



# VIRGINIA EPIDEMIOLOGY BULLETIN

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## **Prevention and Control of Influenza**

### **Recommendations of the Advisory Committee on Immunization Practices (ACIP) - 2006**

#### **Introduction**

Epidemics of influenza typically occur during the winter months in temperate regions and cause approximately 36,000 deaths/year in the United States (1990-1999). As a result of the predictability of the problem, the potential severe impact on the health of a wide range of people, and the numerous strategies available to combat influenza, each year the *Virginia Epidemiology Bulletin* (VEB) reviews the updated influenza recommendations from the Advisory Committee on Immunization Practices (ACIP). This article summarizes the 2006 recommendations by the ACIP for the use of influenza vaccine (inactivated and live attenuated) and the use of antiviral agents for treatment and prophylaxis of influenza for the 2006-2007 influenza season [MMWR: July 28, 2006 / 55;1-41]. The full report and

updated information on influenza can be accessed at [www.cdc.gov/flu](http://www.cdc.gov/flu).

#### **Background**

Influenza A and B are the two main types of influenza viruses that cause epidemic human disease. A person's immunity to the surface antigens reduces the likelihood of infection and the severity of disease if infection occurs. However, waning immunity over time and the development of antigenic variants through point mutations (i.e., antigenic drift) mean that seasonal epidemics occur. This requires annual changes to the

vaccine composition and re-vaccination.

Influenza virus spreads from person to person mainly in droplets produced through the coughing and sneezing of infected persons. However, spread can occur by touching droplets from an infected person and then touching the nose or mouth before hand washing.

The incubation period for influenza is 1-4 days, with an average of two days. Adults typically are infectious from the day before symptoms begin through approximately five days after illness onset. Young children can shed virus for several days before illness



onset, and can be infectious for  $\geq 10$  days after the onset of symptoms. Severely immunocompromised persons can shed influenza viruses for weeks or months.

### Clinical Signs and Symptoms of Influenza

Uncomplicated influenza illness is characterized by the **abrupt** onset of constitutional and respiratory signs and symptoms (e.g., fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis). Among children, otitis media, nausea, and vomiting are commonly reported with influenza illness. Young children with influenza infection can also have initial symptoms mimicking bacterial sepsis with high fevers, and approximately 20% of children hospitalized with influenza can have febrile seizures.

Influenza illness typically resolves after 3-7 days for the majority of persons, although cough and malaise can persist for  $>2$  weeks. However, influenza can exacerbate underlying medical conditions (e.g., pulmonary or cardiac disease), lead to primary influenza viral pneumonia or secondary bacterial pneumonia, or occur as part of a co-infection with other viral or bacterial pathogens. Influenza infection has also been associated with encephalopathy, transverse myelitis, Reye syndrome, myositis, myocarditis, and pericarditis.

The risks for complications, hospitalizations, and deaths from influenza are higher among persons aged  $\geq 65$  years, young children, and persons of any age with certain underlying health conditions (e.g., pulmonary or cardiac disease) than among healthy older children and younger adults. Hospitalization rates among children aged  $<24$  months are comparable to rates reported among persons aged  $\geq 65$  years of age.

Older adults account for  $\geq 90\%$  of deaths attributed to pneumonia and influenza. Deaths from influenza are uncommon among children. Overall, models suggest that during the 1990s annual influenza-related deaths occurred at a rate of 0.4 deaths per 100,000 among children aged  $<5$  years,

compared with 98.3 per 100,000 among adults aged  $\geq 65$  years. During the 2005-06 influenza season 33 laboratory-confirmed influenza-related pediatric deaths were reported in the U.S.

### Role of Laboratory Diagnosis

Appropriate management of patients with respiratory illness depends on accurate and timely diagnosis. Early diagnosis of influenza can reduce the inappropriate use of antibiotics and provide the option of using antiviral therapy. The accuracy of clinical diagnosis of influenza on the basis of signs and symptoms alone is limited since the spectrum of illness caused by other pathogens can overlap considerably with influenza. However, influenza testing does not need to be done on all patients with respiratory illness. For individual patients, tests are most useful when they are likely to give the healthcare professional results that will help with diagnosis and treatment decisions.

Diagnostic tests available for influenza include viral culture, serology, rapid antigen testing, polymerase chain reaction (PCR), and immunofluorescence assays. Sensitivity and specificity of any test for influenza vary by the laboratory that performs the test, the type of test used, the type of specimen tested, and the timing of specimen collection. Among respiratory specimens for viral isolation or rapid detection, **nasopharyngeal specimens** are typically more effective than throat swab specimens. Samples should be collected within the first two days of illness.

Additional information concerning diagnostic testing is available from the CDC at [www.cdc.gov/flu/professionals/labdiagnosis.htm](http://www.cdc.gov/flu/professionals/labdiagnosis.htm).

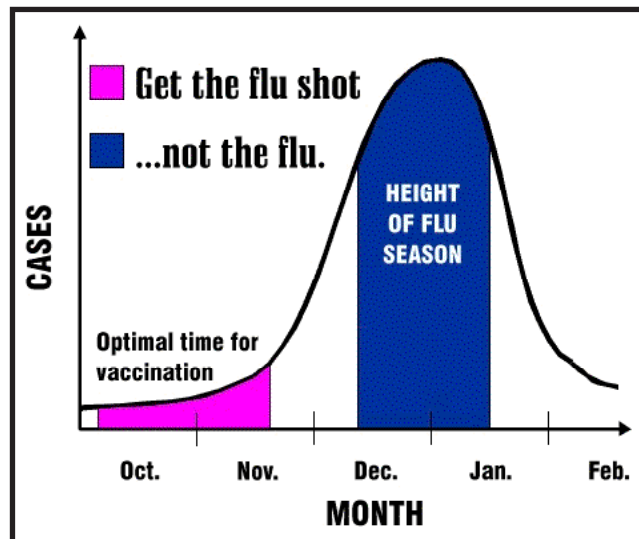
During outbreaks of respiratory illness when influenza is suspected, testing for influenza can be very helpful, and some samples should be tested by both rapid tests and by viral culture. Viral culture can help identify causes of respiratory illness other than influenza (e.g., parainfluenza virus, respiratory syncytial virus, etc.).

