VIRGINIA
EPIDEMIOLOGY BULLETIN

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August 2000 Volume 100, No. 8

Prevention and Control of Influenza:

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Summary

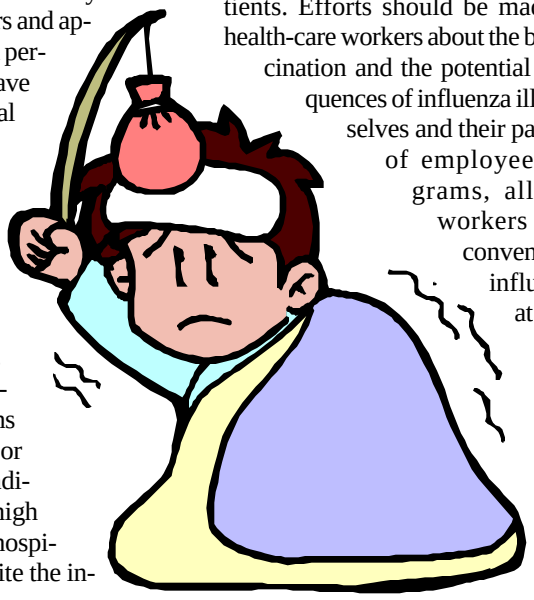
The following article is adapted from the MMWR article with the above title (2000;49[No. RR03]:1-38). This report updates 1999 recommendations by the Advisory Committee on Immunization Practices on the use of influenza vaccine and antiviral agents. The complete report and other information about influenza can be accessed at the website <http://www.cdc.gov/ncidod/diseases/flu/fluvirus.htm>.

Introduction

Influenza vaccine is the primary method for preventing influenza and its more severe complications. In this report from the Advisory Committee on Immunization Practices (ACIP), the primary target group for influenza vaccination includes persons who are at high risk for serious complications from influenza, including approximately 35 million persons aged ≥65 years and approximately 33-39 million persons aged <65 years who have chronic underlying medical conditions.

Beginning with the 2000-2001 influenza season, the ACIP has added persons aged 50-64 years to the primary target group for annual influenza vaccination. This age group was added because 24%-32% of persons aged 50-64 years have one or more chronic medical conditions that place them at high risk for influenza-related hospitalization and death. Despite the increased risk of severe influenza-related illness, only an estimated 40% of persons aged 50-64 years with chronic medical conditions and 28% of those without high-risk conditions were vaccinated against influenza in 1997. Targeting all persons 50-64 years of age will likely increase vaccination rates among persons in this age group with high-risk conditions. In addition, this strategy will also likely help to increase vaccination of persons without high-risk conditions for whom annual vaccination is recommended because they live with or care for persons at increased risk of influenza-related complications.

Annual vaccination also is recommended for health-care workers. However, according to the 1997 National Health Interview Survey, only 34% of health-care workers reported that they received influenza vaccine. Vaccination of health-care workers has been associated with reduced work absenteeism and decreased deaths among nursing home patients. Efforts should be made to educate health-care workers about the benefits of vaccination and the potential health consequences of influenza illness for themselves and their patients. As part of employee health programs, all health-care workers should have convenient access to influenza vaccine at the work site free of charge.



Clinical Signs and Symptoms of Influenza

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. 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). Illness typically resolves after several days for most persons, although cough and malaise can persist for 2 or more weeks. In some persons, influenza can exacerbate underlying medical conditions (e.g., pulmonary or cardiac disease) or lead to secondary bacterial pneumonia or primary influenza viral pneumonia.

Hospitalizations and Deaths from Influenza

Approximately 114,000 excess hospitalizations per year are related to influenza. Since the 1968 influenza A (H3N2) virus pandemic, the greatest numbers of influenza-associated hospitalizations have occurred during epidemics caused by type A (H3N2) viruses, with an estimated average of 142,000 influenza-associated hospitalizations per year.

During influenza epidemics, deaths can increase from influenza, pneumonia, and exacerbations of cardiopulmonary conditions and other chronic diseases. In the United States, pneumonia and influenza deaths might be increasing in part because the number of elderly persons is increasing.

As this issue goes to press, not all manufacturers have released their 2000-2001 vaccine supply. Please refer to the July Epidemiology Bulletin for further information.

Recommendations for the Use of Influenza Vaccine

In the United States, the main option for reducing the impact of influenza is immunoprophylaxis with inactivated (i.e., killed-virus) vaccine. In addition, the use of influenza-specific antiviral drugs for chemoprophylaxis or treatment of influenza is an important adjunct to vaccine (see Recommendations for the Use of Antiviral Agents).

