HTLV-III Antibody Positive Individuals

A Clinician's Guide to Evaluation

Editor's note: This is one of three articles adapted from material provided by the U.S. Public Health Service. It is directed at physicians who will be caring for individuals discovered to be HTLV-III antibody positive. Two accompanying articles, printed on the insert sheet, can be removed, copied and used to educate your patients. The first addresses questions blood donors and other concerned individuals might raise about the HTLV-III antibody test. The second (printed on the reverse) addresses questions that might be raised by individuals discovered to be HTLV-III antibody test positive. A limited number of extra copies of this insert sheet can be obtained by writing the Sexually Transmitted Disease Control Program at the Virginia Department of Health, Room 721, 109 Governor Street, Richmond, Virginia 23219.

The Virus that Causes AIDS

The etiologic agent of the acquired immunodeficiency syndrome (AIDS) is human T-cell lymphotropic virus type III (HTLV-III), also known as LAV and ARV. This distinctive class of RNA virus shares some features with retroviruses previously linked to various disorders in animals, including leukemias, neurologic diseases, and immunodeficiency disorders and to a human virus, HTLV-I, linked to an unusual form of human leukemia. HTLV-III has a cytotoxic effect on T-lymphocytes of the helper type. The diverse infections and tumors which are the ultimate cause of death for AIDS patients result from the fact that the virus renders the immune system incompetent.

Clinical Significance of HTLV-III Seropositivity

Over 90% of patients with full-blown AIDS are positive for HTLV-III antibodies in the screening test, and with the application of additional research techniques close to 100% of such individuals are virus-positive.

Among seropositive persons, the risk for developing frank AIDS may vary depending upon risk group and possibly other factors such as additional environmental exposures and genetic background. Preliminary estimates in cohorts of homosexual men followed Continued to page 2

Acquired Immune Deficiency Syndrome
Cases (N = 80) by Risk Group
Virginia 1982-1985

- A 9%
- B 76%
- C 2%
- D 5%
- E 8%

Risk Group
A—Intravenous drug use
B—Homosexual/bisexual
C—Pediatric
D—Transfusion associated
E—None apparent/unknown
Prospectively for two to five years indicate that between 5% and 20% of persons with detectable HTLV-III antibodies may go on to develop AIDS. However, information that pertains to one risk group may not directly translate to other risk groups. The lack of precise data on the clinical significance of HTLV-III antibody positivity for an individual patient coupled with the fact that many persons in high-risk groups have detectable HTLV-III antibodies, creates a dilemma for the physician confronted with evaluating and counseling such antibody-positive patients. If this virus follows patterns seen in other viruses, the majority of exposed individuals will remain clinically healthy. However, this is a new class of human virus and the long-term implications of exposure to the health of an individual are unknown. Furthermore, the implications of seropositivity in the individual to the potential for transmitting the virus to others are unknown. Epidemiologic data do document that homosexual and probably heterosexual sexual relations, needle sharing, blood transfusion and transplantal and/or perinatal exposure are modes of transmission. Finally, it should be emphasized that the current antibody test is licensed as a blood bank screening and not a diagnostic tool. In this regard, the absence of antibody in a high-risk person does not necessarily mean that the patient is virus negative, since the virus has been isolated from a few at-risk individuals who were antibody negative. Conversely, as with all antibody tests of this type, a few biologic false positives will be detected due to antibodies to non-HTLV-III cross-reactive antigens.

**Dynamics of HTLV-III Infection**

Seroconversion generally antedates the development of clinical or subclinical laboratory signs of viral infection by several years, necessitating extended follow-up. The first sign of subclinical infection may be a laboratory perturbation associated with HTLV-III seropositivity.

The laboratory parameter most frequently linked to HTLV-III infection is a depressed number of peripheral blood lymphocytes bearing the helper T-cell phenotype. Other laboratory parameters which have been associated with this process include elevated immunoglobulin levels; high titers to a variety of viral agents (particularly Epstein Barr virus and cytomegalovirus); and elevated beta-2 microglobulin, thymosin, and acid labile alpha interferon. Although these various observations are of some research interest and reflect the variety of laboratory perturbations which result from fundamental virus-associated immunodeficiency, their relevance in the clinical setting is not sufficiently well-defined to be of practical diagnostic benefit. These are currently a focus of ongoing research studies.

