VIRGINIA
EPIDEMIOLOGY BULLETIN

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Prevention and Control of Influenza

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

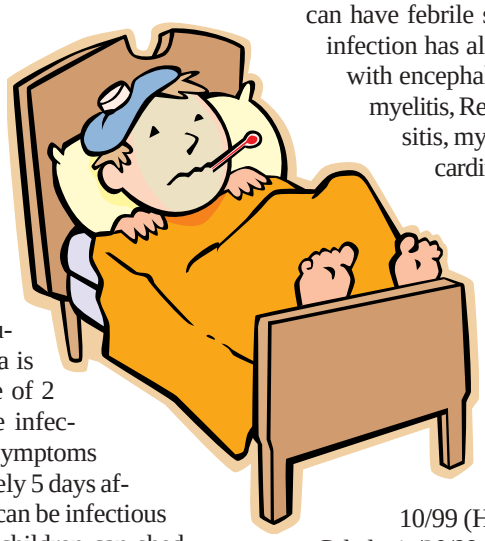
Summary

This article summarizes the 2003 recommendations by the Advisory Committee on Immunization Practices (ACIP) on the use of influenza vaccine and antiviral agents (MMWR 2003;52[No. RR-8]:1-44). The 2003 recommendations include new or updated information regarding 1) the timing of influenza vaccination by age and risk group; 2) influenza vaccine for children aged 6-23 months; 3) the 2003-2004 trivalent inactivated vaccine virus strains; 4) availability of certain influenza vaccine doses with reduced thimerosal content, including single 0.25 mL-dose syringes; and 5) manufacturers of influenza vaccine for the U.S. market. Although the optimal time to vaccinate against influenza is October and November, vaccination in December and later continues to be strongly recommended. The complete report including references and other information regarding influenza can be accessed at the CDC website: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5208a1.htm.

Background

Influenza vaccination is the primary method for preventing influenza and its severe complications. The primary target groups recommended for annual vaccination are 1) persons aged ≥65 years and persons of any age with certain chronic medical conditions; 2) the group aged 50-64 years because this group has an elevated prevalence of certain chronic medical conditions; and 3) 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, information is also presented regarding 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. Adults typically are infectious from the day before symptoms begin through approximately 5 days after illness onset. Children can be infectious for ≥10 days, and young children can shed virus for ≤6 days before their illness onset. Severely immunocompromised persons can shed virus for weeks or months.

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 a limited number of days for the majority of persons, although cough and malaise can persist for >2 weeks. Among certain persons, influenza can exacerbate underlying medical conditions (e.g., pulmonary or cardiac disease), lead to secondary bacterial pneumonia or primary influenza viral pneumonia, or occur as part of a coinfection with other viral or bacterial pathogens. Young children with influenza infection can have initial symptoms mimicking bacterial sepsis with high fevers, and ≤20% of children hospitalized with influenza can have febrile seizures. Influenza infection has also been associated with encephalopathy, transverse myelitis, Reye syndrome, myositis, myocarditis, and pericarditis.

Influenza Vaccine Composition

The trivalent inactivated influenza vaccine prepared for the 2003-04 season will include A/Moscow/10/99 (H3N2)-like, A/New Caledonia/20/99 (H1N1)-like, and B/Hong Kong/330/2001-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 limited amounts of residual egg protein.

Manufacturers might use different compounds to inactivate influenza viruses and may add antibiotics to prevent bacterial contamination. Package inserts should be consulted for additional information.

