overall societal cost savings. Studies comparing adults in different age groups also find that vaccination is economically beneficial. One study that compared the economic impact of vaccination among persons aged $\geq$65 years with those aged 15 to 64 years indicated that vaccination resulted in a net savings per quality-adjusted life year (QALY) and that the Medicare program saved costs of treating illness by paying for vaccination. A study of a larger population comparing persons aged 50 to 64 years with those aged $\geq$65 years estimated the cost-effectiveness of influenza vaccination to be $28,000 per QALY saved (in 2000 dollars) in persons aged 50 to 64 years compared with $980 per QALY saved among persons aged $\geq$65 years.

Economic analyses among adults aged <65 years have reported mixed results regarding influenza vaccination. Two studies in the United States found that vaccination can reduce both direct medical costs and indirect costs from work absenteeism and reduced productivity. However, another United States study indicated no productivity and absentee savings in a strategy to vaccinate healthy working adults, although vaccination was still estimated to be cost-effective.

Cost analyses have documented the considerable cost burden of illness among children. In a study of 727 children at a medical center during 2000--2004, the mean total cost of hospitalization for influenza-related illness was $13,159 ($39,792 for patients admitted to an intensive care unit and $7,030 for patients cared for exclusively on the wards). Strategies that focus on vaccinating children with medical conditions that confer a higher risk for influenza complications are more cost-effective than a strategy of vaccinating all children. An analysis that compared the costs of vaccinating children of varying ages with trivalent inactivated influenza vaccine (TIV) and live, attenuated influenza vaccine (LAIV) indicated that costs per QALY saved increased with age for both vaccines. In 2003 dollars per QALY saved, costs for routine vaccination using TIV were $12,000 for healthy children aged 6 to 23 months and $119,000 for healthy adolescents aged

12 to 17 years, compared with $9,000 and $109,000 using LAIV, respectively. Economic evaluations of vaccinating children have demonstrated a wide range of cost estimates, but have generally found this strategy to be either cost-saving or cost-beneficial.

Economic analyses are sensitive to the vaccination venue, with vaccination in medical care settings incurring higher projected costs. In a published model, the mean cost (year 2004 values) of vaccination was lower in mass vaccination ($17.04) and pharmacy ($11.57) settings than in scheduled doctor's office visits ($28.67). Vaccination in nonmedical settings was projected to be cost saving for healthy adults aged ≥50 years and for high-risk adults of all ages. For healthy adults aged 18 to 49 years, preventing an episode of influenza would cost $90 if vaccination were delivered in a pharmacy setting, $210 in a mass vaccination setting, and $870 during a scheduled doctor's office visit. Medicare payment rates in recent years have been less than the costs associated with providing vaccination in a medical practice.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

These recommendations were presented to the full Advisory Committee on Immunization Practices (ACIP) and approved in February 2008. Modifications were made to the ACIP statement during the subsequent review process at the Centers for Disease Control and Prevention (CDC) to update and clarify wording in the document.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Primary Changes and Updates in the Recommendations

The 2008 recommendations include five principal changes or updates:

- Beginning with the 2008--09 influenza season, annual vaccination of all children aged 5 to 18 years is recommended. Annual vaccination of all children aged 5 to 18 years should begin in September or as soon as vaccine is available for the 2008--09 influenza season, if feasible, but annual vaccination of all children aged 5 to 18 years should begin no later than during the 2009--10 influenza season.
- Annual vaccination of all children aged 6 months to 4 years (59 months) and older children with conditions that place them at increased risk for complications from influenza should continue. Children and adolescents at high risk for influenza complications should continue to be a focus of vaccination efforts as providers and programs transition to routinely vaccinating all children.
- Either trivalent inactivated influenza vaccine (TIV) or live, attenuated influenza vaccine (LAIV) can be used when vaccinating healthy persons aged

2 to 49 years. Children aged 6 months to 8 years should receive 2 doses of vaccine if they have not been vaccinated previously at any time with either LAIV or TIV (doses separated by ≥4 weeks); 2 doses are required for protection in these children. Children aged 6 months to 8 years who received only 1 dose in their first year of vaccination should receive 2 doses the following year. LAIV should not be administered to children aged <5 years with possible reactive airways disease, such as those who have had recurrent wheezing or a recent wheezing episode. Children with possible reactive airways disease, persons at higher risk for influenza complications because of underlying medical conditions, children aged 6 to 23 months, and persons aged >49 years should receive TIV.

- The 2008--09 trivalent vaccine virus strains are A/Brisbane/59/2007 (H1N1)-like, A/Brisbane/10/2007 (H3N2)-like, and B/Florida/4/2006-like antigens

Oseltamivir-resistant influenza A (H1N1) strains have been identified in the United States and some other countries. However, oseltamivir or zanamivir continue to be the recommended antivirals for treatment of influenza because other influenza virus strains remain sensitive to oseltamivir, and resistance levels to other antiviral medications remain high.

Recommendations for Using TIV and LAIV During the 2007–08 Influenza Season

Both TIV and LAIV prepared for the 2008--09 season will include A/Brisbane/59/2007 (H1N1)-like, A/Brisbane/10/2007 (H3N2)-like, and B/Florida/4/2006-like antigens. These viruses will be used because they are representative of influenza viruses that are forecasted to be circulating in the United States during the 2008--09 influenza season and have favorable growth properties in eggs.

TIV and LAIV can be used to reduce the risk for influenza virus infection and its complications. Vaccination providers should administer influenza vaccine to any person who wishes to reduce the likelihood of becoming ill with influenza or transmitting influenza to others should they become infected.

Healthy, nonpregnant persons aged 2 to 49 years can choose to receive either vaccine. Some TIV formulations are U.S. Food and Drug Administration (FDA)-licensed for use in persons as young as age 6 months (see "Recommended Vaccines for Different Age Groups," below). TIV is licensed for use in persons with high-risk conditions. LAIV is FDA-licensed for use only for persons aged 2 to 49 years. In addition, FDA has indicated that the safety of LAIV has not been established in persons with underlying medical conditions that confer a higher risk for influenza complications. All children aged 6 months- to 8 years who have not been vaccinated previously at any time with at least 1 dose of either LAIV or TIV should receive 2 doses of age-appropriate vaccine in the same season, with a single dose during subsequent seasons.

Target Groups for Vaccination

Influenza vaccine should be provided to all persons who want to reduce the risk of becoming ill with influenza or of transmitting it to others. However, emphasis on providing routine vaccination annually to certain groups at higher risk for

influenza infection or complications is advised, including all children aged 6 months to 18 years, all persons aged ≥50 years, and other adults at risk for medical complications from influenza or more likely to require medical care should receive influenza vaccine annually. In addition, all persons who live with or care for persons at high risk for influenza-related complications, including contacts of children aged <6 months, should receive influenza vaccine annually (see Boxes 1 and 2 in the original guideline document). Approximately 83% of the United States population is included in one or more of these target groups; however, <40% of the U.S. population received an influenza vaccination during 2007--2008.

Children Aged 6 Months to 18 Years

Beginning with the 2008--09 influenza season, annual vaccination for all children aged 6 months to 18 years is recommended. Annual vaccination of all children aged 6 months to 4 years (59 months) and older children with conditions that place them at increased risk for complications from influenza should continue. Children and adolescents at high risk for influenza complications should continue to be a focus of vaccination efforts as providers and programs transition to routinely vaccinating all children. Annual vaccination of all children aged 5 to 18 years should begin in September 2008 or as soon as vaccine is available for the 2008--09 influenza season, if feasible. Annual vaccination of all children aged 5 to 18 years should begin no later than during the 2009--10 influenza season.

Healthy children aged 2 to 18 years can receive either LAIV or TIV. Children aged 6 to 23 months, those aged 2 to 4 years who have evidence of possible reactive airways disease (see "Considerations When Using LAIV," below) or who have medical conditions that put them at higher risk for influenza complications should receive TIV. All children aged 6 months to 8 years who have not received vaccination against influenza previously should receive 2 doses of vaccine the first year they are vaccinated.

Persons at Risk for Medical Complications

Vaccination to prevent influenza is particularly important for the following persons who are at increased risk for severe complications from influenza, or at higher risk for influenza-associated clinic, emergency department, or hospital visits. When vaccine supply is limited, vaccination efforts should focus on delivering vaccination to these persons:

- All children aged 6 months to 4 years (59 months)
- All persons aged ≥50 years
- Children and adolescents (aged 6 months to 18 years) who are receiving long-term aspirin therapy and who, therefore, might be at risk for experiencing Reye syndrome after influenza virus infection
- Women who will be pregnant during the influenza season
- Adults and children who have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological, or metabolic disorders (including diabetes mellitus)
- Adults and children who have immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus [HIV])

- Adults and children who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration
- Residents of nursing homes and other chronic-care facilities

Persons Who Live With or Care for Persons at High Risk for Influenza-Related Complications

To prevent transmission to persons identified above, vaccination with TIV or LAIV (unless contraindicated) is recommended for the following persons. When vaccine supply is limited, vaccination efforts should focus on delivering vaccination to these persons:

- Health-care providers (HCP)
- Healthy household contacts (including children) and caregivers of children aged $\leq$59 months (i.e., aged <5 years) and adults aged $\geq$50 years
- Healthy household contacts (including children) and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza

Additional Information Regarding Vaccination of Specific Populations

Children Aged 6 Months to 18 Years

Beginning with the 2008--09 influenza season, all children aged 6 months to 18 years should be vaccinated against influenza annually. The expansion of vaccination to include all children aged 5 to 18 years should begin in 2008 if feasible, but no later than the 2009 to 10 influenza season. In 2004, the Advisory Committee on Immunization Practices (ACIP) recommended routine vaccination for all children aged 6 to 23 months, and in 2006, ACIP expanded the recommendation to include all children aged 24 to 59 months. The committee's recommendation to expand routine influenza vaccination to include all school-age children and adolescents aged 5 to 18 years is based on 1) accumulated evidence that influenza vaccine is effective and safe for school-aged children (see "Influenza Vaccine Efficacy, Effectiveness, and Safety" in the original guideline document), 2) increased evidence that influenza has substantial adverse impacts among school-aged children and their contacts (e.g., school absenteeism, increased antibiotic use, medical care visits, and parental work loss) (see "Health-Care Use, Hospitalizations, and Deaths Attributed to Influenza" in the original guideline document), and, 3) an expectation that a simplified age-based influenza vaccine recommendation for all school-age children and adolescents will improve vaccine coverage levels among the approximately 50% of school-aged children who already had a risk- or contact-based indication for annual influenza vaccination.

