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Neuraminidase Inhibitors for Treatment of Influenza A and B Infections

Summary

The following article is adapted from the MMWR article with the above title (1999;48[No. RR-14]:1-9). Influenza epidemics are responsible for an average of approximately 20,000 deaths per year in the United States. The main method for preventing influenza and its severe complications is influenza vaccination. Influenza-specific antiviral drugs are an important adjunct to vaccine but are not a substitute for vaccine. In the United States, four antiviral agents are approved for preventing or treating influenza: amantadine, rimantadine, zanamivir, and oseltamivir.

This report provides information on two neuraminidase inhibitors, zanamivir and oseltamivir, which were approved in 1999. Neuraminidase inhibitors are a new class of antiviral drugs that inhibit influenza A and B viruses. Zanamivir is approved for treatment of uncomplicated acute illness caused by influenza virus in persons aged ≥12 years who have been symptomatic for no more than 2 days. Oseltamivir is approved for treatment of uncomplicated illness caused by influenza infection in adults aged ≥18 years who have been symptomatic for no more than 2 days. Neither zanamivir nor oseltamivir is approved for influenza prophylaxis. This report and the Advisory Committee on Immunization Practices 1999 recommendations on influenza prevention and control (MMWR 1999;48[No.RR-4]:1-28) can be accessed online at http://www.cdc.gov/ncidod/diseases/flu/fluvirus.htm.

Introduction

Uncomplicated influenza 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). However, 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. Epidemics of influenza occur during the winter months nearly every year and are responsible for an average of approximately 20,000 deaths per year in the United States. The main method for preventing influenza and its more severe complications is immunoprophylaxis with inactivated (i.e., killed-virus) vaccine. Influenza-specific antiviral drugs for chemoprophylaxis or therapy are an important adjunct to vaccine, but they are not a substitute for influenza vaccine. In the United States, four antiviral agents are approved for preventing or treating influenza: amantadine hydrochloride and rimantadine hydrochloride as well as two recently approved neuraminidase inhibitors, zanamivir and oseltamivir.

Antiviral drugs for chemoprophylaxis or therapy are an important adjunct to vaccine, but they are not a substitute for influenza vaccine.

Amantadine and rimantadine are chemically related antiviral drugs active against influenza A viruses but not influenza B viruses. After influenza A viruses enter cells, these drugs inhibit the uncoating of influenza A viruses by blocking the ion-channel activity of the viral M2 protein. Amantadine was approved in 1976 for treatment and prophylaxis of influenza type A infection in adults and children aged ≥1 year. Rimantadine was approved in 1993 for treatment and prophylaxis of influenza type A infection in adults. For children, rimantadine was approved only for prophylaxis; however, many experts consider rimantadine appropriate for treatment of influenza A in children. (For information on the use of amantadine and rimantadine, see the August 1999 *Virginia Epidemiology Bulletin* or the above-mentioned website.)

Zanamivir and oseltamivir, both approved in 1999 by the U.S. Food and Drug Administration, are members of a new class of antiviral agents that selectively inhibit the neuraminidase of both influenza A and B

viruses. Neuraminidase cleaves terminal sialic acid residues from carbohydrate moieties on the surfaces of host cells and influenza virus envelopes; this process promotes the release of progeny viruses from infected cells. Neuraminidase inhibitors are analogues of sialic acid. Their proposed mechanism of action is to block the active site of neuraminidase and leave uncleaved sialic acid residues on the surfaces of host cells and influenza viral envelopes. Viral hemagglutinin binds to the uncleaved sialic acid residues; the result is viral aggregation at the host cell surface and a reduction in the amount of virus that is released and can infect other cells.

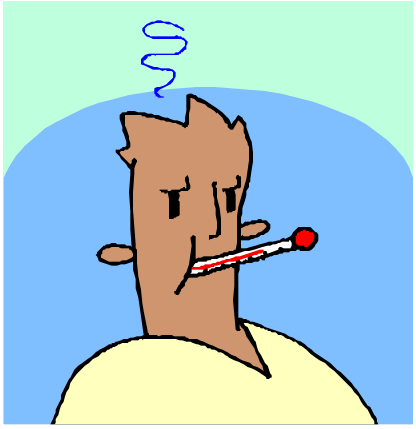
Use of Neuraminidase Inhibitors for Treatment of Influenza A and B Infections

Laboratory Diagnosis of Influenza

The appropriate treatment of patients with viral 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. Surveillance can also identify 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 and vaccine strains, to guide decisions about influenza treatment and prophylaxis, and to formulate vaccine for the coming year. Viral isolates also are needed to monitor the emergence of antiviral resistance.