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. In addition, health-care workers and other individuals (including household members) in close contact with persons in high-risk groups should be vaccinated to decrease the risk of transmitting influenza to persons at high risk. Influenza vaccine also can be administered to any person aged ≥6 months to reduce the chance of becoming infected with influenza.

Composition of the 2000-2001 Influenza Vaccine

Influenza vaccine contains three strains (two type A and one type B), representing the influenza viruses likely to circulate in the United States in the upcoming winter. The trivalent influenza vaccine prepared for the 2000-2001 season will include A/New Caledonia/20/99-like (H1N1), A/Panama/2007/99-like (H3N2), and B/Yamanashi/166/98-like antigens. The vaccine is made from highly purified, egg-grown viruses that have been made noninfectious (i.e., inactivated). Whole-virus, subvirion, and purified-surface-antigen preparations are available.

Because the vaccine viruses are initially grown in embryonated hens' eggs, the vaccine might contain small amounts of residual egg protein. Influenza vaccine distributed in the United States might also contain thimerosal, a mercury-containing compound, as the preservative. Manufacturing processes differ by manufacturer. Some manufacturers might use additional compounds to inactivate the influenza viruses, and they might use an antibiotic to prevent bacterial contamination. The package inserts should be consulted for additional information.

Effectiveness of Inactivated Influenza Vaccine

The effectiveness of influenza vaccine depends primarily on the age and immunocompetence of the vaccine recipient and the degree of similarity between the viruses in the vaccine and those in circulation. When the antigenic match between vaccine and circulating viruses is close, influenza vaccine prevents illness in approximately 70%-90% of healthy persons aged <65 years.

Elderly persons and persons with certain chronic diseases might develop lower post-vaccination antibody titers than healthy young adults, and thus can remain susceptible to influenza-related upper respiratory tract infection. However, among such persons, the vaccine can be effective in preventing secondary complications and reducing the risk for influenza-related hospitalization and death. Among elderly persons living outside of nursing homes or similar chronic-care facilities, influenza vaccine is 30%-70% effective in preventing hospitalization for pneumonia and influenza. Among elderly persons residing in nursing homes, the vaccine can be 50%-60% effective in preventing hospitalization or pneumonia and 80% effective in preventing death, even though the effectiveness in preventing influenza illness ranges from 30% to 40%.

Target Groups for Vaccination

Groups 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 ≥50 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 (including immunosuppression caused by medications or by human immunodeficiency virus);
- children and teenagers aged 6 months to 18 years who are receiving long-term aspirin therapy and therefore might be at risk for developing Reye syndrome after influenza infection;
- women who will be in the second or third trimester of pregnancy during the influenza season.

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 suggests that vaccination of health-care workers is associated with decreased deaths among nursing home patients. Vaccination of health-care workers and others in close contact with persons at high risk is recommended. 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 high-risk groups;
- persons who provide home care to persons in high-risk groups;
- household members (including children) of persons in high-risk groups.

Additional Information on Vaccination of Specific Populations

Nursing Homes and Other Residential Long-Term Care Facilities

Vaccination should be routinely provided to all residents of chronic-care facilities with the concurrence of attending physicians. Consent for vaccination should be obtained from the resident or a family member at the time of admission to the facility or anytime afterwards. All residents should be vaccinated at one time, preceding the influenza season. Residents admitted during the winter months after completion of the vaccination program should be vaccinated at the time of admission.

Use of standing orders programs is recommended for long-term care facilities under the supervision of a medical director to ensure the administration of recommended vaccinations for adults. Other settings (e.g., inpatient and outpatient facilities, managed care organizations, assisted living facilities, correctional facilities, pharmacies, adult workplaces, and home health care agencies) are encouraged to introduce standing orders programs as well.

Pregnant Women

Influenza-associated excess deaths among pregnant women were documented during the pandemics of 1918-1919 and 1957-1958. Case reports and limited studies also suggest that pregnancy can increase the risk for serious medical complications of influenza as a result of increases in heart rate, stroke volume, and oxygen consumption; decreases in lung capacity; and changes in immunologic function.

Women who will be beyond the first trimester of pregnancy (≥14 weeks' gestation) 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, many experts consider influenza vaccination safe during any stage of pregnancy. A study of influenza vaccination of >2,000 pregnant women demonstrated no adverse fetal effects associated with influenza vaccine. However, more data are needed to confirm the safety of vaccination during pregnancy. 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.