Children typically have the highest attack rates during community outbreaks of influenza and serve as a major source of transmission within communities. If sufficient vaccination coverage among children can be achieved, evidence for additional benefits, such as the indirect effect of reducing influenza among persons who have close contact with children and reducing overall transmission within communities, might occur. Achieving and sustaining community-level

reductions in influenza will require mobilization of community resources and development of sustainable annual vaccination campaigns to assist health-care providers and vaccination programs in providing influenza vaccination services to children of all ages. In many areas, innovative community-based efforts, which might include mass vaccination programs in school or other community settings, will be needed to supplement vaccination services provided in health-care providers' offices or public health clinics. In nonrandomized community-based controlled trials, reductions in influenza-like illness (ILI)-related symptoms and medical visits among household contacts have been demonstrated in communities where vaccination programs among school-aged children were established, compared with communities without such vaccination programs. Rates of school absences associated with ILI also were significantly reduced in some studies. In addition, reducing influenza transmission among children through vaccination has reduced rates for self-reported ILI among household contacts and among unvaccinated children.

Reducing influenza-related illness among children who are at high risk for influenza complications should continue to be a primary focus of influenza-prevention efforts. Children who should be vaccinated because they are at high risk for influenza complications include all children aged 6 to 59 months, children with certain medical conditions, children who are contacts of children aged <5 years (60 months) or persons aged $\geq$50 years, and children who are contacts of persons at high risk for influenza complications because of medical conditions. Influenza vaccines are not licensed by FDA for use among children aged <6 months. Because these infants are at higher risk for influenza complications compared with other child age groups, prevention efforts that focus on vaccinating household contacts and out-of-home caregivers to reduce the risk for influenza in these infants is a high priority.

All children aged 6 months to 8 years who have not received vaccination against influenza previously should receive 2 doses of vaccine the first influenza season that they are vaccinated. The second dose should be administered 4 or more weeks after the initial dose. For example, children aged 6 months to 8 years who were vaccinated for the first time during the 2007--08 influenza season but only received 1 dose during that season should receive 2 doses of the 2008--09 influenza vaccine. All other children aged 6 months to 8 years who have previously received 1 or more doses of influenza vaccine at any time should receive 1 dose of the 2008--09 influenza vaccine. Children aged 6 months to 8 years who only received a single vaccination during a season before 2007--08 should receive 1 dose of the 2008--09 influenza vaccine. If possible, both doses should be administered before onset of influenza season. However, vaccination, including the second dose, is recommended even after influenza virus begins to circulate in a community.

HCP and Other Persons Who Can Transmit Influenza to Those at High Risk

Healthy persons who are infected with influenza virus, including those with subclinical infection, can transmit influenza virus to persons at higher risk for complications from influenza. In addition to HCP, groups that can transmit influenza to high risk persons and that should be vaccinated include:

- Employees of assisted living and other residences for persons in groups at high risk
- Persons who provide home care to persons in groups at high risk
- Household contacts (including children) of persons in groups at high risk

In addition, because children aged <5 years are at increased risk for influenza-related hospitalization compared with older children, vaccination is recommended for their household contacts and out-of-home caregivers. Because influenza vaccines have not been licensed by FDA for use among children aged <6 months, emphasis should be placed on vaccinating contacts of children aged <6 months. When vaccine supply is limited, priority for vaccination should be given to contacts of children aged <6 months.

Healthy HCP and persons aged 2 to 49 years who are contacts of persons in these groups and who are not contacts of severely immunosuppressed persons (see "Close Contacts of Immunocompromised Persons," below) should receive either LAIV or TIV when indicated or requested. All other persons, including pregnant women, should receive TIV.

All HCP, as well as those in training for health-care professions, should be vaccinated annually against influenza. Persons working in health-care settings who should be vaccinated include physicians, nurses, and other workers in both hospital and outpatient-care settings, medical emergency-response workers (e.g., paramedics and emergency medical technicians), employees of nursing home and chronic-care facilities who have contact with patients or residents, and students in these professions who will have contact with patients.

Facilities that employ HCP should provide vaccine to workers by using approaches that have been demonstrated to be effective in increasing vaccination coverage. Health-care administrators should consider the level of vaccination coverage among HCP to be one measure of a patient safety quality program and consider obtaining signed declinations from personnel who decline influenza vaccination for reasons other than medical contraindications. Influenza vaccination rates among HCP within facilities should be regularly measured and reported, and ward-, unit-, and specialty-specific coverage rates should be provided to staff and administration. Studies have demonstrated that organized campaigns can attain higher rates of vaccination among HCP with moderate effort and using strategies that increase vaccine acceptance.

Efforts to increase vaccination coverage among HCP are supported by various national accrediting and professional organizations and in certain states by statute. The Joint Commission on Accreditation of Health-Care Organizations has approved an infection-control standard that requires accredited organizations to offer influenza vaccinations to staff, including volunteers and licensed independent practitioners with close patient contact. The standard became an accreditation requirement beginning January 1, 2007. In addition, the Infectious Diseases Society of America recommended mandatory vaccination for HCP, with a provision for declination of vaccination based on religious or medical reasons. Fifteen states have regulations regarding vaccination of HCP in long-term–care facilities, six states require that health-care facilities offer influenza vaccination to HCP, and four states require that HCP either receive influenza vaccination or indicate a religious, medical, or philosophical reason for not being vaccinated.

Close Contacts of Immunocompromised Persons

Immunocompromised persons are at risk for influenza complications but might have insufficient responses to vaccination. Close contacts of immunocompromised persons, including HCP, should be vaccinated to reduce the risk for influenza transmission. TIV is preferred for vaccinating household members, HCP, and others who have close contact with severely immunosuppressed persons (e.g., patients with hematopoietic stem cell transplants) during those periods in which the immunosuppressed person requires care in a protective environment (typically defined as a specialized patient-care area with a positive airflow relative to the corridor, high-efficiency particulate air filtration, and frequent air changes).

LAIV transmission from a recently vaccinated person causing clinically important illness in an immunocompromised contact has not been reported. The rationale for avoiding use of LAIV among HCP or other close contacts of severely immunocompromised patients is the theoretical risk that a live, attenuated vaccine virus could be transmitted to the severely immunosuppressed person. As a precautionary measure, HCP who receive LAIV should avoid providing care for severely immunosuppressed patients for 7 days after vaccination. Hospital visitors who have received LAIV should avoid contact with severely immunosuppressed persons in protected environments for 7 days after vaccination but should not be restricted from visiting less severely immunosuppressed patients.

No preference is indicated for TIV use by persons who have close contact with persons with lesser degrees of immunosuppression (e.g., persons with diabetes, persons with asthma who take corticosteroids, persons who have recently received chemotherapy or radiation but who are not being cared for in a protective environment as defined above, or persons infected with HIV) or for TIV use by HCP or other healthy nonpregnant persons aged 2 to 49 years in close contact with persons in all other groups at high risk.

Pregnant Women

Pregnant women are at risk for influenza complications, and all women who are pregnant or will be pregnant during influenza season should be vaccinated. The American College of Obstetricians and Gynecologists and the American Academy of Family Physicians also have recommended routine vaccination of all pregnant women. No preference is indicated for use of TIV that does not contain thimerosal as a preservative (see "Vaccine Preservative [Thimerosal] in Multidose Vials of TIV" in the original guideline document) for any group recommended for vaccination, including pregnant women. LAIV is not licensed for use in pregnant women. However, pregnant women do not need to avoid contact with persons recently vaccinated with LAIV.

Breastfeeding Mothers

Vaccination is recommended for all persons, including breastfeeding women, who are contacts of infants or children aged $\leq$59 months (i.e., <5 years), because infants and young children are at high risk for influenza complications and are more likely to require medical care or hospitalization if infected. Breastfeeding does not affect the immune response adversely and is not a contraindication for

vaccination. Women who are breastfeeding can receive either TIV or LAIV unless contraindicated because of other medical conditions.

Travelers

The risk for exposure to influenza during travel depends on the time of year and destination. In the temperate regions of the Southern Hemisphere, influenza activity occurs typically during April to September. In temperate climate zones of the Northern and Southern Hemispheres, travelers also can be exposed to influenza during the summer, especially when traveling as part of large tourist groups (e.g., on cruise ships) that include persons from areas of the world in which influenza viruses are circulating. In the tropics, influenza occurs throughout the year. In a study among Swiss travelers to tropical and subtropical countries, influenza was the most frequently acquired vaccine-preventable disease.

Any traveler who wants to reduce the risk for influenza infection should consider influenza vaccination, preferably at least 2 weeks before departure. In particular, persons at high risk for complications of influenza and who were not vaccinated with influenza vaccine during the preceding fall or winter should consider receiving influenza vaccine before travel if they plan to

- Travel to the tropics
- Travel with organized tourist groups at any time of year
- Travel to the Southern Hemisphere during April to September

No information is available regarding the benefits of revaccinating persons before summer travel who already were vaccinated during the preceding fall. Persons at high risk who received the previous season's vaccine before travel should be revaccinated with the current vaccine the following fall or winter. Persons at higher risk for influenza complications should consult with their health-care practitioner to discuss the risk for influenza or other travel-related diseases before embarking on travel during the summer.

General Population

Vaccination is recommended for any person who wishes to reduce the likelihood of becoming ill with influenza or transmitting influenza to others should they become infected. Healthy, nonpregnant persons aged 2 to 49 years might choose to receive either TIV or LAIV. All other persons aged $\geq$6 months should receive TIV. Persons who provide essential community services should be considered for vaccination to minimize disruption of essential activities during influenza outbreaks. Students or other persons in institutional settings (e.g., those who reside in dormitories or correctional facilities) should be encouraged to receive vaccine to minimize morbidity and the disruption of routine activities during epidemics.

Recommended Vaccines for Different Age Groups

When vaccinating children aged 6 to 35 months with TIV, health-care providers should use TIV that has been licensed by the FDA for this age group (i.e., TIV manufactured by Sanofi Pasteur ([FluZone]). TIV from Novartis (Fluvirin) is FDA-

approved in the United States for use among persons aged ≥4 years. TIV from GlaxoSmithKline (Fluarix and FluLaval) or CSL Biotherapies (Afluria) is labeled for use in persons aged ≥18 years because data to demonstrate efficacy among younger persons have not been provided to FDA. LAIV from MedImmune (FluMist) is licensed for use by healthy nonpregnant persons aged 2 to 49 years (see Table 1 in the original guideline document). A vaccine dose does not need to be repeated if inadvertently administered to a person who does not have an age indication for the vaccine formulation given. Expanded age and risk group indications for licensed vaccines are likely over the next several years, and vaccination providers should be alert to these changes. In addition, several new vaccine formulations are being evaluated in immunogenicity and efficacy trials; when licensed, these new products will increase the influenza vaccine supply and provide additional vaccine choices for practitioners and their patients.

Influenza Vaccines and Use of Influenza Antiviral Medications

Administration of TIV and influenza antivirals during the same medical visit is acceptable. 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. Persons receiving antivirals within the period 2 days before to 14 days after vaccination with LAIV should be revaccinated at a later date.