**Range of Clinical Manifestations**

Another condition recognized as being associated with HTLV-III infection is the lymphadenopathy syndrome, a medical complex characterized by the occurrence of persistent, unexplained lymph node enlargement in several extra-inguinal lymph node groups. The relationship of the lymphadenopathy syndrome to progression to overt clinical AIDS is uncertain but probably is as high as 10%.

Another lesser manifestation is the AIDS related complex (ARC), a clinical and laboratory syndrome characterized by minor conditions clinically associated with immunosuppression (e.g., oral thrush) and laboratory evidence of immunosuppression. In addition, unexplained idiopathic thrombocytopenia is probably associated with HTLV-III infection, as are a variety of non-life-threatening fungal, viral, and bacterial infectious processes which probably represent manifestations of virus-induced immunologic perturbation. These manifestations are sometimes termed lesser AIDS.

The clinical presentation of clinical

**Acquired Immune Deficiency Syndrome**

**Cases (N=80) by Year Reported**

**Virginia 1982-1985**

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Epidemiology Bulletin
AIDS, as originally defined, follows four major patterns:

1) A febrile prodrome of weeks to months followed by opportunistic infection.
2) Abrupt onset of opportunistic infection.
3) Presentation with Kaposi's sarcoma.
4) Progression from the AIDS-related complex.

**Approach to Clinical Evaluation**

AIDS and its diverse related clinical disorders challenge the diagnostic acumen of physicians in all branches of medicine. The prospective clinical evaluation of HTLV-III seropositive individuals who may be at risk for AIDS requires a careful multi-system approach to evaluate signs and symptoms. Clearly, it is important to perform thorough physical examinations on these individuals. Listed below is a broad overview of recognized clinical signs and symptoms. A more thorough review of the published literature is strongly recommended (see Background Reading).

**Medical History:** Possible source of exposure, identification of risk group exposure, blood transfusion, acupuncture, tattoos, needle stick exposure, foreign travel, and sexual history.

**Dermatologic:** Kaposi's sarcoma (purple or reddish nodules), which may appear anywhere in the skin and on mucocutaneous surfaces (e.g., mouth and rectum), infectious processes (e.g., Herpes simplex or zoster), seborrheic dermatitis, unexplained diffuse hyperpigmentation, alopecia.

**Ophthalmologic:** Ocular lesions (retinitis due to cytomegalovirus or toxoplasmosis), cottonwool spots, retinal hemorrhages.

**Hematopoietic:** Fluctuating adenopathy associated with aching discomfort. Variable lymph node size and consistency. Soft, moderately enlarged spleen. Large, firm spleen and/or very large lymph nodes are suggestive of intracellular infections (e.g., mycobacterium avium), lymphoma or Kaposi's sarcoma.

**Gastrointestinal:** Oral thrush, candida esophagitis associated with xerostomia and pharyngitis orodynaphagia. Watery diarrhea due to various protozoan infestations and lower GI pain due to herpes proctitis.

**Pulmonary:** Non-productive cough and dyspnea (associated with Pneumocystis carinii or viral pneumonitis), productive cough linked to bacterial or other etiology.

**Musculoskeletal:** Diffuse arthralgias and myalgias associated with febrile prodrome suggestive of vasculitis, autoimmune and rheumatologic diseases.

**Neurologic:** Persistent headache, memory loss, ataxia, confusion, irrational behavior, personality change, focal neurologic signs, and seizure.

**General:** Fatigue, asthenia, night sweats or sweating, decreased libido, withdrawal and other signs of depression, fever including Pel-Ebstein fever pattern.

Laboratory tests that could be helpful in evaluating antibody positives include a complete blood count, differential and platelet count, VDRL, tests of hepatitis B infection, and baseline routine chemistries, including gamma globulin levels. Additional, specific tests should be directed by the clinical findings.

**Therapeutic intervention**

Therapeutic interventions that are specific for the virus or for the immunodeficiency do not yet exist, although there is considerable research being done attempting to develop such modalities. However, rapid diagnostic evaluation and intervention with appropriate antimicrobials in specifically documented illnesses may be lifesaving. Some clinicians have advocated use of prophylactic therapy to prevent common protozoan and fungal diseases (i.e., trimethoprim-sulfamethoxazole and ketoconazole), but there is also a substantial amount of drug-related dermatologic and hematologic toxicity for some of these agents and implementation of such therapy without consulting a specialist would not be recommended.