Inactivated influenza vaccine distributed in the United States might also contain thimerosal, a mercury-containing compound, as the preservative. Because of the known risks of severe illness from influenza infection and the benefits of vaccination and because a sub-

Table 1. Influenza vaccine* dosage, by age group, United States, 2003-2004 season

Age group†	Dose	No. of doses	Route§
6-35 months	0.25 mL	1 or 2¶	Intramuscular
3-8 years	0.50 mL	1 or 2¶	Intramuscular
>9 years	0.50 mL	1	Intramuscular

** Contains 15 mg each of A/Moscow/10/99 (H3N2)-like, A/New Caledonia/20/99 (H1N1)-like, and B/Hong Kong/330/2001-like antigens. For the A/Moscow/10/99 (H3N2)-like antigen, manufacturers will use the antigenically equivalent A/Panama/2007/99 (H3N2) virus. For the B/Hong Kong/330/2001-like antigen, manufacturers will use either B/Hong Kong/330/2001 or the antigenically equivalent B/Hong Kong/1434/2002. Manufacturers include Aventis Pasteur, Inc. (Fluzone® split); Evans Vaccines, Ltd. (Fluvirin™ purified surface antigen vaccine). Fluzone is Food and Drug Administration-approved for use among persons aged ≥6 months. Fluvirin is approved for use among persons aged ≥4 years. For further product information, call Aventis Pasteur at 800-822-2463, or Evans Vaccine, Ltd., at 800-200-4278.*

† Because of their decreased potential for causing febrile reactions, only split-virus vaccines should be used for children aged <13 years. Split-virus vaccine 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. Whole-virus vaccine is not available in the United States.

§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 aged <9 years who are receiving influenza vaccine for the first time.

stantial safety margin has been incorporated into the health guidance values for organic mercury exposure, the benefit of influenza vaccine with reduced or standard thimerosal content outweighs the theoretical risk, if any, from thimerosal.

For the 2003-04 influenza season, a limited number of individually packaged doses (i.e., single-dose syringes) of preservative-free influenza vaccine (<1 mcg mercury/0.5 mL dose) will be available, including single-dose vaccine packaged in doses of 0.5 mL (dose for persons aged ≥3 years) and 0.25 mL (dose for children 6-35 months). Reduced thimerosal-content vaccine is available both from Evans Vaccines, Ltd. (FDA-approved for persons aged ≥4 years) and from Aventis Pasteur (FDA-approved for persons aged ≥6 months).

Effectiveness of 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. The majority of vaccinated children and young adults develop high postvaccination hemagglutination inhibition antibody titers. These antibody titers are protective against illness caused by strains similar to those in the vaccine.

Adults Aged <65 Years. When the vaccine and circulating viruses are antigenically similar, influenza vaccine prevents influenza illness in approximately 70%-90% of healthy adults aged <65 years. Vaccination of healthy adults also has resulted in decreased work absenteeism and decreased use of health-care resources, including use of antibiotics, when the vaccine and circulating viruses are well-matched.

Children. Children aged as young as 6 months can develop protective levels of antibody after influenza vaccination, although the antibody response among children at high risk of influenza-related complications might be lower than among healthy children. Studies among children aged 1-15 years have demonstrated that inactivated influenza vaccine is 77%-91% effective against influenza respiratory illness and is 44%-49%, 74%-76%, and 70%-81% effective against influenza seroconversion among children aged 1-5, 6-10, and 11-15 years, respectively.

Adults Aged ≥65 Years. Older persons and persons with certain chronic diseases might develop lower postvaccination antibody titers than healthy young adults and thus can remain susceptible to influenza-related upper respiratory tract infection. The vaccine can also be effective in preventing secondary complications and reducing the risk for influenza-related hospitalization and death among adults ≥65 years with and without high-risk medical conditions (e.g., heart disease and diabetes). Among elderly persons 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, 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, although the effectiveness in preventing influenza illness often ranges from 30%-40%.

Recommendations for Using Inactivated 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 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 29% 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 medical 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.

In addition, because children aged 0-23 months are at increased risk for influenza-related hospitalization, vaccination is encouraged for their household contacts and out-of-home caregivers, particularly for contacts of children aged 0-5 months because influenza vaccines have not been approved by the U.S. Food and Drug Administration (FDA) for use among children aged <6 months.