Persons Infected with Human Immunodeficiency Virus

Limited information is available regarding the frequency and severity of influenza illness or the benefits of influenza vaccination among persons with human immunodeficiency virus (HIV) infection. However, a recent retrospective study of young and middle-aged women enrolled in Tennessee's Medicaid program found that the attributable risk for cardiopulmonary hospitalizations among women with HIV infection was higher during influenza seasons than in the peri-influenza periods. Other reports suggest that influenza symptoms might be prolonged and the risk for complications from influenza increased for some HIV-infected persons.

Influenza vaccination has been shown to produce substantial antibody titers against influenza in vaccinated HIV-infected persons who have minimal acquired immunodeficiency syndrome-related symptoms and high CD4+ T-lymphocyte cell counts. In patients who have advanced HIV disease and low CD4+ T-lymphocyte cell counts, influenza vaccine might not induce protective antibody titers; a second dose of vaccine does not improve the immune response in these persons.

One study found that HIV RNA levels increased transiently in one HIV-infected patient after influenza infection. Some studies have demonstrated a transient (i.e., 2-4 week) increase in replication of HIV-1 in the plasma or peripheral blood mononuclear cells of HIV-infected persons after vaccine administration. Other studies using similar laboratory techniques have not documented a substantial increase in the replication of HIV. Deterioration of CD4+ T-lymphocyte cell counts or progression of HIV disease have not been demonstrated among HIV-infected persons following influenza vaccination. The effect of antiretroviral therapy on potential increases in HIV RNA levels following either natural influenza infection or influenza vaccination is unknown. Because influenza can result in serious illness and complications and because influenza vaccination can result in the production of protective antibody titers, vaccination will benefit many 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

The risk of exposure to influenza during travel depends on the time of year and destination. In the tropics, influenza can occur throughout the year. In the temperate regions of the Southern Hemisphere, most influenza activity occurs from April through September. In temperate climate zones of the Northern and Southern Hemispheres, travelers also can be exposed to influenza during the summer, especially when traveling as part of large organized tourist groups that include persons from areas of the world where influenza viruses are circulating. 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 from April through 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 of influenza and the advisability of carrying antiviral medications for either prophylaxis or treatment of influenza.

General Population

Physicians should administer influenza vaccine to any person who wishes to reduce the likelihood of becoming ill with influenza (the vaccine can be administered to children as young as 6 months). Persons who provide essential community services should be considered for vaccination to minimize disruption of essential activities during influenza outbreaks. Students or other persons in institutional settings (e.g., those who reside in dormitories) 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). Prophylactic use of the antiviral agents amantadine or rimantadine is an option for preventing influenza A among such persons. 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. Information about vaccine components can be found in package inserts from each manufacturer.

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.

Optimal Timing for Annual Vaccination

The optimal time to vaccinate persons in high-risk groups is usually from the beginning of October through mid-November, because influenza activity in the United States generally peaks between late December and early March. Administering vaccine before October should generally be avoided in facilities such as nursing homes, because antibody levels can begin to decline within a few months after vaccination.

To avoid missed opportunities for vaccination, beginning each September, influenza vaccine should be offered to persons at high risk when they are seen by health-care providers for routine care or are hospitalized, provided that vaccine is available. Health-care providers should offer vaccine to unvaccinated persons even after influenza virus activity is documented in a community and should continue to offer vaccine throughout the influenza season.

Dosage and Route

Dosage recommendations vary according to age group (Table 1). Among previously unvaccinated children aged <9 years, two doses administered at least 1 month 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. Even when the current influenza vaccine contains one or more of the antigens administered in previous years, annual vaccination with the current vaccine is necessary because immunity declines during the year following vaccination. Vaccine prepared for a previous influenza season should not be administered to provide protection for the current season.

The intramuscular route is recommended for influenza vaccine. Adults and older children should be vaccinated in the deltoid muscle; a needle length ≥1 inch can be considered for these age groups. Infants and young children should be vaccinated in the anterolateral aspect of the thigh.

Side Effects and Adverse Reactions

When educating patients about 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.

Local Reactions

In placebo-controlled blinded studies, the most frequent side effect of vaccination is soreness at the vaccination site (affecting 10%-64% of patients) that lasts up to 2 days. 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 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. Recent placebo-controlled trials suggest 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, presumably allergic reactions (e.g., hives, angioedema, allergic asthma, and systemic anaphylaxis) rarely occur after influenza vaccination. These reactions probably result from hypersensitivity 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

Table 1. Influenza vaccine* dosage, by age group, United States, 2000-2001 season