**Despite the availability of rapid diagnostic tests, collecting some clinical specimens for viral culture is critical because only culture isolates can provide specific information regarding circulating influenza subtypes and strains.** 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 are also needed to monitor for the emergence of novel influenza A subtypes that might pose a pandemic threat.

### Options for Controlling Influenza

Overall, the most effective means of reducing the impact of influenza is the annual vaccination of persons at high risk for complications and their contacts. Vaccination may prevent hospitalization and death among persons at high risk, reduce influenza-related respiratory illnesses, and decrease work absenteeism among adults. Trivalent inactivated (i.e., killed virus) influenza vaccine and live, attenuated influenza vaccine (LAIV) are available for use in the United States (Table 1).

Antiviral drugs used for chemoprophylaxis or treatment of influenza are a key adjunct to vaccination. However, antiviral medications are not a substitute for vaccination. Other infection control measures, including respiratory etiquette, handwashing, and isolation, are also critical in reducing the impact of infection.



## 2006-07 Influenza Vaccine

The annual supply of influenza vaccine and the timing of its distribution cannot be guaranteed in any given year. Currently, influenza vaccine manufacturers are projecting that approximately 100 million doses of influenza vaccine will be available in the United States for the 2006-07 influenza season.

Although vaccine distribution has begun, distribution probably will not be completed until December or January. As a result, vaccination efforts should be structured to reflect this phased distribution and ensure the vaccination of as many persons as possible over the course of several months (see below).

### Antigenic Composition

The trivalent inactivated influenza vaccine uses 'killed' viruses and is administered intramuscularly by injection. Sanofi Pasteur, Inc. (formerly Aventis Pasteur, Inc.) produces FluZone<sup>®</sup>, an inactivated influenza vaccine for persons aged  $\geq 6$  months. Novartis (formerly Chiron) produces Fluvirin<sup>™</sup>, an inactivated influenza vaccine licensed for use in persons aged  $\geq 4$  years. GlaxoSmith-Kline, Inc. produces Fluarix<sup>™</sup>, an inactivated influenza vaccine for persons aged  $\geq 18$  years (see Table 2).

MedImmune produces FluMist<sup>™</sup>, an attenuated live virus vaccine that is intranasally administered and approved for use only among healthy persons aged 5-49 years (see Table 2).

Both inactivated influenza vaccine and LAIV prepared for the 2006-07 season will include:

- A/New Caledonia/20/1999 (H1N1)-like;
- A/Wisconsin/67/2005 (H3N2)-like (or A/Hiroshima/52/2005); and,
- B/Malaysia/2506/2004-like (or B/Ohio/1/2005) antigens.

Because circulating influenza A (H1N2) viruses are a re-assortment of influenza A (H1N1) and (H3N2) viruses, antibody directed against influenza A (H1N1) and influenza A (H3N2) vaccine strains provides protection against circulating influenza A (H1N2) viruses.

Package inserts should be consulted for additional information on vaccine composition.

### **Thimerosal and Influenza Vaccine**

Thimerosal, a mercury-containing compound, has been used in multidose vials of inactivated influenza vaccine to reduce the likelihood of bacterial contamination. No scientifically conclusive evidence exists of harm from exposure to thimerosal preservative-containing vaccine. In fact, evidence is accumulating that supports the absence of any harm resulting from exposure to such vaccines. However, vaccine manufacturers have worked to reduce thimerosal in vaccines, resulting in substantially lowered cumulative exposure to thimerosal from vaccination among infants and children. Many of the single-dose syringes and vials of inactivated influenza vaccine are thimerosal-free or contain only trace ( $<1$  mcg mercury/dose) amounts of thimerosal. Since the benefits of influenza vaccination outweigh the theoretical risk, if any, from thimerosal exposure through vaccination, persons for whom inactivated influenza vaccine is recommended may receive vaccine with or without thimerosal, depending on availability.

### Recommendations for Influenza Vaccinations

Inactivated influenza vaccine is approved for persons aged  $\geq 6$  months, including those with high-risk conditions; LAIV is approved only for use among healthy non-pregnant persons aged 5-49 years.

Annual influenza vaccination with inactivated influenza vaccine is now recommended for the following persons:

- children aged 6-59 months;
- children and adolescents (aged 6 months-18 years) who are receiving long-term aspirin therapy and, therefore, might be at risk for experiencing Reye syndrome after influenza virus infection;
- women who will be pregnant during the influenza season (vaccination can occur in any trimester);
- persons aged  $\geq 50$  years;
- persons of any age with certain chronic disorders of the pulmonary or cardiovascular systems, including asthma (note: hypertension is not considered a high-risk condition);
- adults and children who have required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunodeficiency (including immunodeficiency caused by medications or by human immunodeficiency virus [HIV]); and,

- 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. Annual vaccination for influenza is also recommended for:
- healthy household contacts and caregivers of children aged 0-59 months or persons at high risk for severe complications from influenza;
- healthcare workers. This includes:
  - physicians, nurses, and other personnel in both hospital and outpatient-care settings, including medical emergency response workers (e.g., paramedics and emergency medical technicians);
  - employees of nursing homes and chronic-care facilities who have contact with patients or residents;
  - employees of assisted living and other residences for persons in groups at high risk; and,
  - persons who provide home care to persons in groups at high risk;
- any person who wishes to reduce the likelihood of becoming ill with influenza. 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

<b>Factor</b>	<b>LAIV</b>	<b>Inactivated influenza vaccine</b>
Route of administration	Intranasal spray	Intramuscular injection
Type of vaccine	Live virus	Killed virus
No. of included virus strains	3 (2 influenza A, 1 influenza B)	3 (2 influenza A, 1 influenza B)
Vaccine virus strains updated	Annually	Annually
Frequency of administration	Annually	Annually
Approved age and risk groups*	Healthy persons aged 5-49 yrs	Persons aged $\geq 6$ mos
Interval between two doses recommended for children aged 6 mos - <9 yrs who are receiving influenza vaccine for the first time	6-10 weeks	Four weeks
Can be administered to family members or close contacts of immunocompromised persons not requiring a protected environment	Yes	Yes
Can be administered to family members or close contacts of immunocompromised persons requiring a protected environment (e.g., hematopoietic stem cell transplant recipient)	Inactivated influenza vaccine preferred	Yes
Can be administered to family members or close contacts of persons at high risk but not severely immunocompromised	Yes	Yes
Can be simultaneously administered with other vaccines	Yes <sup>†</sup>	Yes <sup>§</sup>
If not simultaneously administered, can be administered within four weeks of another live vaccine	Prudent to space four weeks apart	Yes
If not simultaneously administered, can be administered within four weeks of an inactivated vaccine	Yes	Yes