**What to Tell the Seropositive Patient**

From a clinical perspective, counseling a seropositive, clinically healthy individual presents a challenge since the risk of clinical disease is not well characterized. The possibility that the test reactivity represents a biologic false positive should be discussed particularly in the patients without definable risk exposure.

Continued from page 2

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**Acquired Immune Deficiency Syndrome**

**Cases (N = 80) by Primary Disease**

**Virginia 1982-1985**

![Pie chart showing disease distribution]

- A - Pneumocystis carinii (60%)
- B - Kaposi's sarcoma (19%)
- C - Both KS and PCP (3%)
- D - Other opportunistic (18%)

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Continued from page 3

It is inevitable that substantial psychological stress will derive from the knowledge of antibody positivity, and judicious reassurance is supported by the current data which suggests that the vast majority of antibody positives are clinically well. However, given the fact that clinical problems may take some years to become manifest clinically, long-term follow-up with careful assessment of symptomatology as described above are in order. HTLV-III has also been linked to hematologic and neurologic disorders, a focus of active investigation. With this in mind, clinical symptoms in antibody-positive persons should be pursued vigorously to assure optimal care. The risk for an antibody-positive individual being infectious for another person is not quantified. As summarized above, certain factors (e.g., sexual contact, needle sharing, pregnancy) are linked to virus transmission and may serve as the basis for tailoring recommendations to the antibody positive individual to decrease the likelihood of transmission of the virus.

**Summary**

The practicing physician encountering an HTLV-III antibody-positive person must deal with incomplete knowledge about the natural history of the disease. Clinical long-term follow-up of antibody-positive persons should be a commitment for physicians confronted with such patients. Careful monitoring of the fast-moving medical literature concerning this condition is important to provide optimal care. Where feasible, consideration of referral to a center organized to follow such patients may be appropriate.

**Background Reading**


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**AIDS risk for health care workers**

**Update: Prospective Evaluation of Health-Care Workers Exposed via the Parenteral or Mucous-Membrane Route to Blood or Body Fluids from Patients with Acquired Immunodeficiency Syndrome—United States**

On August 15, 1983, CDC initiated prospective surveillance of health-care workers (HCWs) with documented parenteral or mucous-membrane exposure to potentially infectious body fluids from patients with definite or suspected acquired immunodeficiency syndrome (AIDS). As of December 31, 1984, 361 HCWs with such exposures were enrolled in CDC’s surveillance registry under the auspices of participating hospitals, other health-care institutions, and state and local health departments in the United States. Each enrolled HCW is followed for 3 years with a semiannual interview, physical examination, and blood specimen collection. None of the HCWs have developed signs or symptoms suggestive of AIDS; 143 (40%) have now been followed for 12 months or longer.

Exposed HCWs have been reported from 33 states and the District of Columbia. Fifty-nine percent of the HCWs were reported from six states: New York (61), California (39), New Jersey (36), Pennsylvania (28), Florida (25), and Texas (23). As of December 31, 1984, the length to follow-up of HCWs ranged from 1 month to 45 months (mean 11 months; median 10 months). Two hundred eight (58%) HCWs were nurses; 66 (18%), physicians or medical students; 31 (9%), laboratory workers; 26 (7%), phlebotomists; 15 (4%), respiratory therapists; and the remaining 15 (4%) had less direct patient contact. Eighty-five percent were white, and 78% were female. Ages ranged from 18 years to 62 years (mean 33 years).

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Epidemiology Bulletin
Test for Antibodies to the HTLV-III Virus

Fact Sheet for Blood Donors and Other Concerned Individuals

What is AIDS?
Acquired immunodeficiency syndrome (AIDS) is a serious disease which reduces the body’s ability to fight infection. Over the past several years increasing numbers of persons in certain high-risk groups developed the disease, and by early 1985 about 9,000 cases had been reported. During 1984, a virus (HTLV-III) was discovered which is the cause of AIDS, and a test was developed to detect antibodies to the virus. More detailed information about AIDS is available in Facts About AIDS, which is provided by the U.S. Public Health Service.