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

**Contains 15 µg each of A/Moscow/10/99 (H3N2)-like, A/New Caladonia/20/99 (H1N1)-like, and B/Beijing/184/93-like antigens. For the A/Moscow/10/99 (H3N2)-like antigen, manufacturers will use the antigenically equivalent A/Panama/2007/99 (H3N2) virus, and for the B/Beijing/184/93-like antigen, U.S. manufacturers will use the antigenically equivalent B/Yamanashi/166/98 virus because of their growth properties and because they are representative of currently circulating A (H3N2) and B viruses. Manufacturers include Aventis Pasteur, Inc. (Fluzone® whole or split); Medeva Pharma Ltd. (Fluvirin™ purified surface antigen vaccine); Parkedale Pharmaceuticals, Inc. (Fluogen® split); and Wyeth Lederle Laboratories (Flushield™ split). For further product information, call Aventis Pasteur, (800) 822-2463; Medeva, (800) 234-5535; Parkedale, (888) 358-6436; or Wyeth Lederle, (800) 358-7443.*

†Because of their decreased potential for causing febrile reactions, only split-virus vaccines should be used for children. They may 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 at least 1 month apart are recommended for children <9 years of age who are receiving influenza vaccine for the first time.

***Intramuscular*

or collapse after eating eggs should consult a physician for appropriate evaluation to help determine if vaccine should be administered. Persons who have documented immunoglobulin E (IgE)-mediated hypersensitivity to eggs, including those who have had occupational asthma or other allergic responses to egg protein, 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)

Epidemiologic investigations have found no large increase in GBS associated with influenza vaccines other than the swine influenza vaccine in 1976. Instead, studies suggest that if influenza vaccine does pose a risk, it is probably quite small, slightly more than one additional case per million persons vaccinated. Thus, even if GBS were a true side effect of vaccination in the years after 1976, the estimated risk for GBS is substantially less than the risk for severe influenza. The potential benefits of influenza vaccination in preventing serious illness, hospitalization, and death greatly outweigh the possible risks for developing vaccine-associated GBS.

The incidence of GBS in the general population is very low, but persons with a history of GBS have a substantially greater likelihood of subsequently developing GBS than persons without such a history. Thus, the likelihood of coincidentally developing GBS after influenza vaccination is expected to be greater among persons with a history of GBS than among persons with no history of this syndrome. Whether influenza vaccination specifically might increase the risk for recurrence of GBS is not known. Therefore, it would seem prudent to avoid 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. However, many experts believe that for most 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 yearly vaccination.

Simultaneous Administration of Other Vaccines, Including Childhood Vaccines

The target groups for influenza and pneumococcal vaccination overlap considerably. 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. Children at high risk for influenza-related complications can receive influenza vaccine at the same time they receive other routine vaccinations.

Evolving Developments Related to Influenza Vaccine

Potential New Vaccines

Intranasally administered, cold-adapted, live, attenuated influenza virus vaccines (LAIVs) are being used in Russia and have been under development in the United States since the 1960s. The viruses in these vaccines replicate in the upper respiratory tract and elicit a specific protective immune response. LAIVs consist of live viruses that induce minimal symptoms and that replicate poorly at temperatures found in the lower respiratory tract. The possible advantages of LAIVs are their potential to induce a broad mucosal and systemic immune response, ease of administration, and the acceptability of an intranasal route of administration compared with injectable vaccines. A 5-year study comparing trivalent inactivated vaccine and bivalent LAIVs (administered by nose drops) found the two vaccines to be approximately equivalent in terms of effectiveness. In a recent study of children aged 15-71 months, an intranasally administered trivalent LAIV was 93% effective in preventing culture-positive influenza A (H3N2) and B infections, reduced otitis media among vaccinated children by 30%, and reduced otitis media with concomitant antibiotic use by 35% compared with unvaccinated children. In a follow-up study during the 1997-1998 season, the trivalent LAIV was 86% effective in preventing culture-positive influenza in children, despite a poor match between the vaccine's influenza A (H3N2) component and the predominant circulating influenza A (H3N2) virus. A study conducted among healthy adults during the same season found a 9%-24% reduction in febrile respiratory illnesses and 13%-28% reduction in lost work days. No study has directly compared the efficacy or effectiveness of trivalent inactivated vaccine and trivalent LAIV.

Recommendations for the Use of Antiviral Agents

Antiviral drugs for influenza are an important adjunct to influenza vaccine for the control and prevention of influenza. However, they are not a substitute for vaccination. Four currently licensed agents are available in the United States: amantadine, rimantadine, zanamivir, and oseltamivir.

Amantadine and rimantadine are chemically related antiviral drugs with activity against influenza A viruses but not influenza B viruses. Amantadine is approved for both prophylaxis and treatment of influenza A infection in persons ≥1 year. Rimantadine is approved for treatment and prophylaxis of infection in adults. Although rimantadine is approved only for prophylaxis of infection in children, many experts consider it appropriate for treatment among children.