During the influenza season, the Virginia State Laboratory (Division of Consolidated Laboratory Services, DCLS) provides free testing of specimens submitted for influenza isolation. To obtain a "flu kit" call (804) 786-3756.

Indications for Use of Zanamivir and Oseltamivir

Treatment

Zanamivir is approved for treatment of uncomplicated acute illness caused by influenza virus in adults and adolescents aged ≥12 years who have been symptomatic for no more than 2 days. (No data are available to support zanamivir's efficacy if treatment is initiated >48 hours after onset of illness.) This indication was based on studies in which the predominant influenza infections were influenza A and a limited number of patients with influenza B were also enrolled. Zanamivir is not approved for use in children aged <12 years.

Oseltamivir is approved for treatment of uncomplicated acute illness caused by influenza infection in adults aged ≥18 years who have been symptomatic for no more than 2 days. (No data are available to support oseltamivir's efficacy if treatment is initiated >40 hours after onset of illness.) This indication was based on studies of naturally occurring influenza in which the predominant infection was influenza A and influenza challenge studies in which the antiviral activity of oseltamivir was supported for influenza A and B. Oseltamivir is not approved for use in children <18 years.

When administered within 2 days of illness onset among otherwise healthy adults, zanamivir and oseltamivir can reduce by approximately 1 day the duration of moderate or severe symptoms of uncomplicated influenza. The evidence for the efficacy of both drugs is based primarily on data from patients with fever ≥37.8º C (100º F) at the time therapy was started.

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 data from treatment in mice and ferrets document that zanamivir and oseltamivir have activity against influenza B viruses. Limited data from clinical trials of zanamivir and from studies of oseltamivir treatment of experimental influenza B infections also suggest that zanamivir and oseltamivir are effective for treatment of infections caused by influenza B viruses.

Neither zanamivir nor oseltamivir has been demonstrated to be effective in preventing serious influenza-related complications, such as bacterial or viral pneumonia or exacerbation of chronic diseases. Data are limited and inconclusive concerning the effectiveness of zanamivir for treatment of influenza in persons at high risk for serious complications of influenza. No published data are available concerning the effectiveness of oseltamivir for treatment of influenza in high-risk populations. No clinical data are available regarding the safety or efficacy of zanamivir or oseltamivir for pregnant women.

Prophylaxis

Zanamivir and oseltamivir are not approved for prophylactic use. However, recently published studies of zanamivir and oseltamivir for prophylaxis of influenza in community settings demonstrated both drugs to be similarly effective in preventing laboratory-confirmed clinical influenza with fever (efficacy: zanamivir, 84%; oseltamivir, 82%). Experience with prophylactic use of these agents in institutional settings is limited. Vaccination remains the best prophylaxis for influenza.

Administration of Zanamivir and Oseltamivir

Dosage

The recommended dosage of zanamivir for treatment of influenza in persons aged ≥12 years is two inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) twice daily (approximately 12 hours apart) for 5 days.

The recommended dosage of oseltamivir for treatment of influenza in persons aged ≥18 years is 75 mg orally twice daily for 5 days. A reduction in dosage is recommended for persons with creatinine clearance <30 mL/min (see Persons with Impaired Renal Function).

Route

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. Although the plastic device is similar to devices used to deliver some asthma medications, use of this device should be restricted to delivery of zanamivir. Delivery of the medication requires loading of a medication disk into the plastic device each day. Patients will benefit from instruction and demonstration of proper use of the device. Zanamivir is packaged in a disk with four blisters of medication, each containing a powder mixture of 5 mg of zanamivir and 20 mg of lactose.

Oseltamivir is administered orally. It is available as 75-mg capsules.

Pharmacokinetics

In studies of healthy volunteers, approximately 7%-21% of the orally inhaled zanamivir dose reached the lungs, and 70%-87% was deposited in the oropharynx. Approximately 4%-17% of the total amount of orally inhaled zanamivir is systemically absorbed. Systemically absorbed zanamivir has a half-life of 2.5-5.1 hours and is excreted unchanged in the urine. Unabsorbed drug is excreted in the feces.