What Is the Antibody Test?
When a person is infected by a virus, the body’s white blood cells normally begin to fight the infection by producing substances called antibodies. Antibodies can therefore be used to indicate whether or not a person has been infected by a virus. Research has shown that antibodies to the HTLV-III virus are usually found in the blood of persons who have AIDS or AIDS-related conditions, and in many people who are members of groups at increased risk for AIDS. However, a negative antibody test does not guarantee that a person is free of the virus, especially if he or she is a member of a group at increased risk for AIDS. Antibodies may not have developed if exposure to the virus was recent. That is why it is very important for members of groups at increased risk for AIDS to continue to refrain from donating blood or plasma. It is also possible that other factors, including other viruses, could cause the test to be positive even though the person was never infected with HTLV-III.

What Is the Antibody Test Being Used For?
Until recently, the antibody test was limited to use in research to gain a better understanding of AIDS as an infectious disease. For example, some of those studies showed that 68% to 100% of patients with AIDS had been exposed to the HTLV-III virus. During the past year, commercially available tests for HTLV-III antibody were being developed, and such tests were recently approved by the Food and Drug Administration. The primary purpose of these antibody tests is to screen blood which is donated for use in transfusion and in the production of other blood products.

Why Is the Antibody Test Being Used to Screen Blood?
Because a positive antibody test means that a person may have been infected by the HTLV-III virus, it is now possible to use the test to identify blood which should not be used for transfusion. By not using blood from people who may have been infected by HTLV-III, we believe that transfusions will be even safer than they are now.

What Does a Positive Antibody Test Mean?
The most important thing to understand is that the antibody test is NOT a test for AIDS, and that a positive test does NOT mean that the person definitely will develop AIDS. The test does provide an extra safety check on blood so that the risk of getting AIDS from transfusions will be even lower than it already is. As with many other blood tests, there will be some people who have test results which are called “false-positives”; that is, for some reason the test indicates that HTLV-III antibody is present when, in fact, it is not really HTLV-III antibody which is causing the test to register positive. For this reason it is especially important for persons with positive antibody tests to have follow-up tests to try to determine whether or not the screening test really means that HTLV-III antibody is present.

Based on what is known so far, probably only a small proportion of people infected with the virus will develop AIDS. In fact, many infected people may not develop any illness at all. But there is no information at the present time to be able to predict which persons with the antibodies are more likely or less likely to develop AIDS-related conditions or AIDS itself. For that reason, follow-up medical evaluations are strongly recommended.

A Special Note to Persons Who May Be At Increased Risk for AIDS

It is vital to the safety of the blood supply that persons who are in groups at increased risk for AIDS continue to follow the U.S. Public Health Service recommendations and to voluntarily refrain from donating. These groups are: 1) anyone who has AIDS or one of its signs and symptoms; 2) males who have had sex with more than one male since 1979, and males whose sexual partner has had sex with more than one male since 1979; 3) past or present abusers of intravenous drugs; 4) Haitians who entered the USA after 1977; 5) hemophiliacs; and 6) sexual partners of persons in these groups.

Even though we are now testing blood for antibodies to the HTLV-III virus, the test will not detect all people who may be carriers of the virus because not everyone who is infected with the virus will have antibodies. If you think you are at increased risk for AIDS, or that you may have been exposed to the virus, DO NOT DONATE BLOOD even if you feel perfectly healthy. There is a possibility that antibody for the virus may not be detected when your blood is tested even though you may have been infected. If that were to happen, the blood would be used to treat patients who would then be at risk for infection by HTLV-III and for AIDS.

March, 1985
Information for Persons Who Have a Positive Test for HTLV-III Antibody

A positive HTLV-III antibody test does not always mean that a person has been infected by the virus which causes acquired immunodeficiency syndrome (AIDS). Positive tests in blood and plasma donors may be caused by other things, and that is why a follow-up medical evaluation is important in order to get a better understanding of the meaning of your test results. Your doctor is in the best position to decide what additional tests, if any, need to be done. It is important that you have as open and frank a discussion as possible regarding any possible exposures that you may have had to the virus, so that your physician can make the best evaluation.

Until your doctor has made a medical evaluation, it is best to be cautious, even though you have no symptoms, and to assume that you may have been exposed to the virus, that you may be contagious, and that you might unknowingly spread the virus to others. You will want to take responsible steps to prevent the possibility of spreading the virus to other people, especially your family and close contacts.

