VIRGINIA
EPIDEMIOLOGY BULLETIN

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Prevention and Control of Influenza

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Summary

This article summarizes the 2001 recommendations by the ACIP on the use of influenza vaccine and antiviral agents (MMWR 2001;50[No. RR-4]:1-44). The 2001 recommendations include new or updated information regarding a) the cost-effectiveness of influenza vaccination; b) the influenza vaccine supply; c) neuraminidase-inhibitor antiviral drugs; d) the 2001-2002 trivalent vaccine virus strains; and e) extension of the optimal time period for vaccination through November. The complete report and other information regarding influenza can be accessed at the CDC website at <http://www.cdc.gov/ncidod/diseases/flu/fluvirus.htm>.

Background

Influenza vaccination is the primary method for preventing influenza and its severe complications. The primary target groups recommended for annual vaccination are a) persons aged ≥65 years and persons of any age with certain chronic medical conditions; b) persons aged 50-64 years because this group has an elevated prevalence of certain chronic medical conditions; and c) health-care workers and household members who have frequent contact with persons at high risk for influenza-related complications. Vaccination is associated with reductions in influenza-related respiratory illness and physician visits among all age groups, hospitalization and death among persons at high risk, otitis media among children, and work absenteeism among adults.

Although influenza vaccination remains the cornerstone for the control and treatment of influenza, updated information is also presented on antiviral medications because these agents are an adjunct to vaccine.

Signs and Symptoms of Influenza

Influenza viruses are spread from person-to-person primarily through the coughing and sneezing of infected persons. The incubation period for influenza is 1-4 days, with an average of 2 days. Persons can be infectious starting the day before symptoms begin through approximately 5 days after illness onset; children can be infectious for a longer period.

When educating patients regarding potential side effects, clinicians should emphasize that a) inactivated influenza vaccine contains noninfectious killed viruses and cannot cause influenza; and b) coincidental respiratory disease unrelated to influenza vaccination can occur after vaccination.

Uncomplicated influenza illness is characterized by the abrupt onset of constitutional and respiratory signs and symptoms (e.g., fever, myalgia, headache, severe malaise, nonproductive cough, sore throat, and rhinitis). Respiratory illness caused by influenza is difficult to distinguish from illness caused by other respiratory pathogens on the basis of symptoms alone.

Influenza illness typically resolves after several days for most persons, although cough and malaise can persist for ≥2 weeks. In some persons, influenza can exacerbate underlying medical conditions, lead to secondary bacterial pneumonia or primary influenza viral 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.

Influenza Vaccine Composition

The trivalent influenza vaccine prepared for the 2001-2002 season will include A/Moscow/10/99 (H3N2)-like, A/New Caledonia/20/99 (H1N1)-like, and B/Sichuan/379/99-like antigens. The vaccine is made from highly purified, egg-grown viruses that have been made noninfectious. Subvirion and purified surface-antigen preparations are available (Table 1). Because the vaccine viruses are initially grown in embryonated hens' eggs, the vaccine might contain small amounts of residual egg protein. Influenza vaccine also contains thimerosal, a mercury-containing compound, as the preservative. Certain manufacturers might use additional compounds to inactivate the influenza viruses, and they might use an antibiotic to prevent bacterial contamination. Package inserts should be consulted for additional information.

Effectiveness of Vaccine

When the vaccine and circulating viruses are antigenically similar, influenza vaccine prevents illness in approximately 70%-90% of healthy persons aged <65 years. Other studies suggest that the use of trivalent inactivated influenza vaccine decreases the incidence of influenza-associated otitis media and the use of antibiotics among children.

Among elderly persons residing in nursing homes, influenza vaccine is most effective in preventing severe illness, secondary complications, and deaths. Among this population, the vaccine can be 50%-60% effective in preventing hospitalization or pneumonia and 80% effective in preventing death,

Table 1. Influenza vaccine* dosage, by age group, United States, 2001-2002 season

Age group	Product†	Dose	No. of doses	Route§
6-35 mos	Split-virus only	0.25 mL	1 or 2¶	Intramuscular
3-8 yrs	Split-virus only	0.50 mL	1 or 2¶	Intramuscular
9-12 yrs	Split-virus only	0.50 mL	1	Intramuscular
>12 yrs	Whole- or split-virus**	0.50 mL	1	Intramuscular