Approximately 80% of orally administered oseltamivir is absorbed systemically. Absorbed oseltamivir is metabolized to GS4071 (oseltamivir carboxylate), the active neuraminidase inhibitor, primarily by hepatic esterases. GS4071 has a half-life of 6-10 hours and is excreted in the urine by glomerular filtration and tubular secretion via the anionic pathway. Unmetabolized oseltamivir also is excreted in the urine by glomerular filtration and tubular secretion.

Persons with Impaired Renal Function

Limited data are available regarding the safety and efficacy of zanamivir for patients with impaired renal function. Among patients with renal failure who were administered a single intravenous dose of zanamivir in prelicensure studies, decreases in renal clearance and increases in half-life and 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.

Among patients with impaired renal function, serum concentrations of oseltamivir carboxylate 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

The pharmacokinetics of zanamivir and oseltamivir have not been studied in patients with impaired hepatic function.

Side Effects and Adverse Reactions

In clinical treatment studies of inhaled zanamivir, 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. Caution is advised if zanamivir is prescribed for patients with underlying chronic respiratory disease. In a phase I study of persons with mild or moderate asthma who did not have influenza-like illness, 1 of 13 patients experienced bronchospasm following administration of zanamivir. In addition, 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 greater than 20% decline in forced expiratory volume in 1 second (FEV1) or peak expiratory flow rates after treatment. Patients with asthma or chronic obstructive pulmonary disease are advised to a) have a fast-acting inhaled bronchodilator available when inhaling zanamivir and to b) stop using zanamivir and contact their physician if they develop difficulty breathing.

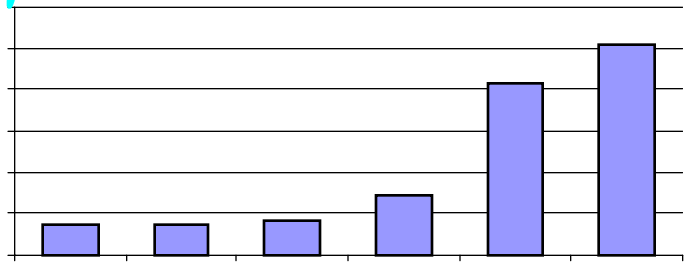
Nausea and vomiting were reported more frequently among persons receiving oseltamivir for treatment (nausea without vomiting, approximately 10%; vomiting, approximately 9%) than among persons receiving placebo (nausea without vomiting, approximately 6%; vomiting, approximately 3%). However, few persons 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.

Drug Interactions

Although clinical data are limited regarding drug interactions with zanamivir, no known drug interactions with zanamivir have been reported, and no clinically important drug interactions have been predicted on the basis of *in vitro* data and data from studies in rats. Zanamivir does not affect the cytochrome P450 isoenzymes in human liver microsomes and is not expected to alter the metabolism of other drugs metabolized by these enzymes. Treatment with zanamivir has not been found to impair the immunologic response to influenza vaccine. No pub-

Flu Corner

As of January 5, 2000, Virginia reported widespread influenza activity. The state laboratory has confirmed 44 cases of influenza type A (40 from the Northern region, 2 from the Eastern region, and 2 from the Central region). One case of influenza type B was confirmed from the Northern region earlier this year (September 1999). For further information on the surveillance of influenza in Virginia, see the website: www.vdh.state.va.us/epi/flu9900.htm.



lished data are available concerning the safety or efficacy of coadministering amantadine or rimantadine with zanamivir.

Limited clinical data are available regarding drug interactions with oseltamivir. Because oseltamivir and its active metabolite, GS4071, 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 a reduction in the clearance of GS4071 by approximately 50% and a corresponding approximate twofold increase in the plasma levels of GS4071. Oseltamivir and GS4071 are not substrates for the cytochrome P450 isoenzymes and are not expected to alter the metabolism of other drugs metabolized by these enzymes. No published data are available concerning the safety or efficacy of coadministering amantadine or rimantadine with oseltamivir.

Antiviral Drug Resistance

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.

Comparison of Current Antiviral Agents

Zanamivir, oseltamivir, amantadine, and rimantadine vary in terms of the types of influenza viruses they inhibit, route of administration, and approved use in different age groups (Table). No studies have directly compared the effectiveness of these drugs for treatment of influenza A; however, available information indicates that all four agents are roughly comparable in reducing the duration of uncomplicated acute illness due to influenza A when treatment is started shortly after onset of symptoms. None of the four agents has been shown to decrease serious complications of influenza (e.g., pneumonia, hospitalization). Information about the use of zanamivir and oseltamivir among persons at high risk for influenza complications is limited.