Persons Who Should Not Be Vaccinated with TIV

TIV should not be administered to persons known to have anaphylactic hypersensitivity to eggs or to other components of the influenza vaccine. Prophylactic use of antiviral agents is an option for preventing influenza among such persons. Information about vaccine components is located in package inserts from each manufacturer. Persons with moderate to severe acute febrile illness usually should not be vaccinated until their symptoms have abated. However, minor illnesses with or without fever do not contraindicate use of influenza vaccine. Guillain-Barré Syndrome (GBS) within 6 weeks following a previous dose of TIV is considered to be a precaution for use of TIV.

Considerations When Using LAIV

LAIV is an option for vaccination of healthy, nonpregnant persons aged 2 to 49 years, including HCP and other close contacts of high-risk persons (excepting severely immunocompromised persons who require care in a protected environment). No preference is indicated for LAIV or TIV when considering vaccination of healthy, nonpregnant persons aged 2 to 49 years. Use of the term "healthy" in this recommendation refers to persons who do not have any of the underlying medical conditions that confer high risk for severe complications (see "Persons Who Should Not Be Vaccinated with LAIV," below). However, during periods when inactivated vaccine is in short supply, use of LAIV is encouraged when feasible for eligible persons (including HCP) because use of LAIV by these persons might increase availability of TIV for persons in groups targeted for vaccination, but who cannot receive LAIV. Possible advantages of LAIV include its potential to induce a broad mucosal and systemic immune response in children,

its ease of administration, and the possibly increased acceptability of an intranasal rather than intramuscular route of administration.

If the vaccine recipient sneezes after administration, the dose should not be repeated. However, if nasal congestion is present that might impede delivery of the vaccine to the nasopharyngeal mucosa, deferral of administration should be considered until resolution of the illness, or TIV should be administered instead. No data exist regarding concomitant use of nasal corticosteroids or other intranasal medications.

Although FDA licensure of LAIV excludes children aged 2 to 4 years with a history of asthma or recurrent wheezing, the precise risk, if any, of wheezing caused by LAIV among these children is unknown because experience with LAIV among these young children is limited. Young children might not have a history of recurrent wheezing if their exposure to respiratory viruses has been limited because of their age. Certain children might have a history of wheezing with respiratory illnesses but have not had asthma diagnosed. The following screening recommendations should be used to assist persons who administer influenza vaccines in providing the appropriate vaccine for children aged 2 to 4 years.

Clinicians and vaccination programs should screen for possible reactive airways diseases when considering use of LAIV for children aged 2 to 4 years, and should avoid use of this vaccine in children with asthma or a recent wheezing episode. Health-care providers should consult the medical record, when available, to identify children aged 2 to 4 years with asthma or recurrent wheezing that might indicate asthma. In addition, to identify children who might be at greater risk for asthma and possibly at increased risk for wheezing after receiving LAIV, parents or caregivers of children aged 2 to 4 years should be asked: "In the past 12 months, has a health-care provider ever told you that your child had wheezing or asthma?" Children whose parents or caregivers answer "yes" to this question and children who have asthma or who had a wheezing episode noted in the medical record during the preceding 12 months should not receive LAIV. TIV is available for use in children with asthma or possible reactive airways diseases.

LAIV can be administered to persons with minor acute illnesses (e.g., diarrhea or mild upper respiratory tract infection with or without fever). However, if nasal congestion is present that might impede delivery of the vaccine to the nasopharyngeal mucosa, deferral of administration should be considered until resolution of the illness.

Persons Who Should Not Be Vaccinated with LAIV

The effectiveness or safety of LAIV is not known for the following groups, and these persons should not be vaccinated with LAIV:

- Persons with a history of hypersensitivity, including anaphylaxis, to any of the components of LAIV or to eggs
- Persons aged <2 years or those aged $\geq$50 years
- Persons with any of the underlying medical conditions that serve as an indication for routine influenza vaccination, including asthma, reactive airways disease, or other chronic disorders of the pulmonary or cardiovascular systems; other underlying medical conditions, including such metabolic

diseases as diabetes, renal dysfunction, and hemoglobinopathies; or known or suspected immunodeficiency diseases or immunosuppressive states
- Children 2 to 4 years whose parents or caregivers report that a health-care provider has told them during the preceding 12 months that their child has wheezing or asthma, or whose medical record indicates a wheezing episode has occurred during the preceding 12 months
- Children or adolescents receiving aspirin or other salicylates (because of the association of Reye syndrome with wild-type influenza virus infection)
- Persons with a history of GBS after influenza vaccination
- Pregnant women

Personnel Who Can Administer LAIV

Low-level introduction of vaccine viruses into the environment probably is unavoidable when administering LAIV. The risk for acquiring vaccine viruses from the environment is unknown but probably low. Severely immunosuppressed persons should not administer LAIV. However, other persons at higher risk for influenza complications can administer LAIV. These include persons with underlying medical conditions placing them at higher risk or who are likely to be at risk, including pregnant women, persons with asthma, and persons aged $\geq$50 years.

Concurrent Administration of Influenza Vaccine with Other Vaccines

Use of LAIV concurrently with measles, mumps, rubella (MMR) alone and MMR and varicella vaccine among children aged 12 to 15 months has been studied, and no interference with the immunogenicity to antigens in any of the vaccines was observed. Among adults aged $\geq$50 years, the safety and immunogenicity of zoster vaccine and TIV was similar whether administered simultaneously or spaced 4 weeks apart. In the absence of specific data indicating interference, following ACIP's general recommendations for vaccination is prudent. Inactivated vaccines do not interfere with the immune response to other inactivated vaccines or to live vaccines. Inactivated or live vaccines can be administered simultaneously with LAIV. However, after administration of a live vaccine, at least 4 weeks should pass before another live vaccine is administered.

Recommendations for Vaccination Administration and Vaccination Programs

Although influenza vaccination levels increased substantially during the 1990s, little progress has been made toward achieving national health objectives, and further improvements in vaccine coverage levels are needed. Strategies to improve vaccination levels, including using reminder/recall systems and standing orders programs, should be implemented whenever feasible. Vaccination coverage can be increased by administering vaccine before and during the influenza season to persons during hospitalizations or routine health-care visits. Vaccinations can be provided in alternative settings (e.g., pharmacies, grocery stores, workplaces, or other locations in the community), thereby making special visits to physicians' offices or clinics unnecessary. Coordinated campaigns such as the National Influenza Vaccination Week (December 8--14, 2008) provide opportunities to refocus public attention on the benefits, safety, and availability of influenza vaccination throughout the influenza season. When educating patients regarding

potential adverse events, clinicians should emphasize that 1) TIV contains noninfectious killed viruses and cannot cause influenza, 2) LAIV contains weakened influenza viruses that cannot replicate outside the upper respiratory tract and are unlikely to infect others, and 3) concomitant symptoms or respiratory disease unrelated to vaccination with either TIV or LAIV can occur after vaccination.

Information About the Vaccines for Children Program

The Vaccines for Children (VFC) program supplies vaccine to all states, territories, and the District of Columbia for use by participating providers. These vaccines are to be provided to eligible children without vaccine cost to the patient or the provider, although the provider might charge a vaccine administration fee. All routine childhood vaccines recommended by ACIP are available through this program, including influenza vaccines. The program saves parents and providers out-of-pocket expenses for vaccine purchases and provides cost savings to states through CDC's vaccine contracts. The program results in lower vaccine prices and ensures that all states pay the same contract prices. Detailed information about the VFC program is available at http://www.cdc.gov/vaccines/programs/vfc/default.htm.

Influenza Vaccine Supply Considerations

The annual supply of influenza vaccine and the timing of its distribution cannot be guaranteed in any year. During the 2007--08 influenza season, 113 million doses of influenza vaccine were distributed in the United States. Total production of influenza vaccine for the United States is anticipated to be >130 million doses for the 2008--09 season, depending on demand and production yields. However, influenza vaccine distribution delays or vaccine shortages remain possible in part because of the inherent critical time constraints in manufacturing the vaccine given the annual updating of the influenza vaccine strains and various other manufacturing and regulatory issues. To ensure optimal use of available doses of influenza vaccine, health-care providers, those planning organized campaigns, and state and local public health agencies should develop plans for expanding outreach and infrastructure to vaccinate more persons in targeted groups and others who wish to reduce their risk for influenza and develop contingency plans for the timing and prioritization of administering influenza vaccine if the supply of vaccine is delayed or reduced.

If supplies of TIV are not adequate, vaccination should be carried out in accordance with local circumstances of supply and demand based on the judgment of state and local health officials and health-care providers. Guidance for tiered use of TIV during prolonged distribution delays or supply shortfalls is available at http://www.cdc.gov/flu/ and will be modified as needed in the event of shortage. CDC and other public health agencies will assess the vaccine supply on a continuing basis throughout the manufacturing period and will inform both providers and the general public if any indication exists of a substantial delay or an inadequate supply.

Because LAIV is only recommended for use in healthy nonpregnant persons aged 2 to 49 years, no recommendations for prioritization of LAIV use are made. Either LAIV or TIV can be used when considering vaccination of healthy, nonpregnant

persons aged 2 to 49 years. However, during shortages of TIV, LAIV should be used preferentially when feasible for all healthy nonpregnant persons aged 2 to 49 years (including HCP) who desire or are recommended for vaccination to increase the availability of inactivated vaccine for persons at high risk.

Timing of Vaccination

Vaccination efforts should be structured to ensure the vaccination of as many persons as possible over the course of several months, with emphasis on vaccinating before influenza activity in the community begins. Even if vaccine distribution begins before October, distribution probably will not be completed until December or January. The following recommendations reflect this phased distribution of vaccine.

In any given year, the optimal time to vaccinate patients cannot be precisely determined because influenza seasons vary in their timing and duration, and more than one outbreak might occur in a single community in a single year. In the United States, localized outbreaks that indicate the start of seasonal influenza activity can occur as early as October. However, in >80% of influenza seasons since 1976, peak influenza activity (which is often close to the midpoint of influenza activity for the season) has not occurred until January or later, and in >60% of seasons, the peak was in February or later (see Figure 1 in the original guideline document). In general, health-care providers should begin offering vaccination soon after vaccine becomes available and if possible by October. To avoid missed opportunities for vaccination, providers should offer vaccination during routine health-care visits or during hospitalizations whenever vaccine is available.

Vaccination efforts should continue throughout the season, because the duration of the influenza season varies, and influenza might not appear in certain communities until February or March. Providers should offer influenza vaccine routinely, and organized vaccination campaigns should continue throughout the influenza season, including after influenza activity has begun in the community. Vaccine administered in December or later, even if influenza activity has already begun, is likely to be beneficial in the majority of influenza seasons. The majority of adults have antibody protection against influenza virus infection within 2 weeks after vaccination.

All children aged 6 months to 8 years who have not received vaccination against influenza previously should receive their first dose as soon after vaccine becomes available as is feasible. This practice increases the opportunity for both doses to be administered before or shortly after the onset of influenza activity.