Zanamivir and oseltamivir are neuraminidase inhibitors with activity against both influenza A and B viruses. Both zanamivir and oseltamivir were approved in 1999 for the treatment of uncomplicated influenza infections, but neither has yet been approved for prophylaxis. Zanamivir was approved for treatment for persons aged ≥12 years, and oseltamivir was approved for treatment for persons aged ≥18 years.

The four drugs differ in terms of their pharmacokinetics, side effects, and costs. An overview of the indications, use, administration, and known primary side effects of these medications is presented in the following sections; however, readers should consult the package inserts for more information.

Role of Laboratory Diagnosis

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

Influenza surveillance information as well as diagnostic testing (e.g., viral culture and rapid tests for influenza) can aid clinical judgment and help guide treatment decisions. Influenza surveillance by state and local health departments and the Centers for Disease Control and Prevention can provide information about the presence of influenza viruses in the community and the predominant circulating types, subtypes, and strains of influenza.

Several commercial rapid diagnostic tests are available that can be used by laboratories

in outpatient settings to detect influenza viruses within 30 minutes. Some of these rapid tests detect only influenza A viruses, whereas other rapid tests detect both influenza A and B viruses but do not distinguish between the two types. Additional commercial diagnostic tests are available for use by laboratories performing tests of high complexity.

Despite the availability of rapid diagnostic tests, the collection of clinical specimens for viral culture is important because only culture isolates can provide specific information on circulating influenza subtypes and strains. This information is needed to compare current circulating influenza strains with vaccine strains, to guide decisions about influenza treatment and prophylaxis, and to formulate vaccine for the coming year. Virus isolates also are needed to monitor the emergence of antiviral resistance.

Indications for Use of Antivirals

Treatment

When administered within 2 days of illness onset to otherwise healthy adults, amantadine and rimantadine can reduce the severity and duration of uncomplicated influenza A illness. Zanamivir and oseltamivir can reduce the duration of uncomplicated influenza A and B illness by approximately 1 day when given within 2 days of illness onset. More clinical data are available concerning the effectiveness of zanamivir and oseltamivir for treatment of influenza A infection than for treatment of influenza B infection. However, in vitro data and animal studies document that zanamivir and oseltamivir have activity against influenza B viruses.

None of the four antiviral agents has been demonstrated to be effective in preventing serious influenza-related complications (e.g., bacterial or viral pneumonia or exacerbation of chronic diseases). Evidence for the effectiveness of these four antiviral drugs is based principally on studies of patients with uncomplicated influenza. Data are limited and inconclusive concerning the effectiveness of amantadine, rimantadine, and zanamivir for treatment of influenza in persons at high risk for serious complications of influenza, and no published data are available concerning the effectiveness of oseltamivir for treatment of influenza in high-risk populations. Studies of the efficacy of any of the four drugs for treatment in children are limited.

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 important adjuncts in the prevention and control of influenza. Both amantadine and rimantadine are approximately 70%-90% effective in preventing 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. Therefore, some persons who take these drugs will develop protective immune responses to circulating influenza viruses. Amantadine and rimantadine do not interfere with the antibody response to the vaccine. Both drugs have been studied extensively in nursing home populations as a component of influenza outbreak control programs.

Zanamivir and oseltamivir have not been approved for prophylaxis, but recent community studies suggest that both drugs are similarly effective in preventing febrile, laboratory-confirmed influenza illness (efficacy: zanamivir, 84%; oseltamivir, 82%). Experience with prophylactic use of these agents in institutional settings or among patients with chronic medical conditions is limited. Use of zanamivir has not been found to impair the immunologic response to influenza vaccine.

When determining the timing and duration for administering amantadine or rimantadine for prophylaxis, factors related to cost, compliance, and potential side effects should be considered. To be maximally effective as prophylaxis, the drug must be taken each day for the duration of influenza activity in the community. However, to be most cost-effective, amantadine or rimantadine prophylaxis should be taken only during the period of peak influenza activity in a community.

Persons at High Risk Who Are Vaccinated After Influenza Activity Has Begun

Persons at high risk for complications of influenza still can be vaccinated after an outbreak of influenza has begun in a community. However, the development of antibodies in adults after vaccination can take as long as 2 weeks. When influenza vaccine is given while influenza A viruses are circulating, chemoprophylaxis with amantadine or rimantadine should be considered for persons at high risk during the time from vaccination until immunity has developed. Children who receive influenza vaccine for the first time can require as long as 6 weeks of prophylaxis (i.e., prophylaxis for 4 weeks after the first dose of vaccine and an additional 2 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 with amantadine or rimantadine during peak influenza A activity can be considered for unvaccinated persons who have frequent contact with persons at high risk. If an outbreak is caused by a variant strain of influenza A 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 Deficiency

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, especially those with advanced disease. No published data are available concerning possible efficacy of chemoprophylaxis among persons with HIV infection or interactions with other drugs used to manage HIV infection. Such patients should be monitored closely if amantadine or rimantadine 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. Amantadine or rimantadine also can be administered prophylactically to persons who wish to avoid influenza A illness. Health-care providers

and patients should make this decision on an individual basis.