Additional Information Regarding Vaccination of Specific Populations

Pregnant Women

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, experts consider influenza vaccine 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.

The majority of influenza vaccine distributed in the United States contains thimerosal, a mercury-containing compound, as a preservative, but influenza vaccine with reduced thimerosal content is available in limited quantities. 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 with reduced or standard thimerosal content outweighs the potential risk, if any, 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 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.

Healthy Young Children

Because children aged 6-23 months are at substantially increased risk for influenza-related hospitalizations, ACIP, the American Academy of Pediatrics, and the American Academy of Family Physicians continue to encourage vaccination of all children in this age group when feasible. However, the benefits of a full recommendation to vaccinate all children aged 6-23 months will depend on the identification and implementation of practical and efficient annual influenza vaccination strategies for providers of health care to children.

ACIP continues to strongly recommend influenza vaccination of persons aged ≥6 months who have high-risk medical conditions. The current inactivated influenza vaccine is not approved by FDA for use among children aged <6 months, the pediatric group at greatest risk for influenza-related complications. Vaccinating their household contacts and out-of-home caregivers might decrease the probability of influenza among these children.

Beginning in March 2003, the group of children eligible for influenza vaccine coverage under the Vaccines for Children (VFC) program was expanded to include all VFC-eligible children aged 6-23 months and VFC-eligible children aged 2-18 years who are household contacts of children aged 0-23 months.

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 with Inactivated Influenza Vaccine

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. Prophylactic use of antiviral agents is an option for preventing influenza among such persons. However, persons who have a history of anaphylactic hypersensitivity to vaccine components but who are also at high risk for complications from influenza can benefit from vaccine after appropriate allergy evaluation and desensitization. Information regarding vaccine components is located 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.

Timing of Annual Vaccination with Inactivated Influenza Vaccine

The optimal time to vaccinate is usually during October-November. ACIP recommends that vaccine providers focus their vaccination efforts in October and earlier primarily on persons aged ≥50, persons aged <50 years at increased risk of influenza-related complications (including children aged 6-23 months), household contacts of persons at high risk (including out-of-home caregivers and household contacts of children aged 0-23 months), and health-care workers. Vaccination of children aged <9 years who are receiving vaccine for the first time should also begin in October because those persons need a booster dose 1 month after the initial dose. Efforts to vaccinate other persons who wish to decrease their risk for influenza infection should begin in November; however, if such persons request vaccination in October, vaccination should not be deferred.

Persons planning substantial organized vaccination campaigns should consider scheduling these events after mid-October because the availability of vaccine in any location cannot be ensured consistently in the early fall. Scheduling campaigns after mid-October will minimize the need for cancellations because vaccine is unavailable. Campaigns conducted before November should focus efforts on vaccination of persons aged ≥50 years, persons aged <50 years at increased risk of influenza-related complications (including children aged 6-23 months), health-care workers, and household contacts of persons at high-risk (including children aged 0-23 months) to the extent feasible.

After November, certain persons who should or want to receive influenza vaccine remain unvaccinated. In addition, substantial amounts of vaccine have remained unused during the past three influenza seasons. To improve vaccine coverage, influenza vaccine should continue to be offered in December and throughout the influenza season as long as vaccine supplies are available, even after influenza activity has been documented in the community. In the United States, seasonal influenza activity can begin to increase as early as November or December, but influenza activity has not reached peak levels in the majority of recent seasons until late December-early March. Therefore, although the timing of influenza activity can vary by region, vaccine administered after November is likely to be beneficial in the majority of influenza seasons. Adults develop peak antibody protection against influenza infection 2 weeks after vaccination.

To avoid missed opportunities for vaccination of persons at high risk for serious complications, such persons should be offered vaccine beginning in September during routine health-care visits or during hospitalizations, if vaccine is available. In facilities housing older persons (e.g., nursing homes), vaccination before October typically should be avoided because antibody levels in such persons can begin to decline within a limited time after vaccination.