\*Populations at high risk for complications of influenza infection include persons aged  $\geq 65$  yrs; residents of nursing homes and other chronic-care facilities that house persons with chronic medical conditions; adults and children with chronic disorders of the pulmonary or cardiovascular systems; adults and children with chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression; children and adolescents receiving long-term aspirin therapy (at risk for Reye syndrome after wild-type influenza infection); pregnant women; and children aged 6-59 months.

<sup>†</sup>No data are available regarding effect on safety or efficacy.

<sup>§</sup>Inactivated influenza vaccine coadministration has been evaluated systematically only among adults with pneumococcal polysaccharide vaccine.

who reside in dormitories) should be encouraged to receive vaccine.

Note: Healthy non-pregnant persons aged 5-49 years in these groups who are not contacts of severely immunosuppressed persons can receive either LAIV or inactivated influenza vaccine (see below). All other persons in these groups should receive inactivated influenza vaccine (note: inactivated vaccine is safe for mothers who are breastfeeding; caution should be exercised if LAIV is administered to nursing mothers).

### **Efficacy and Effectiveness**

The effectiveness of influenza vaccine depends primarily on the age and immunocompetence of the vaccine recipient, the degree of similarity between the viruses in the vaccine and those in circulation, and the outcome being measured. The majority of children and young adults who receive inactivated

influenza vaccine develop high postvaccination hemagglutination inhibition antibody titers. These antibody titers are protective against illness caused by strains similar to those in the vaccine. The protective mechanisms induced by vaccination with LAIV are not completely understood but appear to involve both serum and nasal secretory antibodies. No single laboratory measurement closely correlates with protective immunity induced by LAIV.

**Children.** Children aged  $\geq 6$  months can develop protective levels of antibody after influenza vaccination. Efficacy in preventing influenza illness may be approximately 60% on average, but can reach 90%. One study of healthy children initially aged 15-71 months found that LAIV was 92% effective in preventing culture-confirmed influenza during the two-season investigation.

LAIV also reduced febrile otitis media by 27%.

**Adults Aged <65 Years.** When the vaccine and circulating viruses are antigenically similar, influenza vaccine prevents influenza illness among approximately 70%-90% of healthy adults aged <65 years. In a study of healthy adults aged 18-41 years experimentally challenged by viruses, the overall efficacy of LAIV and inactivated vaccine in preventing laboratory-documented influenza was found to be 85% and 71%, respectively (difference not statistically significant).

**Adults Aged  $\geq 65$  Years.** Older persons and persons with certain chronic diseases might develop lower postvaccination antibody titers than healthy young adults and thus can remain susceptible to influenza-related upper respiratory tract infection. One study of non-institutionalized persons aged

**Table 2. Approved influenza vaccines for different age groups, United States, 2006-07 season**

Trade name	Manufacturer	Dose*/ Presentation	Thimerosal mercury content (mcg Hg/0.5-mL dose)	Age group	No. of doses	Route
<b>Inactivated</b>						
Fluzone®	Sanofi Pasteur	0.25-mL prefilled syringe	0	6-35 mos	1 or 2†	Intramuscular§
		0.5-mL prefilled syringe	0	≥ 36 mos	1 or 2†	Intramuscular§
		0.5-mL vial	0	≥ 36 mos	1 or 2†	Intramuscular§
		5.0-mL multi-dose vial	25	≥ 6 mos	1 or 2†	Intramuscular§
Fluvirin™	Novartis Vaccine (formerly Chiron Corporation)	0.5-mL prefilled syringe	< 1.0	≥ 4 yrs	1 or 2†	Intramuscular§
		5.0-mL multi-dose vial	24.5	≥ 4 yrs	1 or 2†	Intramuscular§
FLUARIX™	GlaxoSmithKline	0.5-mL prefilled syringe	< 1.0	≥ 18 yrs	1	Intramuscular§
<b>Live, attenuated (LAIV)</b>						
FluMist™	MedImmune	0.5-mL sprayer	0	5-49 yrs	1 or 2††	Intranasal**
<p>*A 0.5-mL dose contains 15 mcg each of A/New Caledonia/20/1999 (H1N1)-like, and B/Malaysia/2506/2004-like antigens. For the A/Wisconsin/67/2005 (H3N2)-like antigen, manufacturers may use the antigenically equivalent A/Hiroshima/52/2005 virus, and for the B/Malaysia/2506/2004-like antigen, manufacturers may use the antigenically equivalent B/Ohio/1/2005 virus.</p> <p>†Two doses administered at least 1 month apart are recommended for children aged 6 months - &lt; 9 years who are receiving influenza vaccine for the first time.</p> <p>§For adults and older children, the recommended site of vaccination is the deltoid muscle. The preferred site for infants and young children is the anterolateral aspect of the thigh.</p> <p>††Two doses administered at least six weeks apart are recommended for children aged 5 - &lt; 9 years who are receiving influenza vaccine for the first time.</p> <p>**One dose equals 0.5-mL, divided equally between each nostril.</p>						

≥60 years reported a vaccine efficacy of 58% against influenza respiratory illness, but indicated that efficacy might be lower among those aged ≥70 years. The vaccine can be effective in preventing secondary complications and reducing the risk for influenza-related hospitalization and death among adults ≥65 years with and without high-risk medical conditions (e.g., heart disease and diabetes). Among elderly persons not living in nursing homes or similar chronic-care facilities, influenza vaccine is 30%-70% effective in preventing hospitalization for pneumonia and influenza. Among older persons who do reside in nursing homes the vaccine can be 50%-60% effective in preventing hospitalization or pneumonia, and 80% effective in preventing death, although the effectiveness in preventing influenza illness often ranges from 30%-40%.