Persons and institutions planning substantial organized vaccination campaigns (e.g., health departments, occupational health clinics, and community vaccinators) should consider scheduling these events after at least mid-October because the availability of vaccine in any location cannot be ensured consistently in early fall. Scheduling campaigns after mid-October will minimize the need for cancellations because vaccine is unavailable. These vaccination clinics should be scheduled through December, and later if feasible, with attention to settings that serve children aged 6 to 59 months, pregnant women, other persons aged <50 years at increased risk for influenza-related complications, persons aged $\geq$50

years, HCP, and persons who are household contacts of children aged ≤59 months or other persons at high risk. Planners are encouraged to develop the capacity and flexibility to schedule at least one vaccination clinic in December. Guidelines for planning large-scale immunization clinics are available at http://www.cdc.gov/flu/professionals/vaccination/vax_clinic.htm.

During a vaccine shortage or delay, substantial proportions of TIV doses may not be released and distributed until November and December, or later. When the vaccine is substantially delayed or disease activity has not subsided, providers should consider offering vaccination clinics into January and beyond as long as vaccine supplies are available. Campaigns using LAIV also may extend into January and beyond.

Strategies for Implementing Vaccination Recommendations in Health-Care Settings

See the "Description of Implementation Strategies" field in this summary for information on this topic.

Recommendations for Using Antiviral Agents for Seasonal Influenza

Annual vaccination is the primary strategy for preventing complications of influenza virus infections. Antiviral medications with activity against influenza viruses are useful adjuncts in the prevention of influenza, and effective when used early in the course of illness for treatment. Four influenza antiviral agents are licensed in the United States: amantadine, rimantadine, zanamivir, and oseltamivir. Influenza A virus resistance to amantadine and rimantadine can emerge rapidly during treatment. Because antiviral testing results indicated high levels of resistance, neither amantadine nor rimantadine should be used for the treatment or chemoprophylaxis of influenza A in the United States during the 2007--08 influenza season. Surveillance demonstrating that susceptibility to these antiviral medications has been reestablished among circulating influenza A viruses will be needed before amantadine or rimantadine can be used for the treatment or chemoprophylaxis of influenza A. Oseltamivir or zanamivir can be prescribed if antiviral chemoprophylaxis or treatment of influenza is indicated. Oseltamivir is licensed for treatment of influenza in persons aged ≥1 year, and zanamivir is licensed for treating influenza in persons aged ≥7 years. Oseltamivir and zanamivir can be used for chemoprophylaxis of influenza; oseltamivir is licensed for use as chemoprophylaxis in persons aged ≥1 year, and zanamivir is licensed for use in persons aged ≥5 years.

During the 2007--08 influenza season, influenza A (H1N1) viruses with a mutation that confers resistance to oseltamivir were identified in the United States and other countries. As of June 27, 2008, in the United States, 111 (7.6%) of 1,464 influenza A viruses tested, and none of 305 influenza B viruses tested have been found to be resistant to oseltamivir. All of the resistant viruses identified in the United States and elsewhere are influenza A (H1N1) viruses. Of 1020 influenza A (H1N1) viruses isolated from patients in the United States, 111 (10.9%) exhibited a specific genetic mutation that confers oseltamivir resistance. Influenza A (H1N1) virus strains that are resistant to oseltamivir remain sensitive to zanamivir. Neuraminidase inhibitor medications continue to be the recommended agents for treatment and chemoprophylaxis of influenza in the United States. However,

clinicians should be alert to changes in antiviral recommendations that might occur as additional antiviral resistance data becomes available during the 2008--09 influenza season (http://www.cdc.gov/flu/professionals/antivirals/index.htm).

Role of Laboratory Diagnosis

Influenza surveillance information and diagnostic testing can aid clinical judgment and help guide treatment decisions. However, only 69% of practitioners in one recent survey indicated that they test patients for influenza during the influenza season. The accuracy of clinical diagnosis of influenza on the basis of symptoms alone is limited because symptoms from illness caused by other pathogens can overlap considerably with influenza (see "Clinical Signs and Symptoms of Influenza" in the original guideline document).

Diagnostic tests available for influenza include viral culture, serology, rapid antigen testing, reverse transcriptase-polymerase chain reaction (RT-PCR), and immunofluorescence assays. As with any diagnostic test, results should be evaluated in the context of other clinical and epidemiologic information available to health-care providers. Sensitivity and specificity of any test for influenza can vary by the laboratory that performs the test, the type of test used, the type of specimen tested, the quality of the specimen, and the timing of specimen collection in relation to illness onset. Among respiratory specimens for viral isolation or rapid detection of influenza viruses, nasopharyngeal and nasal specimens have higher yields than throat swab specimens. In addition, positive influenza tests have been reported up to 7 days after receipt of LAIV.

Commercial rapid diagnostic tests are available that can detect influenza viruses within 30 minutes. Certain tests are licensed for use in any outpatient setting, whereas others must be used in a moderately complex clinical laboratory. These rapid tests differ in the types of influenza viruses they can detect and whether they can distinguish between influenza types. Different tests can detect 1) only influenza A viruses; 2) both influenza A and B viruses, but not distinguish between the two types; or 3) both influenza A and B and distinguish between the two. None of the rapid tests provide any information regarding influenza A virus subtypes.

The types of specimens acceptable for use (i.e., throat, nasopharyngeal, or nasal aspirates, swabs, or washes) also vary by test, but all perform best when collected as close to illness onset as possible. The specificity and, in particular, the sensitivity of rapid tests are lower than for viral culture and vary by test. Rapid tests for influenza have high specificity (>90%), but are only moderately sensitive (<70%). A recent study found sensitivity to be as low as 42% in clinical practice. Rapid tests appear to have higher sensitivity when used in young children, compared with adults, possibly because young children with influenza typically shed higher concentrations of influenza viruses than adults. Since RT-PCR has high sensitivity to detect influenza virus infection compared to viral culture, rapid tests have lower sensitivity than viral culture when compared to RT-PCR.

The limitations of rapid diagnostic tests must be understood in order to properly interpret results. Positive rapid influenza test results are generally reliable when community influenza activity is high and are useful in deciding whether to initiate antiviral treatment. Negative rapid test results are less helpful in making

treatment decisions for individual patients when influenza activity in a community is high. Because of the lower sensitivity of the rapid tests, physicians should consider confirming negative tests with viral culture or other means because of the possibility of false-negative rapid test results, especially during periods of peak community influenza activity. The positive predictive value of rapid tests will be lower during periods of low influenza activity, and clinicians should consider the positive and negative predictive values of the test in the context of the level of influenza activity in their community when interpreting results. When local influenza activity is high, persons with severe respiratory symptoms or persons with acute respiratory illness who are at higher risk for influenza complications should still be considered for influenza antiviral treatment despite a negative rapid influenza test unless illness can be attributed to another cause. However, because certain bacterial infections can produce symptoms similar to influenza, if bacterial infections are suspected, they should be considered and treated appropriately. In addition, secondary invasive bacterial infections can be a severe complication of influenza. Package inserts and the laboratory performing the test should be consulted for more details regarding use of rapid diagnostic tests. Additional updated information concerning diagnostic testing is available at http://www.cdc.gov/flu/professionals/diagnosis/.

Despite the availability of rapid diagnostic tests, clinical specimens collected in virus surveillance systems for viral culture are critical for surveillance purposes. Only culture isolates of influenza viruses can provide specific information regarding circulating strains and subtypes of influenza viruses and data on antiviral resistance. This information is needed to compare current circulating influenza strains with vaccine strains, to guide decisions regarding influenza treatment and chemoprophylaxis, and to formulate vaccine for the coming year. Virus isolates also are needed to monitor antiviral resistance and the emergence of novel human influenza A virus subtypes that might pose a pandemic threat. Influenza surveillance by state and local health departments and CDC can provide information regarding the circulation of influenza viruses in the community, which can help inform decisions about the likelihood that a compatible clinical syndrome is indeed influenza.

Antiviral Agents for Influenza

Zanamivir and oseltamivir are chemically related antiviral medications known as neuraminidase inhibitors that have activity against both influenza A and B viruses. The two medications differ in pharmacokinetics, adverse effects, routes of administration, approved age groups, dosages, and costs. An overview of the indications, use, administration, and known primary adverse events of these medications is presented in the following sections. Package inserts should be consulted for additional information. Detailed information regarding amantadine and rimantadine (adamantanes) is available in previous ACIP influenza recommendations.

Indications for Use of Antivirals

Treatment

Initiation of antiviral treatment within 2 days of illness onset is recommended, although the benefit of treatment is greater as the time after illness onset is

reduced. Certain persons have a high priority for treatment (see Box 3 in the original guideline document); however, treatment does not need to be limited to these persons. In clinical trials conducted in outpatient settings, the benefit of antiviral treatment for uncomplicated influenza was minimal unless treatment was initiated within 48 hours after illness onset. However, no data are available on the benefit for severe influenza when antiviral treatment is initiated >2 days after illness onset. The recommended duration of treatment with either zanamivir or oseltamivir is 5 days.

The Infectious Diseases Society of America and the American Thoracic Society have recommended that persons with community-acquired pneumonia and laboratory-confirmed influenza should receive either oseltamivir or zanamivir if treatment can be initiated within 48 hours of symptom onset. Patients who present >48 hours after illness onset are potential candidates for treatment if they have influenza pneumonia or to reduce viral shedding while hospitalized. The American Academy of Pediatrics recommends antiviral treatment of any child with influenza who is also at high risk of influenza complications, regardless of vaccination status, and any otherwise healthy child with moderate-to-severe influenza infection who might benefit from the decrease in duration of clinical symptoms documented to occur with therapy.

Chemoprophylaxis

Chemoprophylactic drugs are not a substitute for vaccination, although they are critical adjuncts in preventing and controlling influenza. Certain persons are at higher priority for chemoprophylaxis (see Box 4 in the original guideline document); however, chemoprophylaxis does not need to be limited to these persons. In community studies of healthy adults, both oseltamivir and zanamivir had similar efficacy in preventing febrile, laboratory-confirmed influenza illness (efficacy: zanamivir, 84%; oseltamivir, 82%). Both antiviral agents also have prevented influenza illness among persons administered chemoprophylaxis after a household member had influenza diagnosed (efficacy: zanamivir, 72%--82%; oseltamivir, 68%--89%. Studies have demonstrated moderate to excellent efficacy for prevention of influenza among patients in institutional settings. For example, a 6-week study of oseltamivir chemoprophylaxis among nursing home residents demonstrated a 92% reduction in influenza illness. A 4-week study among community-dwelling persons at higher risk for influenza complications (median age: 60 years) demonstrated that zanamivir had an 83% effectiveness in preventing symptomatic laboratory-confirmed influenza. The efficacy of antiviral agents in preventing influenza among severely immunocompromised persons is unknown. A small nonrandomized study conducted in a stem cell transplant unit suggested that oseltamivir can prevent progression to pneumonia among influenza-infected patients.