Do’s and Don’ts

A. Do not donate blood or plasma, sperm, body organs, or other tissues.
B. You should let your doctor and dentist know that you have a positive HTLV-III antibody test so that they can do their best in caring for you and in preventing spread of the virus.
C. Limit your sexual contacts, and be frank with your sexual partner(s) about steps you are taking to prevent the spread of the virus. Using a condom may help in this regard.
D. Sexual practices in which exchange of body fluids such as semen takes place should be avoided.
E. Virus has been found in saliva of some infected people, and it is possible that it could be transmitted by open-mouthed, or “French,” kissing and by oral sex.
F. There is no evidence that the virus can be spread through casual kissing or other casual social contacts such as hugging. Such contacts with other people at work or in the community do not need to be modified.
G. Toothbrushes, razors, or other implements that could become contaminated with blood should not be shared.
H. If you are a drug user:
   1. Limit your drug use.
   2. Do not let others use needles you have used and do not use someone else’s needles.
   3. Do not leave your “works” around where others might pick up needles.
I. If you are a woman with a positive antibody test or the sexual partner of a man with a positive antibody test, it would be advisable to avoid pregnancy or to postpone pregnancy until more is learned. Some infants have developed AIDS from their infected mothers.
Continued from page 4

The majority of exposures occurred in direct patient-care areas; 187 (52%) occurred in patients' rooms or on the wards; 99 (27%), in intensive-care units; and seven (2%), in emergency clinics. Thirty-two (9%) incidents took place in laboratories, and 36 (10%) occurred in operating or procedure rooms and morgues. The types of exposures were: needlestick injuries (68%); mucosal exposures (13%); cuts with sharp instruments (10%); and contamination of open skin lesions with potentially infected body fluids (9%). Eighty-eight percent of the exposures were to blood or serum; 6%, to saliva; 2%, to urine; and the remaining 4%, to other body fluids or unknown sources. Postexposure care varied considerably. Forty-eight percent of exposed HCWs received either no specific treatment or local wound care only, while 35% received immune globulin either alone or in combination with other treatment.

Complete epidemiologic data have been collected on 226 of the patients to whom these HCWs were exposed. Two hundred nine (92%) were AIDS patients meeting the CDC surveillance definition, and 17 (8%) were suspected AIDS cases. Two hundred three (97%) of the 209 AIDS patients were in an identified risk group for acquiring AIDS. The distribution of the AIDS cases by disease category included: Pneumocystis carinii pneumonia (PCP), 62%; Kaposi's sarcoma (KS), 12%; both KS and PCP, 5%; and other opportunistic infections, 21%.

Tests for T-cell subsets have been performed at CDC on blood specimens from 269 (75%) of the exposed HCWs. The mean T-helper/T-suppressor (Th/Ts) ratio for the initial whole blood sample from these HCWs was 2.2 with a range of 0.4-5.4 (normal range 1.0-3.9). One hundred eighty-three (68%) of these initial blood specimens were obtained within 180 days from the dates of exposures. Six-month and 12-month follow-up Th/Ts ratios were performed on 69 and six of these 269 HCWs, respectively. All Th/Ts ratios on follow-up specimens were within the normal range, including those from nine HCWs whose initial ratios were less than 1.0.

Serologic testing using the enzyme-linked immunosorbent assay (1) and the Western blot technique (2) for antibody to the human T-lymphotropic virus type III (HTLV-III) has been done, with specific informed consent, on 40 HCWs enrolled in the surveillance system. The mean duration between the date of exposure and the latest serum sample tested was 10.5 months (range 0-29 months; median 8.5 months). The types of exposures included: needlestick injuries (29), cuts with sharp objects (five), mucosal exposures (five), and contamination of open skin lesions (five). None of the HCWs tested were HTLV-III-antibody positive. However, with a sample size of 40, the upper limit of the 95% confidence intervals for this incidence of seropositivity (0%) is 7%.

Editorial Note: Because HTLV-III can be transmitted among intravenous drug abusers by sharing needles and through transfusion of blood and blood products, there is concern that HTLV-III could be transmitted to

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**Acquired Immune Deficiency Syndrome**

**Cases (N = 80) by Age Group**

**Virginia 1982-1985**

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Continued from page 7

HCWs by unintentional needlestick or other parenteral or mucous-membrane exposures. A recent report describes an HCW in England who is believed to have developed HTLV-III antibody following parenteral exposure to the blood of an AIDS patient (3). The HCW reportedly had none of the recognized risk factors for AIDS and remains asymptomatic.