The side effects and cost of zanamivir and oseltamivir differ from those of amantadine and rimantadine. Central nervous system side effects (e.g., nervousness, anxiety, difficulty concentrating, and lightheadedness) have been associated with amantadine and to a lesser extent with rimantadine. Amantadine has also been associated with an increased incidence of seizures among patients with a history of seizure disorders. Whether rimantadine is associated with an increased incidence of seizures among patients with a history of seizure disorders has not been adequately evaluated. Central nervous system side effects have been infrequently reported among patients taking zanamivir and oseltamivir. Because some persons with underlying asthma or chronic obstructive pulmonary disease have experienced reduced FEV1 or peak expiratory flow rate following treatment with zanamivir, caution is advised if zanamivir is used by patients with underlying chronic respiratory disease. Oseltamivir has been associated with nausea and vomiting. The dose of amantadine, rimantadine, and oseltamivir must be reduced for patients with renal failure. Finally, zanamivir and oseltamivir are more expensive than rimantadine, which is more expensive than amantadine.

Conclusion

Zanamivir and oseltamivir offer new options for treatment of influenza. Antiviral agents for influenza — including amantadine, rimantadine, zanamivir, and oseltamivir — are an adjunct to vaccine and are not a substitute for vaccine. Immunoprophylaxis with inactivated (i.e., killed-virus) vaccine remains the principal means for reducing influenza-related morbidity and death.

Table. Comparison of antiviral agents for influenza

	Amantadine	Rimantadine	Zanamivir	Oseltamivir
Types of influenza viruses inhibited	Influenza A	Influenza A	Influenza A and B	Influenza A and B
Route of administration	Oral (tablet, capsule, syrup)	Oral (tablet, syrup)	Oral inhalation*	Oral (capsule)
Ages for which treatment is approved	≥1 year	≥14 years	≥12 years	≥18 years
Ages for which prophylaxis is approved	≥1 year	≥1 year	Not approved for prophylaxis	Not approved for prophylaxis

NOTE: Amantadine manufacturers include Endo Pharmaceuticals (Symetrel®, 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®, for inhalation). Oseltamivir is manufactured by Hoffman-La Roche Inc. (Tamiflu®, capsule).
****Zanamivir is administered by using a specially designed plastic oral inhalation device (Diskhaler®). The device and instructions on its use are included in the package with the medication.***

Cases of Selected Notifiable Diseases Reported in Virginia*

Disease	Total Cases Reported, October 1999: State	Regions: NW	N	SW	C	E	Total Cases Reported Statewide, January through October: This Year	Last Year	5 Yr Avg
AIDS	87	10	16	9	10	42	723	809	955
Campylobacteriosis	68	21	16	10	8	13	555	591	599
***E. coli* O157:H7**	8	4	3	0	0	1	65	64	52
Giardiasis	67	8	38	3	13	5	383	386	310
Gonorrhea	962	38	87	146	218	473	7881	7633	8543
Hepatitis A	27	5	14	3	1	4	146	181	170
B, acute	6	0	1	3	0	2	75	88	104
C/NANB, acute	0	0	0	0	0	0	10	11	18
HIV Infection	99	5	24	7	19	44	732	696	852
Lead in Children†	37	3	8	7	9	10	363	554	654
Legionellosis	4	2	0	1	0	1	28	18	20
Lyme Disease	15	1	12	0	1	1	109	58	66
Measles	10	0	0	10	0	0	13	2	2
Meningococcal Infection	5	3	0	0	1	1	45	36	50
Mumps	2	0	1	0	0	1	10	8	18
Pertussis	12	2	3	0	2	5	29	31	41
Rabies in Animals	77	28	31	6	5	7	483	490	459
Rocky Mountain Spotted Fever	3	0	1	0	1	1	15	13	26
Rubella	0	0	0	0	0	0	0	1	1
Salmonellosis	133	21	22	15	28	47	1118	943	954
Shigellosis	22	1	15	4	0	2	116	175	402
Syphilis, Early§	30	2	3	11	6	8	317	342	746
Tuberculosis	18	1	8	2	0	7	247	245	274