**Contains 15 µg each of A/New Caledonia/20/99 (H1N1)-like, A/Moscow/10/99 (H3N2)-like, and B/Sichuan/379/99-like strains. For the A/Moscow/10/99 (H3N2)-like antigen, manufacturers will use the antigenically equivalent A/Panama/2007/99 (H3N2) virus. For the B/Sichuan/379/99-like antigen, manufacturers will use one of the antigenically equivalent viruses B/Johannesburg/5/99, B/Victoria/504/2000, or B/Guangdong/120/2000. Manufacturers include Aventis Pasteur, Inc. (Fluzone® split); Evans Vaccines, Ltd. (Fluvirin® purified surface antigen vaccine); and Wyeth Lederle Laboratories (Flushield™ split). For further product information, call Aventis Pasteur, (800) 822-2463; Evans Vaccines (800) 200-4278; or Wyeth Lederle, (800) 358-7443.*
†Because of their decreased potential for causing febrile reactions, only split-virus vaccines should be used for children. The vaccines might be labeled as "split," "subvirion," or "purified-surface-antigen" vaccine. Immunogenicity and side effects of split- and whole-virus vaccines are similar among adults when vaccines are administered at the recommended dosage.
§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.
¶Two doses administered ≥1 month apart are recommended for children <9 years who are receiving influenza vaccine for the first time.
***No whole virus vaccine will be distributed in the U.S. during the 2001-2002 influenza season.*

even though the effectiveness in preventing influenza illness often ranges from 30% to 40%.

Recommendations for the Use of Influenza Vaccine

Influenza vaccine is strongly recommended for any person aged ≥6 months who, because of age or underlying medical condition, is at increased risk for complications of influenza.

Target Groups for Vaccination

Persons at Increased Risk for Complications

Vaccination is recommended for the following groups of persons who are at increased risk for complications from influenza:

- persons aged ≥65 years;
- residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions;
- adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including asthma;
- 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 immunosuppression;
- children and teenagers (aged 6 months-18 years) who are receiving long-term aspirin therapy and, therefore, might be at risk for developing Reye syndrome after influenza infection; and
- women who will be in the second or third trimester of pregnancy during the influenza season.

Persons Aged 50—64 Years

Vaccination is recommended for persons aged 50-64 years because approximately 25% of this group has ≥1 high-risk medical conditions.

Persons Who Can Transmit Influenza to Those at High Risk

Persons who are clinically or subclinically infected can transmit influenza virus to persons at high risk for complications from influenza. Evidence from two studies indicates that vaccination of health-care workers is associated with decreased deaths among nursing home patients. The following groups should be vaccinated:

- physicians, nurses, and other personnel in both hospital and outpatient-care settings, including emergency response workers;
- 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;
- persons who provide home care to persons in groups at high risk; and
- household members of persons in groups at high risk.

Additional Information Regarding Vaccination of Specific Populations

Pregnant Women

Women who will be beyond the first trimester of pregnancy during the influenza season should be vaccinated. Pregnant women who have medical conditions that increase their risk for complications from influenza should be vaccinated before the influenza season, regardless of the stage of pregnancy.

Because currently available influenza vaccine is an inactivated vaccine, experts consider influenza vaccination safe during any stage of pregnancy. However, some experts prefer to administer influenza vaccine during the second trimester to avoid a coincidental association with spontaneous abortion, which is common in the first trimester, and because exposures to vaccines traditionally have been avoided during the first trimester.

Influenza vaccine distributed in the United States contains thimerosal, a mercury-containing compound, as a preservative. No data or evidence exists of any harm caused by the level of mercury exposure that might occur from influenza vaccination. Because pregnant women are at increased risk for influenza-related complications and because a substantial safety margin has been incorporated into the health guidance values for organic mercury exposure, the benefit of influenza vaccine outweighs the potential risks for thimerosal.

Persons Infected with HIV

Vaccination will benefit HIV-infected patients, including HIV-infected pregnant women.

Breastfeeding Mothers

Influenza vaccine does not affect the safety of mothers who are breastfeeding or their infants. Breastfeeding does not adversely affect the immune response and is not a contraindication for vaccination.

Travelers

Persons at high risk for complications of influenza 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 large organized tourist groups at any time of year; or
- travel to the Southern Hemisphere during April-September.

No information is available regarding the benefits of revaccinating persons before summer travel who were already vaccinated in the preceding fall. Persons at high risk who received the previous season's vaccine before travel should be revaccinated with the current vaccine in the following fall or winter. Persons aged ≥50 years and others at high risk might wish to consult with their physicians before embarking on travel during the summer to discuss the symptoms and risks for influenza and the advisability of carrying antiviral medications for either prophylaxis or treatment of influenza.