When determining the timing and duration for administering influenza antiviral medications for chemoprophylaxis, factors related to cost, compliance, and potential adverse events should be considered. To be maximally effective as chemoprophylaxis, the drug must be taken each day for the duration of influenza activity in the community. Additional clinical guidelines on the use of antiviral medications to prevent influenza are available.

<u>Persons at High Risk Who Are Vaccinated After Influenza Activity Has Begun</u>

Development of antibodies in adults after vaccination takes approximately 2 weeks. Therefore, when influenza vaccine is administered after influenza activity in a community has begun, chemoprophylaxis should be considered for persons at higher risk for influenza complications during the time from vaccination until immunity has developed. Children aged <9 years who receive influenza vaccination for the first time might require as much as 6 weeks of chemoprophylaxis (i.e., chemoprophylaxis until 2 weeks after the second dose when immunity after vaccination would be expected). Persons at higher risk for complications of influenza still can benefit from vaccination after community influenza activity has begun because influenza viruses might still be circulating at the time vaccine-induced immunity is achieved.

Persons Who Provide Care to Those at High Risk

To reduce the spread of virus to persons at high risk, chemoprophylaxis during peak influenza activity can be considered for unvaccinated persons who have frequent contact with persons at high risk. Persons with frequent contact might include employees of hospitals, clinics, and chronic-care facilities; household members; visiting nurses; and volunteer workers. If an outbreak is caused by a strain of influenza that might not be covered by the vaccine, chemoprophylaxis should be considered for all such persons, regardless of their vaccination status.

Persons Who Have Immune Deficiencies

Chemoprophylaxis can be considered for persons at high risk who are more likely to have an inadequate antibody response to influenza vaccine. This category includes persons infected with HIV, particularly those with advanced HIV disease. No published data are available concerning possible efficacy of chemoprophylaxis among persons with HIV infection or interactions with other drugs used to manage HIV infection. Such patients should be monitored closely if chemoprophylaxis is administered.

Other Persons

Chemoprophylaxis throughout the influenza season or during increases in influenza activity within the community might be appropriate for persons at high risk for whom vaccination is contraindicated, or for whom vaccination is likely to be ineffective. Health-care providers and patients should make decisions regarding whether to begin chemoprophylaxis and how long to continue it on an individual basis.

Antiviral Drug-Resistant Strains of Influenza Virus

See the original guideline document for a discussion of antiviral drug-resistant strains of influenza virus.

Prevention and Treatment of Influenza when Oseltamivir Resistance Is Suspected

Testing for antiviral resistance in influenza viruses is not available in clinical settings. Because the proportion of influenza viruses that are resistant to

oseltamivir remains <5% in the United States, oseltamivir or zanamivir remain the medications recommended for prevention and treatment of influenza. Influenza caused by oseltamivir-resistant viruses appears to be indistinguishable from illness caused by oseltamivir-sensitive viruses. When local viral surveillance data indicates that oseltamivir-resistant viruses are widespread in the community, clinicians have several options. Consultation with local health authorities to aid in decision-making is recommended as a first step. Persons who are candidates for receiving chemoprophylaxis as part of an outbreak known to be caused by oseltamivir-resistant viruses or who are being treated for influenza illness in communities where oseltamivir-resistant viruses are known to be circulating widely can receive zanamivir. However, zanamivir is not licensed for chemoprophylaxis indications in children aged <5 years, and is not licensed for treatment in children aged <7 years. In addition, zanamivir is not recommended for use in persons with chronic cardiopulmonary conditions, and can be difficult to administer to critically ill patients because of the inhalation mechanism of delivery. In these circumstances, a combination of oseltamivir and either rimantadine or amantadine can be considered, because influenza A (H1N1) viruses characterized to date that were resistant to oseltamivir have usually been susceptible to adamantane medications. However, adamantanes should not be used for chemoprophylaxis or treatment of influenza A unless they are part of a regimen that also includes a neuraminidase inhibitor, because viral surveillance data has documented that adamantane resistance among influenza A viruses is common. Influenza B viruses are not sensitive to adamantane drugs.

Control of Influenza Outbreaks in Institutions

Use of antiviral drugs for treatment and chemoprophylaxis of influenza is a key component of influenza outbreak control in institutions. In addition to antiviral medications, other outbreak-control measures include instituting droplet precautions and establishing cohorts of patients with confirmed or suspected influenza, reoffering influenza vaccinations to unvaccinated staff and patients, restricting staff movement between wards or buildings, and restricting contact between ill staff or visitors and patients. Both adamantanes and neuraminidase inhibitors have been successfully used to control outbreaks caused by antiviral susceptible strains when antivirals are combined with other infection control measures.

When confirmed or suspected outbreaks of influenza occur in institutions that house persons at high risk, chemoprophylaxis with a neuraminidase inhibitor medication should be started as early as possible to reduce the spread of the virus. In these situations, having preapproved orders from physicians or plans to obtain orders for antiviral medications on short notice can substantially expedite administration of antiviral medications. Specimens should be collected from ill cases for viral culture to assess antiviral resistance and provide data on the outbreak viruses. Chemoprophylaxis should be administered to all eligible residents, regardless of whether they received influenza vaccinations during the previous fall, and should continue for a minimum of 2 weeks. If surveillance indicates that new cases continue to occur, chemoprophylaxis should be continued until approximately 7 to 10 days after illness onset in the last patient. Chemoprophylaxis also can be offered to unvaccinated staff members who provide care to persons at high risk. Chemoprophylaxis should be considered for all employees, regardless of their vaccination status, if indications exist that the

outbreak is caused by a strain of influenza virus that is not well-matched by the vaccine. Such indications might include multiple documented breakthrough influenza-virus infections among vaccinated persons, studies indicating low vaccine effectiveness, or circulation in the surrounding community of suspected index case(s) of strains not contained in the vaccine.

In addition to use in nursing homes, chemoprophylaxis also can be considered for controlling influenza outbreaks in other closed or semiclosed settings (e.g., dormitories, correctional facilities, or other settings in which persons live in close proximity). To limit the potential transmission of drug-resistant virus during outbreaks in institutions, whether in chronic or acute-care settings or other closed settings, measures should be taken to reduce contact between persons taking antiviral drugs for treatment and other persons, including those taking chemoprophylaxis.

Dosage

Dosage recommendations vary by age group and medical conditions (see Table 4 in the original guideline document).

Adults

Zanamivir is licensed for treatment of adults with uncomplicated acute illness caused by influenza A or B virus, and for chemoprophylaxis of influenza among adults. Zanamivir is not recommended for persons with underlying airways disease (e.g., asthma or chronic obstructive pulmonary diseases).

Oseltamivir is licensed for treatment of adults with uncomplicated acute illness caused by influenza A or B virus and for chemoprophylaxis of influenza among adults. Dosages and schedules for adults are listed (see Table 4 in the original guideline document).

Children

Zanamivir is licensed for treatment of influenza among children aged ≥7 years. The recommended dosage of zanamivir for treatment of influenza is 2 inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) twice daily (approximately 12 hours apart). Zanamivir is licensed for chemoprophylaxis of influenza among children aged ≥5 years; the chemoprophylaxis dosage of zanamivir for children aged ≥5 years is 10 mg (2 inhalations) once a day.

Oseltamivir is licensed for treatment and chemoprophylaxis among children aged ≥1 year. Recommended treatment dosages vary by the weight of the child: 30 mg twice a day for children who weigh ≤15 kg, 45 mg twice a day for children who weigh >15 to 23 kg, 60 mg twice a day for those who weigh >23 to 40 kg, and 75 mg twice a day for those who weigh >40 kg. Dosages for chemoprophylaxis are the same for each weight group, but doses are administered only once per day rather than twice.

Persons Aged ≥65 Years

No reduction in dosage for Oseltamivir or zanamivir is recommended on the basis of age alone.

Persons with Impaired Renal Function

Limited data are available regarding the safety and efficacy of zanamivir for patients with impaired renal function. Among patients with renal failure who were administered a single intravenous dose of zanamivir, decreases in renal clearance, increases in half-life, and increased systemic exposure to zanamivir were reported. However, a limited number of healthy volunteers who were administered high doses of intravenous zanamivir tolerated systemic levels of zanamivir that were substantially higher than those resulting from administration of zanamivir by oral inhalation at the recommended dose. On the basis of these considerations, the manufacturer recommends no dose adjustment for inhaled zanamivir for a 5-day course of treatment for patients with either mild-to-moderate or severe impairment in renal function.

Serum concentrations of oseltamivir carboxylate, the active metabolite of oseltamivir, increase with declining renal function. For patients with creatinine clearance of 10 to 30 mL per minute, a reduction of the treatment dosage of oseltamivir to 75 mg once daily and in the chemoprophylaxis dosage to 75 mg every other day is recommended. No treatment or chemoprophylaxis dosing recommendations are available for patients undergoing routine renal dialysis treatment.

Persons with Liver Disease

Use of zanamivir or oseltamivir has not been studied among persons with hepatic dysfunction.

Persons with Seizure Disorders

Seizure events have been reported during postmarketing use of zanamivir and oseltamivir, although no epidemiologic studies have reported any increased risk for seizures with either zanamivir or oseltamivir use.

Persons with Immunosuppression

A recent retrospective case-control study demonstrated that oseltamivir was safe and well tolerated when used during the control of an influenza outbreak among hematopoietic stem cell transplant recipients living in a residential facility.

Route

Oseltamivir is administered orally in capsule or oral suspension form. Zanamivir is available as a dry powder that is self-administered via oral inhalation by using a plastic device included in the package with the medication. Patients should be instructed about the correct use of this device.

Adverse Events

When considering use of influenza antiviral medications (i.e., choice of antiviral drug, dosage, and duration of therapy), clinicians must consider the patient's age, weight, and renal function (see Table 4 in the original guideline document); presence of other medical conditions; indications for use (i.e., chemoprophylaxis or therapy); and the potential for interaction with other medications.

See the "Potential Harms" field in this summary for more information on side effects and adverse reactions.

Responding to Adverse Events after Vaccination

Health-care professionals should report all clinically significant adverse events after influenza vaccination promptly to the Vaccine Adverse Event Reporting System (VAERS), even if the health-care professional is not certain that the vaccine caused the event. Clinically significant adverse events that follow vaccination should be reported at http://www.vaers.hhs.gov. Reports may be filed securely online or by telephone at 1-800-822-7967 to request reporting forms or other assistance.

National Vaccine Injury Compensation Program

The National Vaccine Injury Compensation Program (VICP), established by the National Childhood Vaccine Injury Act of 1986, as amended, provides a mechanism through which compensation can be paid on behalf of a person determined to have been injured or to have died as a result of receiving a vaccine covered by VICP. The Vaccine Injury Table lists the vaccines covered by VICP and the injuries and conditions (including death) for which compensation might be paid. If the injury or condition is not on the Table, or does not occur within the specified time period on the Table, persons must prove that the vaccine caused the injury or condition.