### *Inactivated Influenza Vaccine*

#### **Dosage and Administration**

Dosage recommendations for inactivated influenza vaccine vary according to age group (Table 2). Among previously **unvaccinated** children aged <9 years, two doses administered ≥1 month apart are recommended to achieve a satisfactory antibody response. If possible, the second dose should be administered before the onset of influenza season (typically late November/early December in Virginia). The intramuscular route is recommended for inactivated influenza vaccine. Adults and older children should be vaccinated in the deltoid muscle. Infants and young children should be vaccinated in the anterolateral aspect of the thigh; influenza vaccine may be administered into the deltoid muscle among children with adequate deltoid muscle mass.

### **Persons Who Should Not Be Vaccinated with Inactivated Influenza Vaccine**

Since influenza vaccine viruses are grown in embryonated hens' eggs, inactivated influenza vaccine should not be administered to persons with a known anaphylactic hypersensitivity to eggs or to other components of the influenza vaccine without first consulting a physician. Chemoprophylaxis with antiviral agents is an option for preventing influenza among such persons. Vaccination may also be an option after appropriate allergy evaluation and desensitization. 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, particularly among children with mild upper respiratory tract infection or allergic rhinitis.

Since inactivated influenza vaccine contains only influenza virus subunits and no live virus, no contraindication exists to the co-administration of inactivated influenza vaccine and influenza antiviral medications.

### **Side Effects and Adverse Reactions**

When educating patients regarding potential side effects, healthcare workers should emphasize:

- 1) inactivated influenza vaccine contains noninfectious killed viruses and cannot cause influenza; and,
- 2) coincidental respiratory disease unrelated to influenza vaccination can occur after vaccination.

The most frequent side effect of vaccination is soreness at the vaccination site that lasts <2 days. These local reactions typically are mild. Fever, malaise, myalgia, and other systemic symptoms can occur after vaccination with inactivated vaccine and most often affect persons who have had no prior exposure to the influenza virus antigens in the vaccine (e.g., young children). These reactions begin 6-12 hours after vaccination and can persist for 1-2 days. Among older persons and healthy young adults, influenza vaccine is not associated with higher rates of systemic symptoms compared with placebo injections.

Immediate, presumably allergic, reactions (e.g., hives, angioedema, allergic asthma, and systemic anaphylaxis) rarely occur after influenza vaccination. These reactions probably result from hypersensitivity to certain vaccine components (e.g., residual egg protein). Persons who have had mild hypersensitivity reactions (e.g., hives or swelling of the lips or tongue) to eggs should consult a physician for appropriate evaluation to help determine if vaccine should be administered. Persons with a history of severe hypersensitivity (e.g., anaphylaxis) to eggs should not receive influenza vaccine.

Evidence exists that multiple infectious agents (most notably *Campylobacter jejuni* but also agents of upper respiratory tract infections) are associated with Guillain-Barré Syndrome (GBS). Investigations to date indicate no substantial increase in GBS associated with

influenza vaccines other than the swine influenza vaccine in 1976. However, persons with a history of GBS do have a 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; therefore, avoiding vaccinating persons who are not at high risk for severe influenza complications and who are known to have experienced GBS within six weeks after a previous influenza vaccination is prudent. Influenza antiviral chemoprophylaxis for these persons is a consideration. Although data are limited, for the majority of persons who have a history of GBS and who are at high risk for severe complications from influenza, the established benefits of influenza vaccination justify annual vaccination.

Healthcare professionals should promptly report all clinically significant adverse events after influenza vaccination to the Food and Drug Administration (FDA)/Centers for Disease Control and Prevention (CDC) Vaccine Adverse Event Reporting System (VAERS) even if the healthcare professional is not certain that the vaccine caused the

### **Vaccines for Children (VFC) 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 administered to eligible children without vaccine cost to the patient or the provider. All routine childhood vaccines recommended by ACIP (including influenza) are available through this program. The program saves parents and providers out-of-pocket expenses for vaccine purchases and provides cost-savings to states through the CDC vaccine contracts. The program results in lower vaccine prices and assures that all states pay the same contract prices.

event. Options for reporting include the VAERS website at <http://vaers.hhs.gov> or by calling the 24-hour national toll-free hotline at 800-822-7967.

### ***Live, Attenuated Influenza Vaccine***

LAIV is an option for the vaccination of healthy, non-pregnant persons aged 5-49 years, including persons in close contact with groups at high risk.

### **Dosage and Administration**

LAIV is intended for intranasal administration only and should not be administered by the intramuscular, intradermal, or intravenous route. LAIV is supplied in a pre-filled single-use sprayer containing 0.5 mL of vaccine. The vaccine can be administered by holding an individual sprayer in the palm of the hand until thawed, with subsequent immediate use. Alternatively, the vaccine can be thawed in a refrigerator and stored at 2-8°C for up to 60 hours before use. Vaccine should not be refrozen after thawing. Approximately 0.25 mL (i.e., half of the total sprayer contents) is sprayed into the first nostril while the recipient is in the upright position. An attached dose-divider clip is removed from the sprayer to administer the second half of the dose into the other nostril. If the vaccine recipient sneezes after administration, the dose should not be repeated.

LAIV should be administered annually according to the following schedule (Note: One dose equals 0.5 mL divided equally between each nostril):

- Children aged 5-<9 years previously unvaccinated at any time with either LAIV or inactivated influenza vaccine should receive two doses of LAIV separated by 6-10 weeks.
- Children aged 5-<9 years previously vaccinated at any time with either LAIV or inactivated influenza vaccine should receive one dose of LAIV. They do not require a second dose.
- Persons aged 9-49 years should receive one dose of LAIV.

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.

Following the ACIP general recommendations when immunizing with two or more vaccines, inactivated vaccines can be administered either simultaneously or at any time before or after LAIV. Two live vaccines not administered on the same day should be administered  $\geq 4$  weeks apart when possible.