General Population

In addition to the groups for which annual influenza vaccination is recommended, physicians should administer influenza vaccine to any person ≥6 months old who wishes to reduce the likelihood of becoming ill with influenza, depending on vaccine availability. 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 should be encouraged to receive vaccine to minimize the disruption of routine activities during epidemics.

Persons Who Should Not Be Vaccinated

Inactivated influenza vaccine should not be administered to persons known to have anaphylactic hypersensitivity to eggs or to other components of the influenza vaccine without first consulting a physician (see Side Effects and Adverse Reactions). However, persons who have a history of anaphylactic hypersensitivity to vaccine components but who are also at high risk for complications of influenza can benefit from vaccine after appropriate allergy evaluation and desensitization.

Persons with acute febrile illness usually should not be vaccinated until their symptoms have abated. However, minor illnesses with or without fever do not contraindicate the use of influenza vaccine, particularly among children with mild upper respiratory tract infection or allergic rhinitis.

Timing of Annual Vaccination

The optimal time to vaccinate persons in groups at high risk is usually during October-November. Very importantly, health-care providers should continue to offer vaccine to unvaccinated persons after November and throughout the influenza season even after influenza activity has been documented in the community. In the United States, seasonal influenza activity has not reached peak levels in the majority of recent seasons until late December through early March. Therefore, although the timing of influenza activity can vary by region, vaccine administered after November is likely to be beneficial in most influenza seasons. Adults develop peak antibody protection against influenza infection 2 weeks after vaccination.

Persons planning substantial organized vaccination campaigns might consider scheduling these events after mid-October. **In facilities housing elderly persons (e.g., nursing homes), vaccination before October generally should be avoided because antibody levels in such individuals can begin to decline within a few months after vaccination.**

Dosage

Dosage recommendations vary according to age group (Table 1). Among previously unvaccinated children aged <9 years, two doses administered ≥1 months apart are recommended for satisfactory antibody responses. If possible, the second dose should be administered before December. Among adults, studies have indicated little or no improvement in antibody response when a second dose is administered during the same season.

Use of Inactivated Influenza Vaccine Among Children

Of the three influenza vaccines currently licensed in the United States, two influenza vaccines (Flushield™, from Wyeth Laboratories, Inc., and Fluzone® split, from Aventis Pasteur, Inc.) are approved for use among persons aged ≥6 months. Fluvirin® (Evans Vaccines Ltd.), is labeled in the United States for use only among persons aged ≥4 years because its efficacy among younger persons has not been demonstrated.

Influenza Vaccine Supply

This season more vaccine is expected to be available than in previous years. Some delays in distribution are projected, but they are not expected to be as great as in the 2000-01 season. Nationally, approximately 55% of the total supply should be distributed by the end of October. An additional 30% will be delivered in November and the remainder is expected in early December. However, vaccine availability may vary greatly by manufacturer. We strongly recommend initial supplies be prioritized for use in your high-risk patients.

In Virginia, influenza usually peaks in late December - February. We recommend you continue to administer vaccine throughout the flu season. If you have been unable to place an order for vaccine or if you have more vaccine than you need, please call Jim Farrell, Director, Division of Immunization, VDH, at 804/786-6246.

Route

The intramuscular route is recommended for influenza vaccine. Adults and older children should be vaccinated in the deltoid muscle. A needle length ≥1 inches can be considered for these age groups because needles <1 inch might be of insufficient length to penetrate muscle tissue in certain adults and older children. Infants and young children should be vaccinated in the anterolateral aspect of the thigh.

Side Effects and Adverse Reactions

Local Reactions

The most frequent side effect of vaccination is soreness at the vaccination site (affecting 10%-64% of patients) that lasts ≤2 days. These local reactions generally are mild and rarely interfere with the person's ability to conduct usual daily activities.

Systemic Reactions

Fever, malaise, myalgia, and other systemic symptoms can occur following vaccination and most often affect persons who have had no prior exposure to the influenza virus antigens in the vaccine. These reactions begin 6-12 hours after vaccination and can persist for 1-2 days. Recent studies demonstrate that among elderly persons and healthy young adults, administration of split-virus influenza vaccine is not associated with higher rates of systemic symptoms when compared with placebo injections.