Dosage

Dosage recommendations vary according to age group (Table 1). Among previously unvaccinated children aged <9 years, two doses administered ≥1 month apart are recommended for satisfactory antibody responses. If possible, the second dose should be administered before December. Among adults, studies have indicated limited or no improvement in antibody response when a second dose is administered during the same season. Even when the current influenza vaccine contains ≥1 antigens administered in previous years, annual vaccination with the current vaccine is necessary because immunity declines during the year after vaccination. Vaccine prepared for a previous influenza season should not be administered to provide protection for the current season.

Use of Inactivated Influenza Vaccine among Children

When vaccinating children aged 6 months-3 years, providers should use inactivated influenza vaccine that has been approved by FDA for this age group. Influenza vaccine from Aventis Pasteur, Inc., (Fluzone® split-virus) is approved for use among persons aged ≥6 months. Influenza vaccine from Evans Vaccines Ltd. (Fluvirin®) is labeled in the United States for use only among persons aged ≥4 years because its efficacy among younger persons has not been demonstrated.

Route

The intramuscular route is recommended for influenza vaccine. Adults and older children should be vaccinated in the deltoid muscle. Infants and young children should be vaccinated in the anterolateral aspect of the thigh.

Side Effects and Adverse Reactions

When educating patients regarding potential side effects, clinicians should emphasize that 1) inactivated influenza vaccine contains noninfectious killed viruses and cannot cause influenza; and 2) coincidental respiratory disease unrelated to influenza vaccination can occur after vaccination.

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 typically 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, presumably allergic, reactions (e.g., hives, angioedema, allergic asthma, and systemic anaphylaxis) rarely occur after influenza vaccination. These reactions probably result from hypersensitivity to certain vaccine components; 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 immunoglobulin E (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.

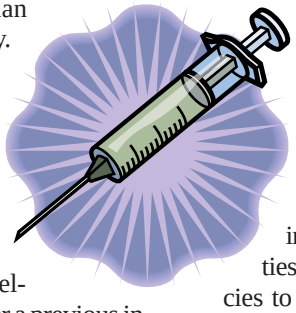
Hypersensitivity reactions to any vaccine component can occur. Although exposure to vaccines containing thimerosal can lead to induction of hypersensitivity, most patients do not have reactions to thimerosal when it is administered as a component of vaccines, even when patch or intradermal tests for thimerosal indicate hypersensitivity. When reported, hypersensitivity to thimerosal usually has consisted of local, delayed type hypersensitivity reactions.

Guillain-Barré Syndrome (GBS)

The potential benefits of influenza vaccination for preventing serious illness, hospi-

talization, 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. As an alternative, physicians might consider using influenza antiviral chemoprophylaxis for these persons. Although data are limited, for the majority of persons who have a history of GBS and who are at high risk for severe complications from influenza, the established benefits of influenza vaccination justify yearly vaccination.



Simultaneous Administration of Other Vaccines, Including Childhood Vaccines

Adult target groups for influenza and pneumococcal polysaccharide 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 polysaccharide and inactivated 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.

No studies regarding the simultaneous administration of inactivated influenza vaccine and other childhood vaccines have been conducted. However, inactivated vaccines usually do not interfere with the immune response to other inactivated or live vaccines and children at high risk for influenza-related complications, including those aged 6-23 months, can receive influenza vaccine at the same time they receive other routine vaccinations.