### **Persons Who Should Not Be Vaccinated with LAIV**

The following populations should not be vaccinated with LAIV:

- Persons aged  $< 5$  years or those aged  $\geq 50$  years;
- Persons with asthma, reactive airways disease, cystic fibrosis, chronic obstructive pulmonary disease, or other chronic disorders of the pulmonary or cardiovascular systems;
- Persons with other underlying medical conditions, including such metabolic diseases as diabetes, renal dysfunction, and hemoglobinopathies;
- Persons with known or suspected immunodeficiency diseases or who are receiving immunosuppressive therapies;
- Household members, healthcare workers, and others who have close contact with severely immunosuppressed persons (e.g., patients with hematopoietic stem cell transplants);
- 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;
- Pregnant women; or,
- Persons with a history of hypersensitivity, including anaphylaxis, to any of the components of LAIV or to eggs.

Protection from influenza using inactivated influenza vaccine or antivirals may be an option for some persons in these groups.

Use of inactivated influenza vaccine is preferred for vaccinating household members, healthcare workers, and others who have close contact with severely immunosuppressed persons (e.g., patients with hematopoietic stem cell transplants) as a result of the theoretical risk that a live, attenuated vaccine virus could be transmitted to the severely immunosuppressed person and cause disease. No preference exists between inactivated influenza vaccine or LAIV use by healthcare workers or other healthy persons aged 5-49 years who have close contact with persons with lesser degrees of immunosuppression (e.g., persons with diabetes, persons



with asthma taking corticosteroids, or persons infected with human immunodeficiency virus) or other groups at high risk from influenza.

If a person receives LAIV, that person should refrain from contact with severely immunosuppressed patients for seven days after vaccine receipt. However, such persons need not be excluded from visitation of patients who are not severely immunocompromised.

### **Personnel Who May Administer LAIV**

Low-level introduction of vaccine viruses into the environment is likely unavoidable when administering LAIV. The risk of acquiring vaccine viruses from the environment is unknown but likely limited. As a result, severely immunosuppressed persons should not administer LAIV. Other persons with underlying medical conditions placing them at high risk for influenza complications (e.g., pregnant women, persons with asthma, and persons aged  $\geq 50$  years) may administer LAIV.

## **LAIV and Use of Influenza**

### **Antiviral Medications**

The effect on safety and efficacy of LAIV co-administration 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 two weeks after receipt of LAIV.

### **LAIV Storage**

LAIV must be stored at  $-15^{\circ}\text{C}$  or colder. The vaccine may be stored in a frost-free freezer (an optional manufacturer-supplied freezer box may be used for additional vaccine protection).

### **Side Effects and Adverse Reactions**

The LAIV virus replicates in the mucosa of the nasopharynx. Available data indicate that both children and adults vaccinated with LAIV can shed vaccine viruses for  $\geq 2$  days after vaccination, although in lower titers than typically occurs with shedding of wild-type influenza viruses. Shedding should not be equated with person-to-person transmission of vaccine viruses, although, in rare instances, vaccine viruses that are shed can be transmitted to non-vaccinated persons.

The incidence of adverse events possibly complicating influenza (e.g., pneumonia, bronchitis, bronchiolitis, or central nervous system events) has not been found to be statistically different among LAIV and placebo recipients aged 5-49 years. Among children, signs and symptoms reported more often among vaccine recipients than placebo recipients included: runny nose or nasal congestion, headache, fever, vomiting, abdominal pain, and myalgias. Symptoms were associated more often with the first dose and were self-limited.

Among adults, runny nose or nasal congestion, headache, cough, chills, fatigue/weakness, and sore throat have been reported more often among vaccine recipients than placebo recipients.

In studies, serious adverse events among healthy children aged 5-17 years or healthy adults aged 18-49 years occurred at a rate of <1%. As with inactivated influenza vaccine, healthcare professionals should promptly report all clinically significant adverse events after LAIV administration to VAERS at <http://vaers.hhs.gov> or by calling the 24-hour national toll-free hotline at 800-822-7967.

### ***Timing of Annual Influenza Vaccination***

In the United States, seasonal influenza activity can begin to increase as early as October or November, although influenza activity has not reached peak levels in the majority of recent seasons until late December-early March. If the supply of inactivated

influenza vaccine is adequate and a sufficient number of doses are available beginning in September, vaccination efforts should be structured to ensure the vaccination of as many persons as possible over the course of several months.

#### **Vaccination Before October**

Persons at increased risk for serious complications and their household contacts (including out-of-home caregivers and household contacts of children aged 0-59 months) should be offered vaccine beginning in September during routine healthcare visits or during hospitalizations, if vaccine is available. In addition, because children aged 6 months-<9 years who have not been previously vaccinated need two doses of vaccine (booster dose 4-10 weeks after the initial dose, depending upon whether they are receiving inactivated influenza vaccine or LAIV) they should receive their first dose in September, if vaccine is available, so that both doses can be administered before the onset of influenza activity.

In facilities housing older persons (e.g., nursing homes) vaccination before October typically should be avoided because antibody levels in such persons can begin to decline relatively rapidly

after vaccination. However, if vaccine supplies are sufficient, vaccination of other persons may begin before October.

#### **Vaccination in October and November**

The optimal time for vaccination efforts is usually during October-November. In October, vaccination in provider-based settings should start or continue for all patients—both high risk and healthy—and extend throughout November. If supplies of vaccine are limited, efforts to vaccinate non-high-risk



persons who wish to decrease their risk for influenza virus infection should not begin until November; however, if such persons request vaccination in October, vaccination should not be deferred.

#### **Vaccination in December and Later**

After November, many persons who should or want to receive influenza vaccine remain unvaccinated. Vaccine administered after November is likely to be beneficial in the majority of influenza seasons. Therefore, **healthcare providers should routinely offer influenza vaccine throughout the influenza season even after influenza activity has been documented in the community** as long as vaccine supplies are available.

If a reduced or delayed supply of inactivated vaccine occurs, then modifications to this general schedule would be developed and made available to healthcare providers.