Localities Reporting Animal Rabies This Month: Accomack 1 fox, 1 raccoon; Albemarle 2 skunks; Alexandria 1 bat; Amherst 1 raccoon, 1 skunk; Arlington 2 raccoons; Augusta 1 raccoon, 5 skunks; Botetourt 1 skunk; Chesapeake 1 fox, 2 raccoons; Chesterfield 1 fox; Culpeper 2 raccoons; Cumberland 1 skunk; Fairfax 2 foxes, 18 raccoons, 2 skunks; Fauquier 1 skunk; Franklin County 1 skunk; Frederick 2 raccoons, 1 skunk; Greensville 1 skunk; Halifax 1 skunk; Henrico 1 raccoon; Isle of Wight 1 raccoon; King George 1 raccoon; Loudoun 2 foxes, 2 raccoons; Lynchburg 1 skunk; Madison 1 cat; Orange 1 raccoon, 1 skunk; Page 2 raccoons; Pittsylvania 1 raccoon; Prince William 2 raccoons; Rockingham 1 skunk; Shenandoah 1 skunk; Spotsylvania 1 raccoon; Stafford 3 raccoons; Virginia Beach 1 raccoon; Warren 2 skunks.

Occupational Illnesses: Asbestosis 39; CAdmium Exposure 2; Lead Exposure 8; Mesothelioma 1; Pneumoconiosis 13.

*Data for 1999 are provisional. †Elevated blood lead levels ≥10µg/dL. §Includes primary, secondary, and early latent.

Index to Volume 1999

(by Issue Number)

Cases of Selected Notifiable Diseases Reported in Virginia*

Disease	Total Cases Reported, November 1999: State	Regions: NW	N	SW	C	E	Total Cases Reported Statewide, January through November: This Year	Last Year	5 Yr Avg
AIDS	46	1	26	0	9	10	723	881	1066
Campylobacteriosis	28	2	7	4	3	12	583	631	654
***E. coli* O157:H7**	6	1	0	1	1	3	71	66	56
Giardiasis	36	5	14	5	4	8	419	432	352
Gonorrhea	859	55	53	66	257	428	8740	8464	9376
Hepatitis A	19	6	4	3	1	5	165	195	190
B, acute	12	0	1	0	1	10	87	92	113
C/NANB, acute	0	0	0	0	0	0	10	11	19
HIV Infection	61	4	34	1	7	15	732	753	929
Lead in Children†	83	6	7	14	24	32	448	603	724
Legionellosis	4	1	1	1	0	1	32	20	23
Lyme Disease	5	1	4	0	0	0	114	65	71
Measles	5	0	0	5	0	0	18	2	2
Meningococcal Infection	5	2	0	1	2	0	50	43	56
Mumps	0	0	0	0	0	0	10	8	22
Pertussis	21	1	0	0	19	1	50	37	51
Rabies in Animals	50	19	7	12	5	7	533	519	507
Rocky Mountain Spotted Fever	2	1	0	0	0	1	17	14	28
Rubella	0	0	0	0	0	0	0	1	1
Salmonellosis	54	12	10	9	7	16	1172	1017	1053
Shigellosis	8	2	3	3	0	0	124	185	438
Syphilis, Early§	25	0	7	6	4	8	342	360	810
Tuberculosis	16	0	3	3	6	4	268	274	299

Localities Reporting Animal Rabies This Month: Accomack 1 raccoon; Albemarle 1 raccoon; Alexandria 1 raccoon; Alleghany 1 skunk; Amherst 1 skunk; Appomattox 1 skunk; Augusta 1 fox, 1 skunk; Bath 2 skunks; Botetourt 1 dog, 1 skunk; Buckingham 1 raccoon; Clarke 1 raccoon; Culpeper 2 raccoons; Danville 1 bat; Fairfax 3 raccoons, 1 skunk; Floyd 1 raccoon, 1 skunk; Fluvanna 1 raccoon; Franklin County 1 raccoon; Frederick 1 raccoon; Gloucester 1 raccoon; Hampton 2 raccoons; Hanover 1 fox; Loudoun 1 raccoon; Louisa 2 skunks; Madison 1 cow; Mecklenburg 1 raccoon; Montgomery 1 raccoon; Newport News 1 raccoon; Page 1 raccoon; Prince Edward 1 skunk; Prince William 1 skunk; Pulaski 1 cow; Richmond County 1 cat; Richmond City 1 raccoon; Rockingham 1 cat; Smyth 1 skunk; Spotsylvania 1 skunk; Stafford 2 raccoons; Warren 1 raccoon; Westmoreland 1 raccoon.
Occupational Illnesses: Asbestosis 42; Lead Exposure 19; Mercury Exposure 1; Pneumoconiosis 4.
*Data for 1999 are provisional. †Elevated blood lead levels ≥10µg/dL. §Includes primary, secondary, and early latent.

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