For a person to be eligible for compensation, the general filing deadlines for injuries require claims to be filed within 3 years after the first symptom of the vaccine injury; for a death, claims must be filed within 2 years of the vaccine-related death and not more than 4 years after the start of the first symptom of the vaccine-related injury from which the death occurred. When a new vaccine is covered by VICP or when a new injury/condition is added to the Table, claims that do not meet the general filing deadlines must be filed within 2 years from the date the vaccine or injury/condition is added to the Table for injuries or deaths that occurred up to 8 years before the Table change. Persons of all ages who receive a VICP-covered vaccine might be eligible to file a claim. Both the intranasal (LAIV) and injectable (TIV) trivalent influenza vaccines are covered under VICP. Additional information about VICP is available at http://www.hrsa.gov/vaccinecompensation or by calling 1-800-338-2382.

Reporting of Serious Adverse Events After Antiviral Medications

Severe adverse events associated with the administration of antiviral medications used to prevent or treat influenza (e.g., those resulting in hospitalization or death) should be reported to MedWatch, FDA's Safety Information and Adverse Event Reporting Program, at telephone 1-800-FDA-1088, by facsimile at 1-800-FDA-0178, or via the Internet by sending Report Form 3500 (available at

http://www.fda.gov/medwatch/safety/3500.pdf). Instructions regarding the types of adverse events that should be reported are included on MedWatch report forms.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Improved vaccination coverage levels
- Appropriate use of antiviral drugs used for chemoprophylaxis or treatment of influenza as adjuncts to vaccine

POTENTIAL HARMS

Trivalent Inactivated Influenza Vaccine (TIV)

Adverse Events after Receipt of TIV

Children

Studies support the safety of annual TIV in children and adolescents. The largest published postlicensure population-based study assessed TIV safety in 215,600 children aged <18 years and 8,476 children aged 6 to 23 months enrolled in one of five health maintenance organizations (HMOs) during 1993--1999. This study indicated no increase in biologically plausible, medically attended events during the 2 weeks after inactivated influenza vaccination, compared with control periods 3 to 4 weeks before and after vaccination. A retrospective study using medical records data from approximately 45,000 children aged 6 to 23 months provided additional evidence supporting overall safety of TIV in this age group. Vaccination was not associated with statistically significant increases in any medically attended outcome, and 13 diagnoses, including acute upper respiratory illness, otitis media and asthma, were significantly less common.

In a study of 791 healthy children aged 1 to 15 years, postvaccination fever was noted among 11.5% of those aged 1 to 5 years, 4.6% among those aged 6 to 10 years, and 5.1% among those aged 11 to 15 years. Fever, malaise, myalgia, and other systemic symptoms that can occur after vaccination with inactivated vaccine most often affect persons who have had no previous exposure to the influenza virus antigens in the vaccine (e.g., young children). These reactions begin 6 to 12

hours after vaccination and can persist for 1 to 2 days. Data about potential adverse events among children after influenza vaccination are available from the Vaccine Adverse Event Reporting System (VAERS). A recently published review of VAERS reports submitted after administration of TIV to children aged 6 to 23 months documented that the most frequently reported adverse events were fever, rash, injection-site reactions, and seizures; the majority of the limited number of reported seizures appeared to be febrile. Because of the limitations of passive reporting systems, determining causality for specific types of adverse events, with the exception of injection-site reactions, usually is not possible using VAERS data alone.

Adults

In placebo-controlled studies among adults, the most frequent side effect of vaccination was soreness at the vaccination site (affecting 10% to 64% of patients) that lasted <2 days. These local reactions typically were mild and rarely interfered with the recipients' ability to conduct usual daily activities. Placebo-controlled trials demonstrate that among older persons and healthy young adults, administration of TIV is not associated with higher rates for systemic symptoms (e.g., fever, malaise, myalgia, and headache) when compared with placebo injections.

Pregnant Women and Neonates

The U.S. Food and Drug Administration (FDA) has classified TIV as a "Pregnancy Category C" medication, indicating that animal reproduction studies have not been conducted to support a labeling change. Available data indicate that influenza vaccine does not cause fetal harm when administered to a pregnant woman or affect reproductive capacity. One study of approximately 2,000 pregnant women who received TIV during pregnancy demonstrated no adverse fetal effects and no adverse effects during infancy or early childhood. A matched case-control study of 252 pregnant women who received TIV within the 6 months before delivery determined no adverse events after vaccination among pregnant women and no difference in pregnancy outcomes compared with 826 pregnant women who were not vaccinated. During 2000--2003, an estimated 2 million pregnant women were vaccinated, and only 20 adverse events among women who received TIV were reported to VAERS during this time, including nine injection-site reactions and eight systemic reactions (e.g., fever, headache, and myalgias). In addition, three miscarriages were reported, but these were not known to be causally related to vaccination. Similar results have been reported in certain smaller studies, and a recent international review of data on the safety of TIV concluded that no evidence exists to suggest harm to the fetus.

Persons with Chronic Medical Conditions

In a randomized cross-over study of children and adults with asthma, no increase in asthma exacerbations was reported for either age group, and a second study indicated no increase in wheezing among vaccinated asthmatic children. One study reported that 20%--28% of children with asthma aged 9 months to 18 years had local pain and swelling at the site of influenza vaccination, and another study reported that 23% of children aged 6 months to 4 years with chronic heart or lung disease had local reactions. A blinded, randomized, cross-over study of

1,952 adults and children with asthma demonstrated that only self-reported "body aches" were reported more frequently after TIV (25%) than placebo-injection (21%). However, a placebo-controlled trial of TIV indicated no difference in local reactions among 53 children aged 6 months to 6 years with high-risk medical conditions or among 305 healthy children aged 3 to 12 years.

Among children with high-risk medical conditions, one study of 52 children aged 6 months to 3 years reported fever among 27% and irritability and insomnia among 25%; and a study among 33 children aged 6 to 18 months reported that one child had irritability and one had a fever and seizure after vaccination. No placebo comparison group was used in these studies.

Immunocompromised Persons

Data demonstrating safety of TIV for human immunodeficiency virus (HIV)-infected persons are limited, but no evidence exists that vaccination has a clinically important impact on HIV infection or immunocompetence. One study demonstrated a transient (i.e., 2 to 4 week) increase in HIV RNA (ribonucleic acid) levels in one HIV-infected person after influenza virus infection. Studies have demonstrated a transient increase in replication of HIV-1 in the plasma or peripheral blood mononuclear cells of HIV-infected persons after vaccine administration. However, more recent and better-designed studies have not documented a substantial increase in the replication of HIV. CD4+ T-lymphocyte cell counts or progression of HIV disease have not been demonstrated to change substantially after influenza vaccination among HIV-infected persons compared with unvaccinated HIV-infected persons. Limited information is available concerning the effect of antiretroviral therapy on increases in HIV RNA levels after either natural influenza virus infection or influenza vaccination.

Hypersensitivity

Immediate and presumably allergic reactions (e.g., hives, angioedema, allergic asthma, and systemic anaphylaxis) occur rarely after influenza vaccination. These reactions probably result from hypersensitivity to certain vaccine components; the majority of reactions probably are caused by residual egg protein. Although influenza vaccines contain only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Manufacturers use a variety of different compounds to inactivate influenza viruses and add antibiotics to prevent bacterial contamination. Package inserts should be consulted for additional information.

Persons who have had hives or swelling of the lips or tongue, or who have experienced acute respiratory distress or who collapse after eating eggs, should consult a physician for appropriate evaluation to help determine if vaccine should be administered. Persons who have documented immunoglobulin E (IgE)-mediated hypersensitivity to eggs, including those who have had occupational asthma related to egg exposure or other allergic responses to egg protein, also might be at increased risk for allergic reactions to influenza vaccine, and consultation with a physician before vaccination should be considered.

Hypersensitivity reactions to other vaccine components can occur but are rare. Although exposure to vaccines containing thimerosal can lead to hypersensitivity,

the majority of patients do not have reactions to thimerosal when it is administered as a component of vaccines, even when patch or intradermal tests for thimerosal indicate hypersensitivity. When reported, hypersensitivity to thimerosal typically has consisted of local delayed hypersensitivity reactions.

Guillain-Barré Syndrome (GBS) and TIV

The annual incidence of Guillain-Barré Syndrome (GBS) is 10 to 20 cases per 1 million adults. Substantial evidence exists that multiple infectious illnesses, most notably *Campylobacter jejuni* gastrointestinal infections and upper respiratory tract infections, are associated with GBS. The 1976 swine influenza vaccine was associated with an increased frequency of GBS, estimated at one case of GBS per 100,000 persons vaccinated. The risk for influenza vaccine-associated GBS was higher among persons aged $\geq$25 years than among persons aged <25 years. However, obtaining strong epidemiologic evidence for a possible small increase in risk for a rare condition with multiple causes is difficult, and no evidence exists for a consistent causal relation between subsequent vaccines prepared from other influenza viruses and GBS.

None of the studies conducted using influenza vaccines other than the 1976 swine influenza vaccine have demonstrated a substantial increase in GBS associated with influenza vaccines. During three of four influenza seasons studied during 1977 to 1991, the overall relative risk estimates for GBS after influenza vaccination were not statistically significant in any of these studies. However, in a study of the 1992-93 and 1993-94 seasons, the overall relative risk for GBS was 1.7 (confidence interval [CI] = 1.0 to 2.8; p = 0.04) during the 6 weeks after vaccination, representing approximately one additional case of GBS per 1 million persons vaccinated; the combined number of GBS cases peaked 2 weeks after vaccination. Results of a study that examined health-care data from Ontario, Canada, during 1992 to 2004 demonstrated a small but statistically significant temporal association between receiving influenza vaccination and subsequent hospital admission for GBS. However, no increase in cases of GBS at the population level was reported after introduction of a mass public influenza vaccination program in Ontario beginning in 2000. Data from VAERS have documented decreased reporting of GBS occurring after vaccination across age groups over time, despite overall increased reporting of other, non-GBS conditions occurring after administration of influenza vaccine. Cases of GBS after influenza virus infection have been reported, but no other epidemiologic studies have documented such an association.

If GBS is a side effect of influenza vaccines other than 1976 swine influenza vaccine, the estimated risk for GBS (on the basis of the few studies that have demonstrated an association between vaccination and GBS) is low (i.e., approximately one additional case per 1 million persons vaccinated). The potential benefits of influenza vaccination in preventing serious illness, hospitalization, and death substantially outweigh these estimates of risk for vaccine-associated GBS. No evidence indicates that the case fatality ratio for GBS differs among vaccinated persons and those not vaccinated.