Immediate and presumably allergic reactions (e.g., hives, angioedema, allergic asthma, and systemic anaphylaxis) rarely occur after influenza vaccination. These reactions probably result from hypersensitiv-

ity to some vaccine component; most reactions likely are caused by residual egg protein. Although current influenza vaccines contain only a small quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Persons who have developed hives, have had swelling of the lips or tongue, or have experienced acute respiratory distress or collapse after eating eggs should consult a physician for appropriate evaluation to help determine if vaccine should be administered. Persons who have documented IgE-mediated hypersensitivity to eggs might also be at increased risk for allergic reactions to influenza vaccine, and consultation with a physician should be considered. Protocols have been published for safely administering influenza vaccine to persons with egg allergies.

Hypersensitivity reactions to any vaccine component can occur. Although exposure to vaccines containing thimerosal can lead to induction of hypersensitivity, most patients do not develop 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 usually has consisted of local, delayed-type hypersensitivity reactions.

Guillain-Barré Syndrome (GBS)

The potential benefits of influenza vaccination in preventing serious illness, hospitalization, and death greatly outweigh the possible risks for developing vaccine-associated GBS. Investigations to date indicate no substantial increase in GBS associated with influenza vaccines other than the swine influenza vaccine in 1976. If influenza vaccine does pose a risk, it is probably slightly more than one additional case per million persons vaccinated.

Persons with a history of GBS have a substantially greater likelihood of subsequently developing GBS than persons without such a history. Whether influenza vaccination specifically might increase the risk for recurrence of GBS is not known; therefore, avoiding vaccinating persons who are not at high risk for severe influenza complications and who are known to have developed GBS within 6 weeks after a previous influenza vaccination is prudent.

Simultaneous Administration of Other Vaccines

For persons at high risk who have not previously been vaccinated with pneumococcal vaccine, health-care providers should strongly consider administering pneumococcal and influenza vaccines concurrently. Both vaccines can be administered at the same time at different sites without increasing side effects. However, influenza vaccine is administered each year, whereas pneumococcal vaccine is not. A patient's verbal history is acceptable for determining prior pneumococcal vaccination status. When indicated, pneumococcal vaccine should be administered to patients who are uncertain regarding their vaccination history. Children at high risk for influenza-related complications can receive influenza vaccine at the same time they receive other routine vaccinations.

Recommendations for the Use of Antiviral Agents

Antiviral drugs for influenza are an adjunct to influenza vaccine for the control and prevention of influenza. However, these agents are not a substitute for vaccination. Four currently licensed influenza antiviral agents are available in the United States: amantadine and rimantadine, chemically-related antivirals with activity against influenza A only; and zanamivir and oseltamivir, neuraminidase inhibitors with activity against both influenza A and B viruses.

An overview of the indications, use, administration, and known side effects of these medications is presented in the following sections. Package inserts should be consulted for additional information.

Role of Laboratory Diagnosis

Appropriate treatment of patients with respiratory illness depends on accurate and timely diagnosis. The early diagnosis of influenza can reduce the inappropriate use of antibiotics and provide the option of using antiviral therapy.

Diagnostic tests available for influenza include viral culture, serology, rapid antigen testing, and immunofluorescence. Sensitivity and specificity of any test vary by the laboratory that performs the test and by the type of test used. As with any diagnostic test, results should be evaluated in the context of other clinical information available to the physician.

Several commercial rapid diagnostic tests are available that can be used by laboratories in outpatient settings to detect influenza viruses within 30 minutes. These rapid tests differ in the types of influenza virus they can detect and whether or not they can distinguish between influenza types. Different tests can detect a) only influenza A viruses; b) both influenza A and B viruses but not distinguish between the two types, or c) both influenza A and B and distinguish between the two. Sensitivity and specificity of rapid tests are lower than for viral culture and vary by test. In addition, the types of specimens acceptable for use (i.e., throat swab, nasal wash, or nasal swab) also vary. Package inserts and the laboratory performing the test should be consulted for more details.

Despite the availability of rapid diagnostic tests, the collection of 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 prophylaxis, and to formulate vaccine for the coming year. Virus isolates also are needed to monitor the emergence of antiviral resistance and the emergence of novel influenza A subtypes that might pose a pandemic threat.

Indications for Use

Treatment

When administered within 2 days of illness onset to otherwise healthy adults, amantadine and rimantadine can reduce the duration of uncomplicated influenza A illness, and zanamivir and oseltamivir can reduce the duration of uncomplicated influenza A and B illness by approximately 1 day.