#### ***Strategies for Implementing Vaccination Recommendations in Healthcare Settings***

Successful vaccination programs combine publicity and education for healthcare workers and other potential vaccine recipients, a plan for identifying persons at high risk, use of reminder/recall systems (e.g., mail or telephone reminders, flagging charts), and efforts to remove administrative and financial barriers that prevent persons from re-

ceiving the vaccine. **When possible, the use of standing orders programs is recommended for long-term care facilities, hospitals, and home health agencies to ensure the administration of recommended vaccinations for adults.**

Assisted living housing, retirement communities, and recreation centers should offer annual programs to immunize unvaccinated residents and attendees on-site before the start of influenza season. 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 as well.

Beginning in October each year, healthcare facilities should offer convenient access to influenza vaccine at the work site, free of charge, to all personnel, including night and weekend staff. Particular emphasis should be placed on providing vaccinations to persons who care for members of groups at high risk. Efforts should be made to educate healthcare personnel regarding the benefits of vaccination and the potential health consequences of influenza illness for themselves and their patients.

### **Recommendations for Using Antiviral Agents for Influenza**

The primary methods of controlling the spread of influenza consist of immunization and good respiratory etiquette. However, influenza antiviral medications can play an important role in the management of influenza both as chemoprophylaxis to prevent illness and as treatment of influenza infection.

#### ***Influenza Antiviral Agents***

Currently, four influenza antiviral agents are licensed and available in the United States: amantadine, rimantadine, zanamivir, and oseltamivir (Table 3).

Amantadine and rimantadine are chemically related drugs known as adamantanes (or M2 inhibitors)—this class has activity **only** against **influenza A viruses**. The CDC recently reported that 193 (92%) of 209 influenza A (H3N2) viruses isolated from patients in 26 states demonstrated a change at amino



acid 31 in the M2 gene that confers resistance to adamantanes. In addition, two of eight influenza A (H1N1) viruses tested were resistant. As a result, ACIP recommends that **neither amantadine nor rimantadine be used for the treatment or chemoprophylaxis of influenza** in the United States until susceptibility to these antiviral medications has been re-established among circulating influenza A viruses. Information on amantadine and rimantadine is available in previous publications of the ACIP influenza recommendations.

Zanamivir and oseltamivir belong to the class of drugs known as neuraminidase inhibitors—they have activity against **both influenza A and B viruses**. When considering use of influenza antiviral medications, clinicians must consider the patient's age, weight, and renal function (Table 3); the presence of other medical conditions; the indications for use (i.e., chemoprophylaxis or treatment); and the potential for interaction with other medications. An overview of the neuraminidase class of medications is presented below. Package inserts should be consulted for additional information as needed.

### Treatment

Oseltamivir is approved for treatment of persons aged  $\geq 1$  year, and zanamivir is approved for treatment of persons aged  $\geq 7$  years (Table 3). When administered within **two days** of illness onset to otherwise healthy adults, zanamivir and oseltamivir can reduce the duration of uncomplicated influenza A and B illness by approximately one day. The recommended duration of treatment with either zanamivir or oseltamivir is five days.

Data are limited regarding the effectiveness of these agents in preventing serious influenza-related complications (e.g., bacterial or viral pneumonia or exacerbation of chronic diseases) or their effectiveness for the treatment of influenza among persons at high risk for serious complications of influenza. Among influenza virus infected participants in 10 clinical trials, the risk for

pneumonia among those participants receiving oseltamivir was approximately 50% lower than among those persons receiving a placebo. Even fewer studies of the efficacy of influenza antivirals have been conducted among pediatric populations.

### Chemoprophylaxis

Oseltamivir is licensed for influenza chemoprophylaxis in persons aged  $\geq 1$  year, and zanamivir is licensed for influenza chemoprophylaxis in persons aged  $> 5$  years (Table 3). While influenza chemoprophylaxis is not generally a substitute for vaccination, antivirals are critical adjuncts in the prevention and control of influenza. They may be used, for example, as a component of influenza outbreak-control programs to limit the spread of influenza within chronic-care institutions.

Community studies of healthy adults indicate that both oseltamivir and zanamivir are similarly effective in preventing febrile, laboratory-confirmed influenza illness (efficacy: zanamivir, 84%; oseltamivir, 82%). Both agents have also been reported to prevent influenza illness among persons administered chemoprophylaxis after a household member was diagnosed with influenza.

Experience with prophylactic use of these agents in institutional settings or among patients with chronic medical

conditions is limited, but one 6-week study of oseltamivir prophylaxis among nursing home residents reported a 92% reduction in influenza illness.

When determining the timing and duration for admin-

istering influenza antiviral medications for chemoprophylaxis, factors related to cost, compliance, and potential side effects should be considered. To be maximally effective as prophylaxis, antivirals must be taken each day for the duration of influenza activity in the community.

Appropriate use of influenza chemoprophylaxis includes:

- Persons at High Risk Who Are Vaccinated After Influenza Activity

Has Begun. Persons at high risk for complications of influenza can still be vaccinated after an outbreak of influenza has begun in a community. However, development of antibodies in adults after vaccination takes approximately two weeks. When influenza vaccine is administered while influenza viruses are circulating, chemoprophylaxis should be considered for persons at high risk from the time of vaccination until immunity has developed. Of note, children aged  $< 9$  years who receive influenza vaccine for the first time would require at least six weeks of prophylaxis (e.g., prophylaxis for four weeks after the first dose of inactivated vaccine and an additional two weeks of prophylaxis after the second dose).

- Persons Who Provide Care to Those at High Risk. To reduce the spread of virus to persons at high risk during community or institutional outbreaks, chemoprophylaxis during peak influenza activity can be considered for **unvaccinated** persons who have frequent contact with persons at high risk. This may include employees of hospitals, clinics, and chronic-care facilities, household members, visiting nurses, and volunteer workers. If an outbreak is caused by a variant strain of influenza that might not be controlled 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 expected to have an inadequate antibody response to influenza vaccine. This category includes persons infected with HIV, chiefly those with advanced HIV disease. Such patients should be monitored closely if chemoprophylaxis is administered.
- Other Persons. Chemoprophylaxis throughout the influenza season or during peak influenza activity might be appropriate for persons at high risk who should not be vaccinated. In general, chemoprophylax-



is could be used by any person who wishes to avoid influenza illness, but healthcare professionals and patients should make this decision on an individual basis. Persons aged  $\geq 50$  years and others at high risk should consult with their healthcare workers before embarking on travel during the summer to discuss the advisability of carrying antiviral medications for either prophylaxis or treatment of influenza.