Control of Influenza Outbreaks in Institutions

Most published reports on the use of amantadine or rimantadine to control institutional outbreaks of influenza A are based on studies of nursing home populations. When confirmed or suspected outbreaks of influenza A 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 vaccine during the previous fall. Chemoprophylaxis should continue for at least 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 A that is not well matched by the vaccine. Chemoprophylaxis also can be considered for controlling influenza A 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. In addition to using antiviral drugs for treatment and prophylaxis of influenza, other outbreak control measures include instituting droplet precautions, establishing cohorts of patients with confirmed or suspected influenza, reoffering influenza vaccine to unvaccinated staff and patients, restricting staff movement between wards or buildings, and restricting contact between ill staff or visitors and patients.

Dosage

Dosage recommendations vary by age group and medical conditions (Table 2). Additional information for elderly persons and those with renal, liver, or seizure disorders is presented below.

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

	Age group			
Antiviral agent	**1-9 yrs**	**10-13 yrs**	**14-64 yrs**	**≥65 yrs**
Amantadine*				
Treatment	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	100 mg twice daily§	100 mg twice daily	≤100 mg/day
Rimantadine¶				
Treatment	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	100 mg twice daily§	100 mg twice daily	100 or 200 mg/day††
Zanamivir				
Treatment§§	NA	10 mg §§ twice daily (approximately 12 hours apart for 5 days)	10 mg twice daily	10 mg twice daily
Prophylaxis¶¶	NA	NA	NA	NA
Oseltamivir				
Treatment***	NA	NA	75 mg*** twice daily	75 mg twice daily
Prophylaxis¶¶	NA	NA	NA	NA

NOTE: Amantadine manufacturers include Endo Pharmaceuticals (Symmetrel®, tablet and syrup); Invamed 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).

**Consult the drug package insert 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 ≥10 years of age who weigh <40 kg should be administered amantadine or rimantadine at a dosage of 5mg/kg/day.

¶A reduction in dosage to 100 mg/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.

***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 ≥65 years of age if they experience possible side effects when taking 200 mg/day.

§§Zanamivir is approved for persons ≥12 years of age and is administered as two 5mg inhalations of medicated powder twice a day (i.e., 10 mg twice a day). The medication is administered via inhalation using a plastic device included in the package with the medication. Patients will benefit from instruction and demonstration of proper use of the device.

¶¶Neither zanamivir nor oseltamivir is approved for prophylaxis.

****Oseltamivir is approved for persons ≥18 years of age. A reduction in the dose of oseltamivir is recommended for persons with creatinine clearance <30 mL/min.*

Persons Aged ≥65 Years

Amantadine. The daily dose of amantadine for persons aged ≥65 years should not exceed 100 mg for prophylaxis or treatment, because renal function declines with increasing age. For some elderly persons, the dose should be further reduced.

Rimantadine. Among elderly persons, the incidence and severity of central nervous system (CNS) side effects are substantially lower among those taking rimantadine at a dosage of 100 mg/day than among those taking amantadine at dosages adjusted for estimated renal clearance. However, at dosages of 200 mg/day, chronically ill elderly persons have had a higher incidence of CNS side effects, gastrointestinal symptoms, and elevated serum concentrations when compared to healthy, younger persons taking the same dose.

For elderly nursing home residents, the dosage of rimantadine should be reduced to 100 mg/day for prophylaxis or treatment. For other elderly persons, further studies are needed to determine the optimal dosage. However, a reduction in dosage to 100 mg/day should be considered for all persons aged ≥65 years who experience side effects when taking a dosage of 200 mg/day.

Zanamivir and Oseltamivir. No reduction in dosage is recommended on the basis of age alone.

Persons with Impaired Renal Function

Amantadine. A reduction in dosage is recommended for patients with creatinine clearance ≤50 mL/min/1.73m^2. Guidelines for amantadine dosage based on creatinine clearance are found in the packet insert. Because recommended dosages based on creatinine clearance might provide only an approximation of the optimal dose for a given patient, such persons should be observed carefully for adverse reactions. If necessary, further reduction in the dose or discontinuation of the drug might be indicated because of side effects. Hemodialysis contributes minimally to amantadine clearance.