None of the four antiviral agents has been demonstrated to be effective in preventing serious influenza-related complications, such as bacterial or viral pneumonia or exacerbation of chronic diseases. Evidence for the effectiveness of these four antiviral drugs is based principally on studies of adults with uncomplicated influenza. Fewer studies of the efficacy of influenza antivirals have been conducted among pediatric populations. One study of oseltamivir treatment documented a decreased incidence of otitis media among children.

To reduce the emergence of antiviral drug-resistant viruses, amantadine or rimantadine therapy for persons with influenza-like illness should be discontinued as soon as clinically warranted, generally after 3-5 days of treatment or within 24-48 hours after the disappearance of signs and symptoms. The recommended duration of treatment with either zanamivir or oseltamivir is 5 days.

Prophylaxis

Chemoprophylactic drugs are not a substitute for vaccination, although they are critical adjuncts in the prevention and control of influenza. Both amantadine and rimantadine are approximately 70%-90% effective in pre-

venting illness from influenza A infection. When used as prophylaxis, these antiviral agents can prevent illness while permitting subclinical infection and the development of protective antibody against circulating influenza viruses. Amantadine and rimantadine do not interfere with the antibody response to the vaccine. Both drugs have been studied extensively among nursing home populations as a component of influenza outbreak control programs.

Among the neuraminidase inhibitor antivirals, only oseltamivir has been approved for prophylaxis, but community studies of healthy adults indicate that both drugs are approximately 80% effective in preventing febrile, laboratory-confirmed influenza illness. Both antiviral agents also have been reported to prevent influenza illness among persons given 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. One 6-week study of oseltamivir prophylaxis among nursing home residents found a 92% reduction in influenza illness.

To be maximally effective as prophylaxis, an antiviral drug must be taken each day for the duration of influenza activity in the community. However, to be most cost-effective, one study of amantadine or rimantadine prophylaxis reported that the drugs should be taken only during the period of peak influenza activity in a community. Data are not available on the efficacy of any of the four antiviral agents in preventing influenza among severely immune compromised persons.

Control of Outbreaks in Institutions

The use of antiviral drugs for treatment and prophylaxis of influenza is an important component of institutional outbreak control. In addition to the use of antiviral medications, other outbreak control measures include instituting droplet precautions, cohorting patients with confirmed or suspected influenza, vaccinating staff and patients who are unvaccinated, restricting staff movement between wards or buildings, and restricting contact between ill staff or visitors and patients.

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 preapproved orders from physicians or plans to obtain orders for antiviral medications on short notice is extremely useful.

When institutional outbreaks occur, chemoprophylaxis should be administered to all residents, regardless of whether they received influenza vaccinations during the previous fall, and should continue for ≥2 weeks or until approximately 1 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. Prophylaxis 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.

In addition to nursing homes, chemoprophylaxis also can be considered for controlling influenza outbreaks in other closed or semiclosed settings (e.g., dormitories or other settings where persons live in close proximity).

To limit the potential transmission of drug-resistant virus during institutional outbreaks, whether in chronic or acute-care settings or other closed settings, measures should be taken to reduce contact as much as possible between persons taking antiviral drugs for treatment and other persons, including those taking chemoprophylaxis.

Dosage

Dosage recommendations vary by age group and medical conditions (Table 2).

Route

Amantadine, rimantadine, and oseltamivir are administered orally. Amantadine and rimantadine are available in tablet or syrup form, and oseltamivir is available 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 receive instruction and demonstration of correct use of this device.

Side Effects and Adverse Reactions

Amantadine and Rimantadine

Both amantadine and rimantadine can cause central nervous system (CNS) and gastrointestinal side effects when administered to young, healthy adults at equivalent dosages of 200 mg/day. However, incidence of CNS side effects (e.g., nervousness, anxiety, difficulty concentrating, and lightheadedness) is higher among persons taking amantadine than among those taking rimantadine. A study of elderly persons also demonstrated fewer CNS side effects associated with rimantadine compared with amantadine. Gastrointestinal side effects (e.g., nausea and anorexia) occur in approximately 1%-3% of persons taking either drug, compared with 1% of persons receiving the placebo.

An increased incidence of seizures has been reported among patients with a history of seizure disorders who have received amantadine. Patients with seizure disorders should be observed closely for possible increased seizure activity when taking amantadine. Seizures (or seizure-like activity) also have been reported among persons with a history of seizures who were not receiving anticonvulsant medication while taking rimantadine.