- **Residents of Institutions During Outbreaks.** Using antiviral drugs for the treatment and prophylaxis of influenza is a key component of influenza outbreak control in institutions (or other closed or semi-closed settings) in addition to other infection control measures such as droplet precautions, cohorting, vaccinations, and restricting staff movement between wards. When confirmed or suspected outbreaks of influenza occur in institutions that house persons at high risk, chemoprophylaxis should be started as early as possible to reduce the spread of the virus. In these situations, having pre-approved orders from physicians or plans to obtain orders for antiviral medications on short notice can expedite administration of antiviral medications. When outbreaks occur in institutions, chemoprophylaxis should be administered to all residents, regardless of whether they received influenza vaccinations during the previous fall, and should continue for a minimum of two weeks. If surveillance indicates that new cases continue to occur, chemoprophylaxis should be continued until approximately one week after the end of the outbreak. The dosage for each resident should be determined individually. Chemoprophylaxis also can be offered to unvaccinated staff who provide

care to persons at high risk; it should be considered for all employees, regardless of their vaccination status, if the outbreak is caused by a variant strain of influenza that is not well-matched by the vaccine.

To limit the potential transmission of drug-resistant influenza virus during outbreaks in institutions, measures should be taken to reduce contact as much as possible between persons taking antiviral drugs for treatment and other persons, including those taking antiviral drugs for chemoprophylaxis.

### **Dosage and Administration**

Dosage recommendations vary by antiviral medication, age group, weight, and medical conditions (e.g., impaired renal function) (Table 3). 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 will benefit from instruction and demonstration of correct use of this device). Duration of treatment is typically five days. Note: none of the current influenza antiviral medications are approved for use in children  $< 1$  year of age. Otherwise, no reduction in dosage of oseltamivir or zanamivir is recommended on the basis of age alone.

As noted in Table 3, for patients with creatinine clearance of 10-30 mL/min, 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 for oseltamivir are available for patients undergoing routine renal dialysis treatment. No dose adjustment is necessary for zanamivir for a 5-day course of treatment for patients with either mild-to-moderate or severe impairment in renal function.

Neither zanamivir nor oseltamivir

has been studied among persons with hepatic dysfunction. Zanamivir is not recommended for use in patients with underlying airway disease (e.g., asthma or chronic obstructive pulmonary disease) because of the risk for serious adverse events and because efficacy has not been demonstrated.

### **Side Effects and Adverse Reactions**

In studies, nausea and vomiting were reported more frequently among adults receiving oseltamivir for treatment than among those receiving placebo. Among children treated with oseltamivir, 14% had vomiting, compared with 8.5% of placebo recipients. Similar types and rates of adverse events were reported in studies of oseltamivir prophylaxis. Nausea and vomiting might be less severe if oseltamivir is taken with food.

In clinical treatment studies of persons with uncomplicated influenza, the frequencies of adverse events were similar for persons receiving inhaled zanamivir and 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. Allergic reactions, including oropharyngeal or facial edema, have been reported.

While seizure events have been reported during post-marketing use of zanamivir and oseltamivir, no epidemiologic studies have reported any increased risk for seizures with either zanamivir or oseltamivir use.

### **Use During Pregnancy**

Oseltamivir and zanamivir are both "Pregnancy Category C" medications. Therefore, no clinical studies have been conducted regarding the safety or efficacy of zanamivir or oseltamivir 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.



**Table 3. Recommended daily dosage of influenza antiviral medications for treatment and chemoprophylaxis, United States**

Antiviral agent	Age group (yrs)				
	1 - 6	7 - 9	10 - 12	13 - 64	≥ 65
<b>Zanamivir*</b>					
Treatment, influenza A and B	N/A†	10 mg (two inhalations) twice daily	10 mg (two inhalations) twice daily	10 mg (two inhalations) twice daily	10 mg (two inhalations) twice daily
Chemoprophylaxis, influenza A and B	<b>Ages 1 - 4</b> N/A†	<b>Ages 5 - 9</b> 10 mg (two inhalations) once daily	10 mg (two inhalations) once daily	10 mg (two inhalations) once daily	10 mg (two inhalations) once daily
<b>Oseltamivir</b>					
Treatment,§ influenza A and B	Dose varies by child's weight¶	Dose varies by child's weight¶	Dose varies by child's weight¶	75 mg twice daily	75 mg twice daily
Chemoprophylaxis, influenza A and B	Dose varies by child's weight**	Dose varies by child's weight**	Dose varies by child's weight**	75 mg once daily	75 mg once daily

NOTE: Zanamivir is manufactured by GlaxoSmithKline (Relenza® - inhaled powder). Oseltamivir is manufactured by Roche Pharmaceuticals (Tamiflu® - tablet). This information is based on information published by the U.S. Food and Drug Administration (FDA), which is available at [www.fda.gov](http://www.fda.gov).

\*Zanamivir is administered through oral inhalation by using a plastic device included in the medication package. Patients will benefit from instruction and demonstration of the correct use of the device. Zanamivir is not recommended for those persons with underlying airway disease.

†Not applicable.

§A reduction in the dose of oseltamivir is recommended for persons with creatinine clearance < 30 mL/min.

¶The treatment dosing recommendations of oseltamivir for children weighing ≤ 15 kg is 30 mg twice a day; for children weighing > 15 - 23 kg, the dose is 45 mg twice a day; for children weighing > 23 - 40 kg, the dose is 60 mg twice a day; and for children weighing > 40 kg, the dose is 75 mg twice a day.

\*\*The chemoprophylaxis dosing recommendations of oseltamivir for children weighing ≤ 15 kg is 30 mg once a day; for children weighing > 15 - 23 kg, the dose is 45 mg once a day; for children weighing > 23 - 40 kg, the dose is 60 mg once a day; and for children weighing > 40 kg, the dose is 75 mg once a day.