Strategies for Implementing These Recommendations in Health-Care Settings

Successful vaccination programs combine publicity and education for health-care workers and other potential vaccine recipients, a plan for identifying persons at high risk, use of reminder/recall systems, and efforts to remove administrative and financial barriers that prevent persons from receiving the vaccine, including use of standing orders programs. Using standing orders programs is recommended for long-term care facilities (e.g., nursing homes and skilled nursing facilities), hospitals, and home health agencies to ensure the administration of recommended vaccinations for adults. Standing orders programs for both influenza and pneumococcal vaccination should be conducted under the supervision of a licensed practitioner according to a physician-approved facility or agency policy by health-care personnel trained to screen patients for contraindications to vaccination, to administer vaccine, and to monitor for adverse events. A rule from the Centers for Medicare and Medicaid Services (CMS) recently removed the physician signature requirement for the administration of influenza and pneumococcal vaccines to Medicare and Medicaid patients in hospitals, long-term care facilities, and home health agencies. To the extent allowed by local and state law, these facilities and agencies may implement standing orders for influenza and pneumococcal vaccination of Medicare- and Medicaid-eligible patients. Other settings (e.g., outpatient facilities, managed care organizations, assisted living facilities, correctional facilities, pharmacies, and adult workplaces) are encouraged to introduce standing orders programs as well.

Inactivated Influenza Vaccine Supply

For 2003, only two companies will be producing influenza vaccine for the U.S. market (Aventis Pasteur, Inc., and Evans Vaccines, Ltd.), in comparison with 2002, when three companies manufactured influenza vaccine for the U.S. market.

Influenza vaccine delivery delays or vaccine shortages remain possible in part because of the inherent critical time constraints in manufacturing the vaccine given the annual updating of the influenza vaccine strains. [A statement released by CDC in late August 2003 predicts that vaccine supplies should be sufficient to immunize everyone desiring influenza vaccine to avoid influenza, regardless of age or health status, as soon as the vaccine becomes available in October.]

Live, Attenuated Intranasal Influenza Vaccine

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. LAIVs consist of live viruses that replicate in the upper respiratory tract, that induce minimal symptoms (i.e., are attenuated), and that replicate poorly at temperatures in the lower respiratory tract (i.e., are temperature-sensitive). Possible advantages of LAIVs are their potential to induce a broad mucosal and systemic immune response, their ease of administration, and the acceptability of an intranasal rather than intramuscular route of administration. Studies comparing trivalent inactivated vaccine and bivalent LAIVs have demonstrated that the two vaccines are approximately equivalent in terms of effectiveness. In children aged 15-71 months, intranasally administered trivalent LAIV has been shown to be 93% effective in preventing culture-positive influenza A (H3N2) and B infections, to reduce febrile otitis media among vaccinated children by 30%, and to reduce otitis media with concomitant antibiotic use by 35% compared with unvaccinated children. The trivalent LAIV has been demonstrated to be 86% effective in preventing culture-positive influenza among children and among healthy adults to reduce febrile respiratory illnesses by 9%-24% and lost work days by 13%-28%. No study has directly compared the efficacy or effectiveness of trivalent inactivated vaccine and trivalent LAIV. An application for licensure of a LAIV is under review by FDA.

[In June 2003 FDA approved FluMist, the first LAIV and the first live influenza vaccine to be licensed and marketed in the United States. The ACIP has not made an official statement on the use of this new vaccine, as yet. However CDC has made the following recommendations (http://www.cdc.gov/nip/publications/VIS/vis-flulive.pdf) for the use of this new vaccine pending a statement from the ACIP:

"Live, intranasal influenza vaccine is approved for healthy children and adults from 5 through 49 years of age, including household contacts of some people at high risk for influenza complications. However, because its safety has not been studied in some other groups, FluMist should not be used by many people at risk for flu or its complications.

The following people should **not** get intranasal influenza vaccine. They should check with their health care provider about getting inactivated influenza vaccine.

- Adults 50 years of age or older or children younger than 5.
- People who have long-term health problems with:
  - » heart disease
  - » kidney disease
  - » lung disease
  - » metabolic disease, such as diabetes
  - » asthma
  - » anemia, and other blood disorders
- People with a weakened immune system due to:
  - » HIV/AIDS or another disease that affects the immune system
  - » long-term treatment with drugs that weaken the immune system
  - » cancer treatment with x-rays of drugs
- Children or adolescents on long-term aspirin treatment (these people could develop Reye syndrome if they catch influenza).
- Pregnant women.
- Anyone with a history of Gillain-Barré Syndrome (GBS).