Use of TIV among Patients with a History of GBS

The incidence of GBS among the general population is low, but persons with a history of GBS have a substantially greater likelihood of subsequently experiencing GBS than persons without such a history. Thus, the likelihood of coincidentally experiencing GBS after influenza vaccination is expected to be greater among persons with a history of GBS than among persons with no history of this syndrome. Whether influenza vaccination specifically might increase the risk for recurrence of GBS is unknown. However, avoiding vaccinating persons who are not at high risk for severe influenza complications and who are known to have experienced GBS within 6 weeks after a previous influenza vaccination might be prudent as a precaution. As an alternative, physicians might consider using influenza antiviral chemoprophylaxis for these persons. Although data are limited, the established benefits of influenza vaccination might outweigh the risk for many persons who have a history of GBS and who are also at high risk for severe complications from influenza.

Vaccine Preservative (Thimerosal) in Multidose Vials of TIV

Thimerosal, a mercury-containing anti-bacterial compound, has been used as a preservative in vaccines since the 1930s and is used in multidose vial preparations of TIV to reduce the likelihood of bacterial contamination. No scientific evidence indicates that thimerosal in vaccines, including influenza vaccines, is a cause of adverse events other than occasional local hypersensitivity reactions in vaccine recipients. In addition, no scientific evidence exists that thimerosal-containing vaccines are a cause of adverse events among children born to women who received vaccine during pregnancy. Evidence is accumulating that supports the absence of any risk for neurodevelopment disorders or other harm resulting from exposure to thimerosal-containing vaccines. However, continuing public concern about exposure to mercury in vaccines was viewed as a potential barrier to achieving higher vaccine coverage levels and reducing the burden of vaccine-preventable diseases. Therefore, the U.S. Public Health Service and other organizations recommended that efforts be made to eliminate or reduce the thimerosal content in vaccines as part of a strategy to reduce mercury exposures from all sources. Since mid-2001, vaccines routinely recommended for infants aged <6 months in the United States have been manufactured either without or with greatly reduced (trace) amounts of thimerosal. As a result, a substantial reduction in the total mercury exposure from vaccines for infants and children already has been achieved. ACIP and other federal agencies and professional medical organizations continue to support efforts to provide thimerosal preservative–free vaccine options.

The benefits of influenza vaccination for all recommended groups, including pregnant women and young children, outweigh concerns on the basis of a theoretical risk from thimerosal exposure through vaccination. The risks for severe illness from influenza virus infection are elevated among both young children and pregnant women, and vaccination has been demonstrated to reduce the risk for severe influenza illness and subsequent medical complications. In contrast, no scientifically conclusive evidence has demonstrated harm from exposure to vaccine containing thimerosal preservative. For these reasons, persons recommended to receive TIV may receive any age-and risk-factor–appropriate vaccine preparation, depending on availability. An analysis of VAERS reports found no difference in the safety profile or preservative-containing compared with preservative-free TIV vaccines in infants aged 6 to 23 months.

Nonetheless, certain states have enacted legislation banning the administration of vaccines containing mercury; the provisions defining mercury content vary. LAIV and many of the single dose vial or syringe preparations of TIV are thimerosal-free, and the number of influenza vaccine doses that do not contain thimerosal as a preservative is expected to increase (see Table 2 in the original guideline document). However, these laws may present a barrier to vaccination unless influenza vaccines that do not contain thimerosal as a preservative are easily available in those states.

The U.S. vaccine supply for infants and pregnant women is in a period of transition during which the availability of thimerosal-reduced or thimerosal-free vaccine intended for these groups is being expanded by manufacturers as a feasible means of further reducing an infant's cumulative exposure to mercury. Other environmental sources of mercury exposure are more difficult or impossible to avoid or eliminate.

Live Attenuated Influenza Vaccine (LAIV)

Adverse Events after Receipt of LAIV

Healthy Children Aged 2 to 18 Years

In a subset of healthy children aged 60 to 71 months from one clinical trial, certain signs and symptoms were reported more often after the first dose among LAIV recipients (n = 214) than among placebo recipients (n = 95), including, runny nose (48% and 44%, respectively); headache (18% and 12%, respectively); vomiting (5% and 3%, respectively); and myalgias (6% and 4%, respectively). However, these differences were not statistically significant. In other trials, signs and symptoms reported after LAIV administration have included runny nose or nasal congestion (20% to 75%), headache (2% to 46%), fever (0 to 26%), vomiting (3% to 13%), abdominal pain (2%), and myalgias (0 to 21%). These symptoms were associated more often with the first dose and were self-limited.

In a randomized trial published in 2007, LAIV and TIV were compared among children aged 6 to 59 months. Children with medically diagnosed or treated wheezing within 42 days before enrollment, or a history of severe asthma, were excluded from this study. Among children aged 24 to 59 months who received LAIV, the rate of medically significant wheezing, using a pre-specified definition, was not greater compared with those who received TIV; wheezing was observed more frequently among younger LAIV recipients in this study (see "Persons at Higher Risk from Influenza-Related Complications," below). In a previous randomized placebo-controlled safety trial among children aged 12 months to 17 years without a history of asthma by parental report, an elevated risk for asthma events (RR = 4.06, CI = 1.29--17.86) was documented among 728 children aged 18 to 35 months who received LAIV. Of the 16 children with asthma-related events in this study, seven had a history of asthma on the basis of subsequent medical record review. None required hospitalization, and elevated risks for asthma were not observed in other age groups.

Another study was conducted among >11,000 children aged 18 months to 18 years in which 18,780 doses of vaccine were administered for 4 years. For

children aged 18 months to 4 years, no increase was reported in asthma visits 0 to 15 days after vaccination compared with the prevaccination period. A significant increase in asthma events was reported 15 to 42 days after vaccination, but only in vaccine year 1.

Initial data from VAERS during 2007--2008, following ACIP recommendation for LAIV use in children aged 2 to 4 years, do not suggest a concern for wheezing after LAIV in young children. However data also suggest uptake of LAIV is limited and continued safety monitoring for wheezing events after LAIV is indicated.

Adults Aged 19 to 49 Years

Among adults, runny nose or nasal congestion (28% to 78%), headache (16% to 44%), and sore throat (15% to 27%) have been reported more often among vaccine recipients than placebo recipients. In one clinical trial among a subset of healthy adults aged 18 to 49 years, signs and symptoms reported more frequently among LAIV recipients (n = 2,548) than placebo recipients (n = 1,290) within 7 days after each dose included cough (14% and 11%, respectively), runny nose (45% and 27%, respectively), sore throat (28% and 17%, respectively), chills (9% and 6%, respectively), and tiredness/weakness (26% and 22%, respectively).

Persons at Higher Risk for Influenza-Related Complications

Limited data assessing the safety of LAIV use for certain groups at higher risk for influenza-related complications are available. In one study of 54 HIV-infected persons aged 18 to 58 years and with CD4 counts $\geq$200 cells/mm^3 who received LAIV, no serious adverse events were reported during a 1-month follow-up period. Similarly, one study demonstrated no significant difference in the frequency of adverse events or viral shedding among HIV-infected children aged 1 to 8 years on effective antiretroviral therapy who were administered LAIV, compared with HIV-uninfected children receiving LAIV. LAIV was well-tolerated among adults aged $\geq$65 years with chronic medical conditions. These findings suggest that persons at risk for influenza complications who have inadvertent exposure to LAIV would not have significant adverse events or prolonged viral shedding and that persons who have contact with persons at higher risk for influenza-related complications may receive LAIV.

Serious Adverse Events

Serious adverse events after administration of LAIV requiring medical attention among healthy children aged 5 to 17 years or healthy adults aged 18 to 49 years occurred at a rate of <1%. Surveillance will continue for adverse events, including those that might not have been detected in previous studies. Reviews of reports to VAERS after vaccination of approximately 2.5 million persons during the 2003-04 and 2004-05 influenza seasons did not indicate any new safety concerns. Health-care professionals should report all clinically significant adverse events occurring after LAIV administration promptly to VAERS after LAIV administration.

Influenza Antiviral Medications

Adverse Events

When considering use of influenza antiviral medications (i.e., choice of antiviral drug, dosage, and duration of therapy), clinicians must consider the patient's age, weight, and renal function (see Table 4 in the original guideline document); presence of other medical conditions; indications for use (i.e., chemoprophylaxis or treatment); and the potential for interaction with other medications.

Zanamivir

Limited data are available regarding the safety or efficacy of zanamivir for persons with underlying respiratory disease or for persons with complications of acute influenza, and zanamivir is licensed only for use in persons without underlying respiratory or cardiac disease. In a study of zanamivir treatment of influenza-like illness (ILI) among persons with asthma or chronic obstructive pulmonary disease in which study medication was administered after use of a B2-agonist, 13% of patients receiving zanamivir and 14% of patients who received placebo (inhaled powdered lactose vehicle) experienced a >20% decline in forced expiratory volume in 1 second (FEV1) after treatment. However, in a phase-I study of persons with mild or moderate asthma who did not have ILI, one of 13 patients experienced bronchospasm after administration of zanamivir. In addition, during postmarketing surveillance, cases of respiratory function deterioration after inhalation of zanamivir have been reported. Because of the risk for serious adverse events and because efficacy has not been demonstrated among this population, zanamivir is not recommended for treatment for patients with underlying airway disease. Allergic reactions, including oropharyngeal or facial edema, also have been reported during postmarketing surveillance.

In clinical treatment studies of persons with uncomplicated influenza, the frequencies of adverse events were similar for persons receiving inhaled zanamivir and for those receiving placebo (i.e., inhaled lactose vehicle alone). The most common adverse events reported by both groups were diarrhea; nausea; sinusitis; nasal signs and symptoms; bronchitis; cough; headache; dizziness; and ear, nose, and throat infections. Each of these symptoms was reported by <5% of persons in the clinical treatment studies combined. Zanamivir does not impair the immunologic response to TIV.

Oseltamivir

Nausea and vomiting were reported more frequently among adults receiving oseltamivir for treatment (nausea without vomiting, approximately 10%; vomiting, approximately 9%) than among persons receiving placebo (nausea without vomiting, approximately 6%; vomiting, approximately 3%). Among children treated with oseltamivir, 14% had vomiting, compared with 8.5% of placebo recipients. Overall, 1% discontinued the drug secondary to this side effect, and a limited number of adults who were enrolled in clinical treatment trials of oseltamivir discontinued treatment because of these symptoms. Similar types and rates of adverse events were reported in studies of oseltamivir chemoprophylaxis. Nausea and vomiting might be less severe if oseltamivir is taken with food. No published studies have assessed whether oseltamivir impairs the immunologic response to TIV.

Transient neuropsychiatric events (self-injury or delirium) have been reported postmarketing among persons taking oseltamivir; the majority of reports were among adolescents and adults living in Japan. FDA advises that persons receiving oseltamivir be monitored closely for abnormal behavior.