### **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* data and data from studies using rats.

Limited clinical data are available regarding drug interactions with oseltamivir. Because oseltamivir and its active metabolite, 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 (e.g., probenecid) excreted by this pathway.

### **Antiviral Drug-Resistant Strains of Influenza**

Resistance to zanamivir and oseltamivir can be induced in influenza A and B viruses *in vitro* but induction of resistance usually requires multiple passages in cell culture. Development of viral resistance to zanamivir and

oseltamivir during treatment has been identified but does not appear to be frequent. Post-marketing surveillance for neuraminidase inhibitor-resistant influenza viruses is being conducted.

### **Conclusions**

Although influenza vaccination levels increased substantially during the 1990s, estimated national adult vaccine

coverage for 2004 was 65% for adults aged ≥65 years and 36% for adults aged 50-64 years. Vaccination levels are low among children at increased risk for influenza complications (approximately 9-10% in children with asthma) and pregnant women (approximately 13%). Annual vaccination is also recommended for healthcare workers to protect patients, but coverage averaged only 42% among healthcare workers in 2004. Therefore, there are many opportunities, such as reminder/recall systems and standing orders programs, for every healthcare provider in Virginia to work towards improving vaccination levels and the health of the population.

The appropriate use of antiviral agents in the treatment and prophylaxis of influenza can reduce influenza morbidity and mortality, especially in select populations. In particular, antivirals may significantly benefit people at risk for complications from influenza but who cannot take the vaccine, or in the prevention or control of an outbreak.



**Cases of Selected Notifiable Diseases Reported in Virginia\***

Disease	Total Cases Reported, July 2006						Total Cases Reported Statewide, January - July		
	State	Regions					This Year	Last Year	5 Yr Avg
		NW	N	SW	C	E			
<b>AIDS</b>	47	4	12	2	16	13	296	343	401
<b>Campylobacteriosis</b>	127	24	30	25	12	36	335	307	330
<b>Chickenpox</b>	118	15	41	17	19	26	1,114	271	370
<b><i>E. coli</i>, Shiga toxin-producing</b>	22	7	7	5	0	3	71	33	25
<b>Giardiasis</b>	42	6	24	4	4	4	233	290	210
<b>Gonorrhea</b>	376	22	20	74	103	157	3,623	4,762	5,378
<b>Group A Strep, Invasive</b>	6	1	0	2	2	1	89	59	61
<b>Hepatitis, Viral</b>									
<b>A</b>	6	2	3	0	0	1	30	50	55
<b>B, acute</b>	10	1	2	0	3	4	29	88	103
<b>C, acute</b>	1	0	0	0	1	0	4	8	5
<b>HIV Infection</b>	63	2	14	6	17	24	511	427	500
<b>Lead in Children†</b>	42	8	4	14	9	7	317	280	357
<b>Legionellosis</b>	11	3	0	4	1	3	34	25	24
<b>Lyme Disease</b>	50	1	35	6	5	3	88	85	61
<b>Measles</b>	0	0	0	0	0	0	0	0	0
<b>Meningococcal Infection</b>	1	0	1	0	0	0	14	19	19
<b>Pertussis</b>	27	2	6	4	3	12	126	238	101
<b>Rabies in Animals</b>	61	13	15	15	4	14	362	291	288
<b>Rocky Mountain Spotted Fever</b>	23	1	3	6	7	6	40	27	15
<b>Rubella</b>	0	0	0	0	0	0	0	0	0
<b>Salmonellosis</b>	164	30	34	24	40	36	458	528	566
<b>Shigellosis</b>	9	0	2	4	1	2	35	61	210
<b>Syphilis, Early§</b>	25	1	5	3	7	9	172	161	127
<b>Tuberculosis</b>	20	2	12	0	1	5	152	171	145

*Localities Reporting Animal Rabies This Month:* Albemarle 1 fox; Appomattox 1 raccoon; Arlington 1 bat; Augusta 1 raccoon, 1 skunk; Botetourt 1 fox; Clarke 1 fox; Culpeper 1 raccoon; Fairfax 1 bat, 3 cats, 3 foxes, 3 raccoons; Fauquier 1 fox; Frederick 1 cat; Galax 1 raccoon; Gloucester 3 foxes, 1 raccoon; Grayson 1 fox, 2 raccoons; Henrico 1 cat; Isle of Wight 1 raccoon; Loudoun 1 cat, 1 raccoon; Middlesex 2 raccoons; Montgomery 1 dog, 1 skunk; Newport News 1 fox, 1 raccoon; Page 1 dog; Pittsylvania 1 raccoon, 1 skunk; Prince Edward 1 skunk; Prince William 1 fox, 1 raccoon; Pulaski 1 fox, 1 skunk; Richmond City 1 groundhog; Rockbridge 1 groundhog, 1 skunk; Shenandoah 1 cat, 1 fox; Smyth 1 raccoon; Spotsylvania 1 cat; Sussex 1 fox; Virginia Beach 1 fox; Warren 1 cat; Wythe 2 skunks; York 3 raccoons.

*Toxic Substance-related Illnesses:* Adult Lead Exposure 14; Asbestosis 1; Mesothelioma 1; Pneumoconiosis 8.

\*Data for 2006 are provisional. †Elevated blood lead levels  $\geq 10\mu\text{g/dL}$ . §Includes primary, secondary, and early latent.

However, the expense of these medications, as well as the risk of side effects, the risk of developing more wide-spread viral resistance, and the likely limited availability of such drugs during major outbreaks, makes judicious use important and reinforces the importance of primary prevention (through vaccination and respiratory etiquette).

**Information regarding influenza surveillance, prevention, detection,**

**and control is available at [www.cdc.gov/flu/weekly/fluactivity.htm](http://www.cdc.gov/flu/weekly/fluactivity.htm). State and local health departments should be consulted concerning availability of influenza vaccine, access to vaccination programs, information related to state or local influenza activity, for reporting influenza outbreaks and influenza-related pediatric deaths, and for receiving advice concerning outbreak control. Additional infor-**

**mation about the status of influenza in Virginia is available on the VDH website ([www.vdh.virginia.gov/epi/newhome.asp](http://www.vdh.virginia.gov/epi/newhome.asp)).**

**References**

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