Side effects associated with amantadine and rimantadine are usually mild and cease soon after discontinuing the drug. Side effects can diminish or disappear after the first week, despite continued drug ingestion. Serious side effects such as marked behavioral changes, delirium, hallucinations, agitation, and seizures have been associated with high plasma drug concentrations. These have been observed most often among persons who have renal insufficiency, seizure disorders, certain psychiatric disorders, and among elderly persons who have been taking amantadine as prophylaxis at a dosage of 200 mg/day. In acute overdosage of amantadine, CNS, renal, respiratory, and cardiac toxicity, including arrhythmias, have been reported.

Zanamivir

Zanamivir is generally not recommended for treatment for patients with underlying airway disease because of the risk for serious adverse events and because the efficacy has not been demonstrated in this population. If physicians decide to prescribe zanamivir to patients with underlying chronic respiratory disease, the drug should be used with caution under conditions of proper monitoring and supportive care. Patients with asthma or chronic obstructive pulmonary disease who use zanamivir are advised to a) have a fast-acting inhaled bronchodilator available when inhaling zanamivir and b) stop using zanamivir and contact their physician if they develop difficulty breathing. No clear evidence is available regarding the safety or efficacy of zanamivir for persons with underlying respiratory or cardiac disease or for persons with complications of acute influenza.

In clinical treatment studies of persons with uncomplicated influenza, the frequencies of other adverse events were similar for persons receiving inhaled zanamivir and those receiving placebo. 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.

Oseltamivir

Nausea and vomiting were reported more frequently among adults receiving oseltamivir for treatment than among persons receiving placebo. Among children treated with oseltamivir, 14.3% had vomiting compared with 8.5% of placebo recipients. Overall, 1% discontinued the drug secondary to this side effect, whereas a limited number of adults enrolled in clinical treatment trials of oseltamivir discontinued treatment because of these symptoms. Similar types and rates of adverse events were found in studies of oseltamivir prophylaxis. Nausea and vomiting might be less severe if oseltamivir is taken with food.

Use During Pregnancy

No clinical studies have been conducted regarding the safety or efficacy of amantadine, rimantadine, zanamivir, or oseltamivir for pregnant women. However, both amantadine and rimantadine have been demonstrated in animal studies to be teratogenic and embryotoxic when administered at very high doses. Because of the unknown effects of influenza antiviral drugs on pregnant women and their fetuses, these four drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus.

Drug Interactions

Careful observation is advised when amantadine is administered concurrently with drugs that affect the CNS, especially CNS stimulants. Concomitant administration of antihistamines or anticholinergic drugs can increase the incidence of adverse CNS reactions. No clinically significant interactions between rimantadine and other drugs have been identified.

Clinical data are limited regarding drug interactions with zanamivir. However, no known drug interactions have been reported, and no clinically important drug interactions have been predicted on the basis of in vitro data and data from studies of rats.

Limited clinical data are available regarding drug interactions with oseltamivir. Be-

Table 2. Recommended daily dosage of influenza antiviral medications for treatment and prophylaxis

	Age group				
Antiviral agent	**1-6 yrs**	**7-9 yrs**	**10-12 yrs**	**13-64 yrs**	**≥65 yrs**
Amantadine*					
Treatment	5mg/kg/day up to 150 mg per day in two divided doses†	5mg/kg/day up to 150 mg per day in two divided doses†	100 mg twice daily§	100 mg twice daily§	≤100 mg/day
Prophylaxis	5mg/kg/day up to 150 mg per day in two divided doses†	5mg/kg/day up to 150 mg per day in two divided doses†	100 mg twice daily§	100 mg twice daily§	≤100 mg/day
Rimantadine¶					
Treatment**	NA††	NA	NA	100 mg twice daily§	100 or 200§§ mg/day
Prophylaxis	5mg/kg/day up to 150 mg per day in two divided doses†	5mg/kg/day up to 150 mg per day in two divided doses†	100 mg twice daily§	100 mg twice daily§	100 or 200§§ mg/day
Zanamivir¶¶***					
Treatment	NA	10 mg twice daily	10 mg twice daily	10 mg twice daily	10 mg twice daily
Oseltamivir					
Treatment†††	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
Prophylaxis	NA	NA	NA	75 mg/day	75 mg/day

***NOTE**: Amantadine manufacturers include Endo Pharmaceuticals (Symmetrel®, tablet and syrup); Geneva Pharmaceuticals and Rosemont (Amantadine HCL, capsule); and Alpharma, Copley Pharmaceutical, HiTech Pharma, Mikart, Morton Grove, and Pharmaceutical Associates (Amantadine HCL, syrup). Rimantadine is manufactured by Forest Laboratories (Flumadine®, tablet and syrup). Zanamivir is manufactured by Glaxo Wellcome (Relenza®, inhaled powder). Oseltamivir is manufactured by Hoffman-LaRoche (Tamiflu®, tablet and suspension).*

**The drug package insert should be consulted for dosage recommendations for administering amantadine to persons with creatinine clearance ≤50 mL/min/1.73m^2.*

†5 mg/kg of amantadine or rimantadine syrup = 1 tsp/22 lbs.