Use During Pregnancy

Oseltamivir and zanamivir are both "Pregnancy Category C" medications, indicating that no clinical studies have been conducted to assess the safety of these medications for pregnant women. Because of the unknown effects of influenza antiviral drugs on pregnant women and their fetuses, these two drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus; the manufacturers' package inserts should be consulted. However, no adverse effects have been reported among women who received oseltamivir or zanamivir during pregnancy or among infants born to such women.

Drug Interactions

Clinical data are limited regarding drug interactions with zanamivir. However, no known drug interactions have been reported, and no clinically critical drug interactions have been predicted on the basis of in vitro and animal study data.

Limited clinical data are available regarding drug interactions with oseltamivir. Because oseltamivir and oseltamivir carboxylate are excreted in the urine by glomerular filtration and tubular secretion via the anionic pathway, a potential exists for interaction with other agents excreted by this pathway. For example, coadministration of oseltamivir and probenecid resulted in reduced clearance of oseltamivir carboxylate by approximately 50% and a corresponding approximate twofold increase in the plasma levels of oseltamivir carboxylate.

No published data are available concerning the safety or efficacy of using combinations of any of these influenza antiviral drugs. Package inserts should be consulted for more detailed information concerning potential drug interactions.

CONTRAINDICATIONS

CONTRAINDICATIONS

Trivalent Inactivated Influenza Vaccine (TIV)

Persons Who Should Not Be Vaccinated with TIV

TIV should not be administered to persons known to have anaphylactic hypersensitivity to eggs or to other components of the influenza vaccine. Prophylactic use of antiviral agents is an option for preventing influenza among such persons. Information about vaccine components is located in package inserts from each manufacturer. Persons with moderate-to-severe acute febrile illness usually should not be vaccinated until their symptoms have abated. However, minor illnesses with or without fever do not contraindicate use of influenza

vaccine. Guillain-Barré syndrome (GBS) within 6 weeks following a previous dose of TIV is considered to be a precaution for use of TIV.

Live Attenuated Influenza Vaccine (LAIV)

Persons Who Should Not Be Vaccinated with LAIV

The effectiveness or safety of LAIV is not known for the following groups, and these persons should not be vaccinated with LAIV:

- Persons with a history of hypersensitivity, including anaphylaxis, to any of the components of LAIV or to eggs
- Persons aged <2 years or those aged ≥50 years
- Persons with any of the underlying medical conditions that serve as an indication for routine influenza vaccination, including asthma, reactive airways disease, or other chronic disorders of the pulmonary or cardiovascular systems; other underlying medical conditions, including such metabolic diseases as diabetes, renal dysfunction, and hemoglobinopathies; or known or suspected immunodeficiency diseases or immunosuppressed states
- Children aged 2 to 4 years whose parents or caregivers report that a health-care provider has told them during the preceding 12 months that their child had wheezing or asthma, or whose medical record indicates a wheezing episode has occurred during the preceding 12 months
- Children or adolescents receiving aspirin or other salicylates (because of the association of Reye syndrome with wild-type influenza infection)
- Persons with a history of GBS after influenza vaccination
- Pregnant women

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Strategies for Implementing Vaccination Recommendations in Health-Care Settings

Successful vaccination programs combine publicity and education for health-care personnel (HCP) and other potential vaccine recipients, a plan for identifying persons recommended for vaccination, use of reminder/recall systems, assessment of practice-level vaccination rates with feedback to staff, and efforts to remove administrative and financial barriers that prevent persons from receiving the vaccine, including use of standing orders programs. The use of standing orders programs by long-term–care facilities (e.g., nursing homes and skilled nursing facilities), hospitals, and home health agencies ensures that

vaccination is offered. Standing orders programs for influenza vaccination should be conducted under the supervision of a licensed practitioner according to a physician-approved facility or agency policy by HCP trained to screen patients for contraindications to vaccination, administer vaccine, and monitor for adverse events. The Centers for Medicare and Medicaid Services (CMS) has removed the physician signature requirement for the administration of influenza and pneumococcal vaccines to Medicare and Medicaid patients in hospitals, long-term care facilities, and home health agencies. To the extent allowed by local and state law, these facilities and agencies can implement standing orders for influenza and pneumococcal vaccination of Medicare- and Medicaid-eligible patients. Payment for influenza vaccine under Medicare Part B is available. Other settings (e.g., outpatient facilities, managed care organizations, assisted living facilities, correctional facilities, pharmacies, and adult workplaces) are encouraged to introduce standing orders programs. In addition, physician reminders (e.g., flagging charts) and patient reminders are recognized strategies for increasing rates of influenza vaccination. Persons for whom influenza vaccine is recommended can be identified and vaccinated in the settings described in the following sections.

Outpatient Facilities Providing Ongoing Care

Staff in facilities providing ongoing medical care (e.g., physicians' offices, public health clinics, employee health clinics, hemodialysis centers, hospital specialty-care clinics, and outpatient rehabilitation programs) should identify and label the medical records of patients who should receive vaccination. Vaccine should be offered during visits throughout the influenza season. The offer of vaccination and its receipt or refusal should be documented in the medical record. Patients for whom vaccination is recommended and who do not have regularly scheduled visits during the fall should be reminded by mail, telephone, or other means of the need for vaccination.

Outpatient Facilities Providing Episodic or Acute Care

Acute health-care facilities (e.g., emergency departments and walk-in clinics) should offer vaccinations throughout the influenza season to persons for whom vaccination is recommended or provide written information regarding why, where, and how to obtain the vaccine. This written information should be available in languages appropriate for the populations served by the facility.

Nursing Homes and Other Residential Long-Term–Care Facilities

Vaccination should be provided routinely to all residents of chronic-care facilities. If possible, all residents should be vaccinated at one time, before influenza season. In the majority of seasons, trivalent inactivated influence vaccine (TIV) will become available to long-term–care facilities in October or November, and vaccination should commence as soon as vaccine is available. As soon as possible after admission to the facility, the benefits and risks of vaccination should be discussed and education materials provided. Signed consent is not required. Residents admitted after completion of the vaccination program at the facility should be vaccinated at the time of admission through March.

Since October 2005, CMS has required nursing homes participating in the Medicare and Medicaid programs to offer all residents influenza and pneumococcal vaccines and to document the results. According to the requirements, each resident is to be vaccinated unless contraindicated medically, the resident or a legal representative refuses vaccination, or the vaccine is not available because of shortage. This information is to be reported as part of the CMS Minimum Data Set, which tracks nursing home health parameters.

Acute-Care Hospitals

Hospitals should serve as a key setting for identifying persons at increased risk for influenza complications. Unvaccinated persons of all ages (including children) with high-risk conditions and persons aged 6 months to 18 years or $\geq$50 years who are hospitalized at any time during the period when vaccine is available should be offered and strongly encouraged to receive influenza vaccine before they are discharged. Standing orders to offer influenza vaccination to all hospitalized persons should be considered.

Visiting Nurses and Others Providing Home Care to Persons at High Risk

Nursing-care plans should identify patients for whom vaccination is recommended, and vaccine should be administered in the home, if necessary, as soon as influenza vaccine is available and throughout the influenza season. Caregivers and other persons in the household (including children) should be referred for vaccination.

Other Facilities Providing Services to Persons Aged $\geq$50 Years

Facilities providing services to persons aged $\geq$50 years (e.g., assisted living housing, retirement communities, and recreation centers) should offer unvaccinated residents, attendees, and staff annual on-site vaccination before the start of the influenza season. Continuing to offer vaccination throughout the fall and winter months is appropriate. Efforts to vaccinate newly admitted patients or new employees also should be continued, both to prevent illness and to avoid having these persons serve as a source of new influenza infections. Staff education should emphasize the need for influenza vaccine.

Health-Care Personnel

Health-care facilities should offer influenza vaccinations to all HCP, including night, weekend, and temporary staff. Particular emphasis should be placed on providing vaccinations to workers who provide direct care for persons at high risk for influenza complications. Efforts should be made to educate HCP regarding the benefits of vaccination and the potential health consequences of influenza illness for their patients, themselves, and their family members. All HCP should be provided convenient access to influenza vaccine at the work site, free of charge, as part of employee health programs.

IMPLEMENTATION TOOLS

Foreign Language Translations
Patient Resources
Resources
Wall Poster

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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Advisory Committee on Immunization Practices

Committee Members, August 2008

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ACIP Influenza Working Group

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Fiore AE, Shay DK, Haber P, Iskander JK, Uyeki TM, Mootrey G, Bresee JS, Cox NJ, Advisory Committee on Immunization Practices (ACIP), Centers for Disease. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2007. MMWR Recomm Rep 2007 Jul 13;56(RR-6):1-54. PubMed

GUIDELINE AVAILABILITY

Electronic copies: Available from the Centers for Disease Control and Prevention (CDC) Web site.

Print copies: Available from the Centers for Disease Control and Prevention, MMWR, Atlanta, GA 30333. Additional copies can be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402-9325; (202) 783-3238.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Cover your cough. Printable flyers and posters for use in health care settings. Available in Spanish, Vietnamese, Chinese, Tagalog, Portuguese, French, Hmong, Khmer, and English from the CDC Web site.

PATIENT RESOURCES

The following are available:

- Influenza vaccine information statements (VISs). Available in Spanish and English and as an audio file from the CDC Web site.
- Fact sheets in other languages. Available in Chinese, Spanish, Tagalog, and Vietnamese from the CDC Web site.
- Cover your cough. Printable flyers and posters for use in public settings. Available in Spanish, Vietnamese, Chinese, Tagalog, Portuguese, French, Hmong, Khmer, and English from the CDC Web site.

NGC STATUS

The original summary was completed by ECRI on July 17, 2000, and updated on October 20, 2000. The original summary was verified by the guideline developer as of January 18, 2001. The summary was updated by ECRI on August 6, 2001, June 12, 2002, May 14, 2003, December 18, 2003, June 15, 2004, October 6, 2004, October 30, 2004, and on December 29, 2004 in response to interim recommendations published by the CDC on December 24, 2004. This NGC summary was updated by ECRI on July 21, 2005. This NGC summary was updated on September 23, 2005, in response to the update issued on September 16, 2005 for the 2005-2006 influenza season. It was updated on January 19, 2006, in response to updated guidelines for the use of antivirals. This NGC summary was updated on July 6, 2006, in response to the recommendations issued on June 28, 2006 for the 2006-2007 influenza season. This summary was updated by ECRI on November 21, 2006 following the FDA advisory on Tamiflu. This NGC summary was updated by ECRI Institute most recently on July 5, 2007. This summary was updated by ECRI Institute on March 10, 2008 following the U.S. Food and Drug Administration (FDA) advisory on Tamiflu (oseltamivir phosphate). This summary was updated by ECRI Institute on April 9, 2008 following the U.S. Food and Drug Administration (FDA) advisory on Relenza (zanamivir). This summary was updated by ECRI Institute on August 25, 2008.

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