To date, there are no reported cases of AIDS among HCWs in the United States that can be linked to a specific occupational exposure. Of the 8,218 AIDS patients reported to CDC as of February 11, 1985, 278 (3%) have been HCWs. All but 24 (9%) of these HCWs belong to known AIDS risk groups. Epidemiologic investigations have been completed on 17 of these 24 HCWs; four are currently under investigation, and three died before investigations were completed. In six of the 17 completed investigations, non-occupational exposures were the most likely sources of infection. No known risk factors for infection were identified in the remaining 11 patients; however, specific occupational exposures to definite or suspected AIDS patients could not be documented.

In December 1984, CDC began testing sera from HCWs enrolled in the surveillance system for antibody for HTLV-III. Testing was performed only with the specific informed consent of enrolled personnel and the agreement of cooperating investigators. Initial results from this analysis and from other similar investigations (4) suggest the risk of transmission of HTLV-III infection from AIDS patients to HCWs may be very small. Thus, to accurately determine the true risk of transmission of HTLV-III from AIDS patients to HCWs, large cohorts of exposed HCWs must be studied. Additional studies with larger cohorts of HCWs are in progress, the CDC will continue immunologic and serologic testing of HCWs from whom institutional investigators have obtained informed consent.

Studies of seroprevalence of HTLV-III among exposed HCWs are of great value from an epidemiologic perspective. However, serologic testing of asymptomatic HCWs for HTLV-III antibody should be done only with informed consent, and a mechanism should exist for transmitting the test results to the HCW in an appropriate manner. The U.S. Public Health Service has developed specific recommendations for individuals, within or outside known risk groups for AIDS, who test positive for HTLV-III antibody (5-7). Health-care professionals should become familiar with and consider these recommendations when serologic testing of asymptomatic HCWs for HTLV-III antibody is contemplated.

Until additional data are available, HCWs should continue to follow previously published precautions when caring for persons with definite or suspected AIDS or when handling specimens from these patients (8,9).

References

HTLV-III Antibody Testing by The State Laboratory

At the present time, the HTLV-III antibody test is intended to serve as a screening tool for protecting the nation’s blood supply. Research into this test’s possible utility as a clinical or epidemiologic tool is ongoing. Until the results of such research are available, however, it is realized that there will be a limited need for the State Laboratory (Division of Consolidated Laboratory Services, Department of General Services) to serve as a reference facility for HTLV-III antibody testing. Arrangements are being made to perform such testing, to begin when funds are identified for performing these tests. Only requests from physicians will be honored. If a physician requests that the test be performed, he should submit a brief history and physical findings about the individual so that the laboratory can determine what priority the request should be given. Physicians are strongly discouraged from testing contacts of AIDS patients. Referrals from non-physicians will not be accepted, with the exception of blood banks. A referral from a blood bank will be accepted if a repeat screening test on the same specimen has been found positive.

Continued from page 8
7. CDC. Provisional Public Health Service interagency recommendations for screening donated blood and plasma for antibody to the virus causing acquired immunodeficiency syndrome. MMWR 1985;34:1-5.

Influenza Surveillance
Reports by Sentinel Physicians (N = 30)
Virginia 1984-1985

Cases of influenza-like illness reported by 30 sentinel physicians peaked during the last week of February. The outbreak subsequently subsided during March. The only influenza virus strain isolated in Virginia this season was A(H3N2).

March, 1985
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<td>Other</td>
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**Counties Reporting Animal Rabies:** Augusta 1 bovine, 1 fox; Fauquier 2 raccoons; Louisa 1 raccoon, 1 skunk; Orange 1 skunk; Rockingham 1 skunk; Shenandoah 2 raccoons; Arlington 1 raccoon; Fairfax 3 raccoons; Loudoun 3 raccoons, 1 skunk; Louisa 1 raccoon; Prince William 1 raccoon; Lee 1 skunk; Washington 2 skunks; Henrico 1 bat

**Occupational Illnesses:** Pneumoconiosis 29; Carpal tunnel syndrome 18; Silicosis 7; Asbestosis 6; Hearing loss 3; Poisoning, carbon monoxide 2; Byssinosis 1

*other than meningococcal

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