Rimantadine. A reduction in dosage to 100 mg/day is recommended for persons with creatinine clearance ≤10 mL/min. Because of the potential for accumulation of rimantadine and its metabolites, patients with any degree of renal insufficiency, including elderly persons, should be monitored for adverse effects, and either the dosage should be reduced or the drug should be discontinued, if necessary. Hemodialysis contributes minimally to drug clearance.

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

Oseltamivir. Serum concentrations of oseltamivir carboxylate (GS4071), the active metabolite of oseltamivir, increase with declining renal function. A reduction of the dose of oseltamivir to 75 mg once daily is recommended for patients with creatinine clearance <30 mL/min. No data are available concerning the safety or efficacy of oseltamivir in patients with creatinine clearance <10 mL/min.

Persons with Liver Disease

Amantadine. No increase in adverse reactions to amantadine has been observed among persons with liver disease. Rare instances of reversible elevation of liver enzymes in patients receiving amantadine have been reported, although a specific relationship between the drug and such changes has not been established.

Rimantadine. A reduction in dosage to 100 mg/day is recommended for persons with severe hepatic dysfunction.

Zanamivir and Oseltamivir. Neither of these medications has been studied in persons with hepatic dysfunction.

Persons with Seizure Disorders

Amantadine. 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.

Rimantadine. Seizures or seizure-like activity have been reported among persons with a history of seizures who were not receiving anticonvulsant medication while taking rimantadine. The extent to which rimantadine might increase the incidence of seizures among persons with seizure disorders has not been adequately evaluated.

Zanamivir and Oseltamivir. No information is available regarding the use of zanamivir or oseltamivir among persons with a history of seizure disorder.

Route

Amantadine, rimantadine, and oseltamivir are administered orally. Amantadine and rimantadine are available in tablet or syrup form, and oseltamivir is available as a capsule. 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 proper use of this device.

Side Effects and Adverse Reactions

Amantadine and Rimantadine

Both amantadine and rimantadine can cause CNS and gastrointestinal side effects when administered to young, healthy adults at equivalent dosages of 200 mg/day. However, the incidence of CNS side effects (e.g., nervousness, anxiety, difficulty concentrating, and lightheadedness) is higher among persons taking amantadine than among those taking rimantadine. In a 6-week study of prophylaxis among healthy adults, approximately 6% of participants taking rimantadine at a dosage of 200 mg/day experienced at least one CNS symptom, compared with approximately 13% of those taking the same dosage of amantadine and 4% of those taking placebo. 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.

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. However, serious side effects have been observed (e.g., marked behavioral changes, delirium, hallucinations, agitation, and seizures). These more severe side effects have been associated with high plasma drug concentrations and have been observed most often among persons who have renal insufficiency, seizure disorders, or certain psychiatric disorders. These severe side effects have also been seen among elderly persons who have been taking amantadine as prophylaxis at a dosage of 200 mg/day. Clinical observations and studies have indicated that lowering the dosage of amantadine among these persons reduces the incidence and severity of such side effects (Table 2). In acute overdosage of amantadine, CNS, renal, respiratory, and cardiac toxicity, including arrhythmias, have been reported. Because rimantadine has been marketed for a shorter period than amantadine, its safety in certain patient populations (e.g., chronically ill and elderly persons) has been evaluated less frequently.

When considering amantadine or rimantadine, clinicians must take into account the patient's age, weight, and renal function; the presence of other medical conditions; indications for the use of amantadine or rimantadine (i.e., prophylaxis or therapy); and the potential for interaction with other medications.

Zanamivir

Preliminary results of a study of zanamivir treatment of influenza-like illness among persons with asthma or chronic obstructive pulmonary disease indicated that more patients receiving zanamivir than placebo experienced a >20% decline in forced expiratory volume in 1 second (FEV1) or peak expiratory flow rates after treatment. Moreover, in a phase I study of persons with mild or moderate asthma who did not have influenza-like illness, one of 13 patients experienced bronchospasm following administration of zanamivir. In addition, during postmarketing surveillance, cases of respiratory function deterioration following inhalation of zanamivir have been reported among patients with underlying asthma or chronic obstructive pulmonary disease. If physicians decide to prescribe zanamivir to patients with underlying chronic respiratory disease after carefully considering potential risks and benefits, the drug should be used with caution under conditions of proper monitoring and supportive care, including the availability of short-acting bronchodilators. 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 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.