The flu shot (inactivated vaccine) is preferred over live, intranasal influenza vaccine for physicians, nurses, family members, or anyone else coming in close contact with anyone with a weakened immune system."]

Recommendations for the Use of Antiviral Agents

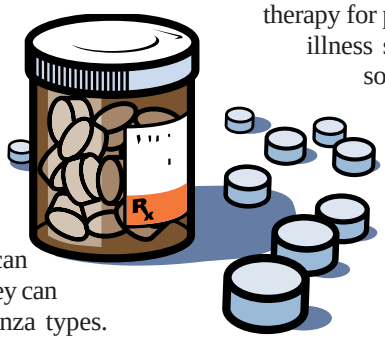
Antiviral drugs for influenza are an adjunct to influenza vaccine for controlling and preventing influenza. However, these agents are not a substitute for vaccination. Four licensed influenza antiviral agents are available in the United States: amantadine and rimantadine, chemically-related antiviral drugs known as adamantanes with activity against influenza A viruses 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, polymerase chain reaction (PCR) and immunofluorescence. Sensitivity and specificity of any test vary by the laboratory that performs the test and by the type of test used. Among respiratory specimens for viral isolation or rapid detection, nasopharyngeal specimens are typically more effective than throat swab specimens. As with any diagnostic test, results should be evaluated in the context of other clinical information available to the physician.



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 viruses 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, collecting 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 preventing illness from influenza A infection. When used as prophylaxis, these antiviral agents can prevent illness while permitting subclinical infection and 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 administered chemoprophylaxis after a household member was diagnosed with influenza. Experience with prophylactic use of these agents in institutional settings or among patients with chronic medical conditions is limited. One 6-week study of oseltamivir prophylaxis among nursing home residents reported 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 pro-

phylaxis 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 immunocompromised persons.

Control of Outbreaks in Institutions

Using antiviral drugs for treatment and prophylaxis of influenza is an important component of influenza outbreak control in institutions. 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 pre-approved orders from physicians or plans to obtain orders for antiviral medications on short notice is extremely useful.

When outbreaks occur in institutions, chemoprophylaxis should be administered to all residents, regardless of whether they received influenza vaccinations during the previous fall, and should continue for a minimum of 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 outbreaks in institutions, 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 will benefit from instruction and demonstration of correct use of this device.

Side Effects and Adverse Reactions

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

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, insomnia, difficulty concentrating, and lightheadedness) is higher among persons taking amantadine. 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. 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 and among older 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. 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 among certain patient populations (e.g., chronically ill and older persons) has been evaluated less frequently. Because amantadine has anticholinergic effects and might cause mydriasis, it should not be used in patients with untreated angle closure glaucoma.

Zanamivir

Zanamivir is generally not recommended for treatment for patients with underlying air-

Proposed Amendments
Disease Reporting and Control Regulations

The Virginia Department of Health ***Regulations for Disease Reporting and Control*** are in the process of being amended. The period for public comments on the proposed amendments began in late August and extends through October 31, 2003. The proposed amendments and how to submit comments may be viewed at the Virginia Register web site: **http://legis.state.va.us/codecomm/register/vol19/iss25/v19i25.pdf**

At the *Table of Contents*, scroll down to the *State Board of Health* and click on Page 3694 to view. Hard copies may be obtained by calling (804) 786-6261 or writing:

Division of Surveillance and Investigation
Office of Epidemiology
Virginia Department of Health
P.O. Box 2448, Room 113
Richmond, VA 23218