§Children aged ≥10 years who weigh <40kg should be administered amantadine or rimantadine at a dosage of 5 mg/kg/day.

¶A reduction in dosage to 100mg/day of rimantadine is recommended for persons who have severe hepatic dysfunction or those with creatinine clearance ≤10 mL/min. Other persons with less severe hepatic or renal dysfunction taking 100 mg/day of rimantadine should be observed closely, and the dosage should be reduced or the drug discontinued, if necessary.

***Only approved for treatment for persons ≥13 years old.*

††NA=Not applicable.

§§Elderly nursing home residents should be administered only 100 mg/day of rimantadine. A reduction in dosage to 100 mg/day should be considered for all persons aged ≥65 years if they experience side effects when taking 200 mg/day.

¶¶Zanamivir is administered via inhalation by using a plastic device included in the package with the medication. Patients will benefit from instruction and demonstration of correct use of the device.

****Zanamivir is not approved for prophylaxis.*

†††For persons with creatinine clearance <30mL/min, a reduction of the treatment dose of oseltamivir to 75mg/day and in the prophylaxis dose to 75mg every other day is recommended.

§§§The dose recommendation for children who weigh ≤15kg is 30mg twice a day; for children weighing >15-23kg, the dose is 45mg twice a day; for children weighing >23-40kg, the dose is 60mg twice a day; and for children weighing>40kg, the dose is 75mg twice a day.

Cases of Selected Notifiable Diseases Reported in Virginia*

Disease	Total Cases Reported, July 2001: State	Regions: NW	N	SW	C	E	Total Cases Reported Statewide, January through July: This Year	Last Year	5 Yr Avg
AIDS	52	3	20	3	18	8	523	454	553
Campylobacteriosis	60	15	14	18	5	8	288	316	346
***E. coli* O157:H7**	8	1	2	2	2	1	28	25	33
Giardiasis	34	8	18	1	5	2	214	219	201
Gonorrhea	1443	76	79	167	508	613	6043	5685	5087
Hepatitis A	9	1	4	4	0	0	76	88	106
B, acute	12	1	2	1	5	3	88	92	74
C/NANB, acute	0	0	0	0	0	0	0	3	9
HIV Infection	71	3	26	3	19	20	546	407	498
Lead in Children†	54	7	4	9	23	11	330	380	323
Legionellosis	7	2	2	3	0	0	14	12	12
Lyme Disease	30	5	24	0	1	0	83	71	37
Measles	0	0	0	0	0	0	0	2	2
Meningococcal Infection	5	0	1	0	2	2	30	34	32
Mumps	0	0	0	0	0	0	2	5	7
Pertussis	1	1	0	0	0	0	13	33	22
Rabies in Animals	31	6	5	5	6	9	249	358	339
Rocky Mountain Spotted Fever	9	0	1	4	4	0	12	3	8
Rubella	0	0	0	0	0	0	0	0	1
Salmonellosis	280	17	32	58	150	23	779	489	542
Shigellosis	29	1	7	3	3	15	122	238	195
Syphilis, Early§	13	0	2	2	2	7	154	169	314
Tuberculosis	12	2	6	0	1	3	132	157	186

Localities Reporting Animal Rabies This Month: Accomack 1 fox, 1 raccoon; Alleghany 1 fox; Amelia 1 skunk; Arlington 1 raccoon; Bath 1 cat, 1 fox; Bedford 2 skunks; Buckingham 1 raccoon; Chesterfield 1 bat; Culpeper 1 raccoon; Fairfax 1 bat, 3 raccoons; Goochland 1 raccoon; Henry 1 raccoon; King William 1 raccoon; Montgomery 1 cat; New Kent 1 fox; Newport News 1 raccoon; Norfolk 1 raccoon; Northampton 1 raccoon; Northumberland 1 raccoon; Prince George 1 raccoon; Rockingham 1 cat; Shenandoah 2 raccoons; Virginia Beach 1 fox, 1 raccoon.
Toxic Substance-related Illnesses: Asbestosis 20; Lead Exposure 10; Pneumoconiosis 4.
*Data for 2001 are provisional. †Elevated blood lead levels ≥10µg/dL.
§Includes primary, secondary, and early latent.

cause 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.