Oseltamivir

Nausea and vomiting were reported more frequently among persons receiving oseltamivir for treatment (nausea without vomiting, approximately 10%; vomiting, approximately 9%) than among persons receiving placebo (nausea without vomiting, approximately 6%; vomiting, approximately 3%). However, few persons enrolled in the clinical treatment trials of oseltamivir discontinued treatment because of these symptoms. 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; only two cases of amantadine use for severe influenza illness during the third trimester have been reported. However, both amantadine and rimantadine have been shown 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 (see package inserts).

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

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

Antiviral Drug-Resistant Strains of Influenza

Amantadine-resistant viruses are cross-resistant to rimantadine and vice versa. Drug-resistant viruses can appear in up to 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.

Resistance to zanamivir and oseltamivir can be induced in influenza A and B viruses *in vitro*, but induction of resistance requires several passages in cell culture. By contrast, resistance to amantadine and rimantadine *in vitro* can be induced with fewer passages in cell culture. Whether these *in vitro* findings indicate that clinical drug resistance will occur less frequently with zanamivir and oseltamivir than with amantadine and rimantadine is unknown. Development of viral resistance to zanamivir and oseltamivir during treatment has been identified but does not appear to be frequent. Currently available diagnostic tests are not optimal for detecting clinical resistance, and better tests as well as more testing are needed before firm conclusions can be reached. Postmarketing surveillance for neuraminidase inhibitor-resistant influenza viruses is planned.

Cases of Selected Notifiable Diseases Reported in Virginia*

Disease	Total Cases Reported, July 2000: State	Regions: NW	N	SW	C	E	Total Cases Reported Statewide, January through July: This Year	Last Year	5 Yr Avg
AIDS	47	5	7	3	16	16	452	459	613
Campylobacteriosis	106	23	23	24	13	23	316	367	348
***E. coli* O157:H7**	9	2	2	2	1	2	25	35	31
Giardiasis	39	5	10	7	7	10	220	199	183
Gonorrhea	740	26	52	64	211	387	5688	5599	5204
Hepatitis A	18	1	7	3	5	2	88	97	109
B, acute	18	2	3	5	5	3	93	58	67
C/NANB, acute	2	0	0	2	0	0	3	10	10
HIV Infection	42	5	14	5	4	14	413	433	544
Lead in Children†	152	20	12	21	60	38	369	211	317
Legionellosis	4	0	1	3	0	0	12	16	11
Lyme Disease	34	2	28	4	0	0	71	48	29
Measles	2	0	2	0	0	0	2	3	2
Meningococcal Infection	5	0	2	1	0	2	36	32	34
Mumps	0	0	0	0	0	0	5	8	9
Pertussis	12	7	0	0	1	4	33	13	17
Rabies in Animals	63	13	19	11	8	12	338	304	317
Rocky Mountain Spotted Fever	2	0	1	1	0	0	3	8	9
Rubella	0	0	0	0	0	0	0	0	1
Salmonellosis	143	28	31	30	28	26	493	661	550
Shigellosis	81	3	18	55	5	0	240	58	175
Syphilis, Early§	16	0	1	4	1	10	169	224	422
Tuberculosis	19	6	9	0	0	4	152	127	186

Localities Reporting Animal Rabies This Month: Accomack 4 raccoons; Augusta 1 raccoon; Bath 1 raccoon, 1 skunk; Bedford 1 raccoon, 1 skunk; Botetourt 2 raccoons, 1 skunk; Carroll 1 raccoon; Culpeper 1 bat; Fairfax 1 bat, 1 cat, 3 raccoons; Floyd 1 raccoon; Giles 1 skunk; Gloucester 1 raccoon; Greensville 1 fox, 1 raccoon; Halifax 2 dogs; Hampton 1 raccoon; Hanover 2 foxes; Highland 1 raccoon; King William 1 raccoon; Loudoun 1 bat, 1 cat, 3 raccoons, 2 skunks; Lynchburg 1 raccoon; Mathews 1 fox; Montgomery 1 raccoon; Northampton 3 raccoons; Page 2 foxes; Powhatan 1 raccoon; Prince Edward 1 fox; Prince William 1 bat, 1 fox, 2 groundhogs, 3 raccoons; Rappahannock 1 raccoon, 1 skunk; Rockingham 1 skunk; Russell 1 horse; Stafford 1 fox, 2 raccoons; Virginia Beach 1 raccoon.

Occupational Illnesses: Asbestosis 13; CAdmium Exposure 1; Lead Exposure 13; Pneumoconiosis 6.

*Data for 2000 are provisional. †Elevated blood lead levels ≥10µg/dL.

§Includes primary, secondary, and early latent.

Published monthly by the
VIRGINIA DEPARTMENT OF HEALTH
Office of Epidemiology
P.O. Box 2448
Richmond, Virginia 23218
http://www.vdh.state.va.us
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