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, influenza A	5 mg/kg/day up to 150 mg per day in two divided doses†	5 mg/kg/day up to 150 mg per day in two divided doses†	100 mg twice daily§	100 mg twice daily§	≤100 mg/day
Prophylaxis, influenza A	5 mg/kg/day up to 150 mg per day in two divided doses†	5 mg/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,** influenza A	NA††	NA	NA	100mg twice daily§ §§	100 mg/day
Prophylaxis, influenza A	5 mg/kg/day up to 150 mg per day in two divided doses†	5 mg/kg/day up to 150 mg per day in two divided doses†	100 mg twice daily§	100 mg twice daily§	100 mg/day¶¶
Zanamivir*†††					
Treatment, influenza A and B	NA	10 mg twice daily	10 mg twice daily	10 mg twice daily	10 mg twice daily
Oseltamivir					
Treatment,§§§ influenza A and B	Dose varies by child's weight¶¶¶	Dose varies by child's weight¶¶¶	Dose varies by child's weight¶¶¶	75 mg twice daily	75 mg twice daily
Prophylaxis, influenza A and B	NA	NA	NA	75 mg/day	75 mg/day

NOTE: Amantadine manufacturers include Endo Pharmaceuticals (Symmetrel®, tablet and syrup); Geneva Pharms Tech and Rosemont (Amantadine HCL, capsule); USL Pharma (Amantadine HCL, capsule and tablet); and Alpharma, Copley Pharmaceutical, HiTech Pharma, Mikart, Morton Grove, Carolina Medical, and Pharmaceutical Associates (Amantadine HCL, syrup). Rimantadine is manufactured by Forest Laboratories (Flumadine®, tablet and syrup) and Corepharma, Impax Labs (Rimantadine HCL, tablet), and Amide Pharmaceuticals (Rimantadine ACL, tablet). Zanamivir is manufactured by GlaxoSmithKline (Relenza®, inhaled powder). Oseltamivir is manufactured by Hoffman-LaRoche, Inc. (Tamiflu®, tablet). This information is based on data published by the Food and Drug Administration (FDA), which is available at http://www.fda.gov.

** 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 <40 kg should be administered amantadine or rimantadine at a dosage of 5 mg/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.

*** Only approved by FDA for treatment among adults.*

†† Not applicable.

§§ Rimantadine is approved by FDA for treatment among adults. However, certain specialists in the management of influenza consider rimantadine appropriate for treatment among children (see American Academy of Pediatrics. 2000 red book: report of the Committee on Infectious Diseases. 25th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2000).

¶¶ Older 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 possible side effects when taking 200 mg/day.

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

††† Zanamivir is not approved for prophylaxis.

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

¶¶¶ The dose recommendation for children who weigh ≤15 kg is 30 mg twice a day. For children who weigh >15–23 kg, the dose is 45 mg twice a day. For children who weigh >23–40 kg, the dose is 60 mg twice a day. And, for children who weigh >40 kg, the dose is 75 mg twice a day.

way disease because of the risk for serious adverse events and because 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 1) have a fast-acting inhaled bronchodilator available when inhaling zanamivir and 2) stop using zanamivir and contact their physician if they experience 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. 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 who were enrolled in clinical treatment trials of oseltamivir discontinued treatment because of these symptoms. Similar types and rates of adverse events were reported in studies of oseltamivir 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 CNS, including CNS stimulants. Concomitant administration of antihistamines or anticholinergic drugs can increase the incidence of adverse CNS reactions. No clinically substantial 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 using 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.

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, including 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.

Sources of Information Regarding Influenza and Its Surveillance

Information regarding influenza surveillance, prevention, detection, and control is available on the CDC/National Center for Infectious Diseases website at http://www.cdc.gov/ncidod/diseases/flu/weekly.htm. Surveillance information is available through the CDC Voice Information System (influenza update) at 888-232-3228 or CDC Fax Information Service at 888-232-3299. Additional information regarding influenza vaccine can be obtained at the CDC/National Immunization Program website at http://www.cdc.gov/nip/flu or by calling their hotline at 800-232-2522 (English) or 800-232-0233 (Spanish).