Drug-Resistant Strains of Influenza

Amantadine-resistant viruses are cross-resistant to rimantadine and vice versa. Drug-resistant viruses can appear in approximately one third of patients when either amantadine or rimantadine is used for therapy. During the course of amantadine or rimantadine therapy, resistant influenza strains can replace sensitive strains within 2-3 days of starting therapy. Resistant viruses have been isolated from persons who live at home or in an institution where other residents are taking or have recently taken amantadine or rimantadine as therapy; however, the frequency with which resistant viruses are transmitted and their impact on efforts to control influenza are unknown. Amantadine- and rimantadine-resistant viruses are not more virulent or transmissible than sensitive viruses. The screening of epidemic strains of influenza A has rarely detected amantadine- and rimantadine-resistant viruses.

Persons who have influenza A infection and who are treated with either amantadine or rimantadine can shed sensitive viruses early in the course of treatment and later shed drug-resistant viruses, especially after 5-7 days of therapy. Such persons can benefit from therapy even when resistant viruses emerge.

Development of viral resistance to zanamivir and oseltamivir during treatment has been identified but does not appear to be frequent. Surveillance for neuraminidase inhibitor-resistant influenza viruses is being conducted.

Cases of Selected Notifiable Diseases Reported in Virginia*

Disease	Total Cases Reported, August 2001						Total Cases Reported Statewide, January through August		
		Regions							
	State	NW	N	SW	C	E	This Year	Last Year	5 Yr Avg
AIDS	121	5	31	3	16	66	646	506	642
Campylobacteriosis	71	16	18	21	5	11	358	384	437
E. coli O157:H7	10	2	2	3	1	2	38	43	47
Giardiasis	35	11	13	6	4	1	249	255	251
Gonorrhea	1499	90	81	173	413	742	7540	6645	5977
Hepatitis A	13	1	4	4	3	1	89	102	124
B, acute	13	2	2	4	2	3	101	101	83
C/NANB, acute	0	0	0	0	0	0	0	3	11
HIV Infection	121	5	30	8	10	68	665	465	585
Lead in Children†	96	4	10	16	32	34	429	500	412
Legionellosis	3	1	0	2	0	0	17	17	16
Lyme Disease	11	4	5	0	2	0	94	95	56
Measles	1	0	1	0	0	0	1	2	2
Meningococcal Infection	1	0	0	0	1	0	31	35	35
Mumps	4	1	1	1	0	1	6	8	8
Pertussis	15	10	3	0	0	2	28	44	29
Rabies in Animals	29	9	6	4	4	6	278	404	390
Rocky Mountain Spotted Fever	3	0	0	1	2	0	15	4	12
Rubella	0	0	0	0	0	0	0	0	1
Salmonellosis	124	20	22	37	30	15	902	622	693
Shigellosis	65	0	11	2	3	49	187	303	252
Syphilis, Early§	20	0	5	1	3	11	174	194	354
Tuberculosis	34	2	15	6	3	8	166	192	214

Localities Reporting Animal Rabies This Month: Accomack 1 fox; Alexandria 1 raccoon; Augusta 1 raccoon; Bedford 1 raccoon; Botetourt 1 raccoon; Chesapeake 1 raccoon; Fairfax 2 bats, 2 skunks; Fauquier 1 raccoon; Franklin County 1 raccoon; Gloucester 1 cat; Greensville 1 raccoon; Hanover 1 cat, 1 raccoon, 1 skunk; Highland 1 skunk; James City 1 fox; Loudoun 1 raccoon; Louisa 1 raccoon; Nelson 1 skunk; Northumberland 1 skunk; Pittsylvania 1 skunk; Rockingham 1 raccoon; Spotsylvania 2 raccoons; Stafford 1 raccoon; Virginia Beach 1 raccoon.

Toxic Substance-related Illnesses: Asbestosis 21; Cadmium Exposure 1; Lead Exposure 14; Mesothelioma 1; Pneumoconiosis 9.

*Data for 2001 are provisional. †Elevated blood lead levels ≥10µg/dL.

§Includes primary, secondary, and early latent.

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