State and local health departments should be consulted concerning availability of influenza vaccine, access to vaccination programs, information related to state or local influenza activity, and for reporting influenza outbreaks and receiving advice concerning outbreak control.

The Virginia Department of Health's Division of Surveillance and Investigation welcomes the following new staff members:

Angelique DeLonde, MSPH, Surveillance Specialist
Lesliann Helmus, MSPH, Surveillance Chief
Christopher Novak, MD, MPH, Medical Epidemiologist
Julie Plagenhoef, MPH, Statistical Analyst Senior
Paula Vest, Program Support Technician Senior
Mary Beth White-Russell, Nurse Epidemiologist

The Office of Epidemiology also welcomes **Asim Jani**, MD, MPH, as our Epidemic Intelligence Service Officer. Dr. Jani is assigned by CDC to Virginia for the next two years.

Cases of Selected Notifiable Diseases Reported in Virginia*

Disease	Total Cases Reported, July 2003: State	Regions: NW	N	SW	C	E	Total Cases Reported Statewide, January through July: This Year	Last Year	5 Yr Avg
AIDS	61	2	25	4	9	21	485	472	480
Campylobacteriosis	145	30	41	35	23	16	439	285	320
E. coli O157:H7	4	1	1	1	1	0	21	27	30
Giardiasis	50	10	29	4	2	5	205	117	187
Gonorrhea	791	36	38	79	205	433	5,182	5,822	5,421
Hepatitis A	4	0	3	1	0	0	47	54	90
B, acute	22	3	0	6	7	6	97	122	83
C/NANB, acute	2	0	0	1	0	1	4	1	4
HIV Infection	68	6	25	5	9	23	451	576	490
Lead in Children†	94	9	7	18	31	29	416	388	323
Legionellosis	41	14	6	6	4	11	50	10	12
Lyme Disease	17	6	1	0	2	8	38	43	55
Measles	0	0	0	0	0	0	0	0	1
Meningococcal Infection	2	0	0	2	0	0	19	28	30
Mumps	0	0	0	0	0	0	1	3	5
Pertussis	2	0	0	0	0	2	60	94	32
Rabies in Animals	48	11	10	12	9	6	323	325	319
Rocky Mountain Spotted Fever	8	3	0	3	0	2	11	15	9
Rubella	0	0	0	0	0	0	0	0	0
Salmonellosis	142	26	46	25	22	23	507	493	586
Shigellosis	47	2	22	1	13	9	242	551	210
Syphilis, Early§	21	2	10	2	4	3	105	94	181
Tuberculosis	39	2	30	3	1	3	151	130	157

Localities Reporting Animal Rabies This Month: Accomack 2 raccoons; Albemarle 1 bat; Alexandria 2 raccoons; Alleghany 1 raccoon; Amherst 1 raccoon; Appomattox 1 bobcat; Arlington 2 raccoons; Augusta 1 fox, 1 skunk; Bath 1 fox; Bedford 1 fox; Buckingham 1 cat; Charlotte 1 skunk; Chesterfield 1 cat; Clarke 1 raccoon; Fairfax 1 bat, 3 raccoons; Fauquier 2 raccoons; Giles 2 skunks; Grayson 1 skunk; Greensville 1 raccoon; Hanover 3 raccoons; Loudoun 1 fox, 1 raccoon; Louisa 1 skunk; Newport News 1 raccoon; Northampton 1 fox; Petersburg 1 raccoon; Pittsylvania 1 raccoon; Prince George 1 raccoon; Rockbridge 1 horse; Russell 1 horse; Stafford 1 cat, 1 fox; Suffolk 1 raccoon; Tazewell 3 bats; Westmoreland 1 fox.

Toxic Substance-related Illnesses: Arsenic 1; Asbestosis 14; Lead Exposure 10; Pneumoconiosis 8.

*Data for 2003 are provisional. †Elevated blood lead levels ≥10µg/dL.

§Includes primary, secondary, and early latent.

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