# Manual for the Surveillance of Vaccine-Preventable Diseases

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

**5th Edition, 2012**

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# Manual for the Surveillance of Vaccine-Preventable Diseases

## 5th Edition, 2012

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**This manual is not intended to be a therapeutic guide; therefore, while dosages of antimicrobials and immunobiologics are discussed in the context of prophylaxis and treatment for case-patients and contacts, physicians and other health-care professionals should review the package inserts prepared by the manufacturers to determine appropriate dosages.**

**This manual is designed to provide general guidance regarding surveillance activities for vaccine-preventable diseases. Because recommendations for use of vaccines may change, readers should consult their local or state health departments or CDC's Vaccines website at http://www.cdc.gov/vaccines/.**

**Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Public Health Service or the U.S. Department of Health and Human Services.**

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# Introduction

This manual was first developed in 1996 to provide general guidance to state and local health department personnel who are involved in surveillance activities for vaccine-preventable diseases. This manual answers commonly asked questions regarding the surveillance and reporting of vaccine-preventable diseases and provides information on enhancing existing surveillance systems.

Several reference documents, tables, and worksheets have been included in this manual for your convenience and information. The worksheets in this manual are in the public domain and may be copied and distributed for use in public health surveillance activities.

Please forward any suggestions and comments regarding this manual to:

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# Acronyms

| | |
|---|---|
| ACIP | Advisory Committee on Immunization Practices |
| APHL | Association of Public Health Laboratories |
| CDC | Centers for Disease Control and Prevention |
| CF | Complement fixation |
| CMV | Cytomegalovirus |
| CPHA | Commission on Professional and Hospital Activities |
| CRS | Congenital rubella syndrome |
| CSF | Cerebrospinal fluid |
| CSTE | Council of State and Territorial Epidemiologists |
| DAT | Diphtheria antitoxin |
| DFA | Direct fluorescent antibody |
| DHHS | Department of Health and Human Services |
| DRSP | Drug-resistant *Streptococcus pneumoniae* |
| DT | Diphtheria and tetanus toxoids |
| DTP | Diphtheria and tetanus toxoids and whole-cell pertussis vaccine |
| DTaP | Diphtheria and tetanus toxoids and acellular pertussis vaccine |
| EBV | Epstein-Barr virus |
| EIA | Enzyme-immunoassay |
| ELISA | Enzyme-linked immunosorbent assay |
| ELR | Electronic laboratory reporting |
| FAMA | Fluorescent antibody to membrane antigen |
| FDA | Food and Drug Administration |
| HA | Hemagglutinin |
| HAV | Hepatitis A virus |
| HBcAg | Hepatitis B core antigen |
| HBIG | Hepatitis B immune globulin |
| HBeAg | Hepatitis B e antigen |
| HBsAg | Hepatitis B surface antigen |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HDV | Hepatitis D virus |
| HI | Hemagglutination inhibition |
| Hi | *Haemophilus influenzae* |
| Hib | *Haemophilus influenzae* type b |
| HMO | Health maintenance organization |
| IFA | Indirect fluorescent antibody |
| IG | Immune globulin |
| IOM | Institute of Medicine |
| IPV | Inactivated poliovirus vaccine |
| LA | Latex agglutination |
| MMR | Measles-mumps-rubella vaccine |
| MMWR | Morbidity and Mortality Weekly Report |
| MR | Measles-rubella vaccine |
| MSAEFI | Monitoring System for Adverse Events Following Immunization |
| NA | Neuraminidase |

| | |
|---|---|
| NCCLS | National Committee for Clinical Laboratory Standards |
| NCHS | National Center for Health Statistics |
| NCIRD | National Center for Immunization and Respiratory Diseases |
| NCRSR | National Congenital Rubella Syndrome Registry |
| NCVIA | National Childhood Vaccine Injury Act of 1986 |
| NEDSS | National Electronic Disease Surveillance System |
| NETSS | National Electronic Telecommunications System for Surveillance |
| NHANES | National Health and Nutrition Examination Survey |
| NHIS | National Health Interview Survey |
| NNDSS | National Notifiable Diseases Surveillance System |
| NVICP | National Vaccine Injury Compensation Program |
| OPV | Oral poliovirus vaccine |
| P&I | Pneumonia and influenza |
| PCR | Polymerase chain reaction |
| PHA | Passive hemagglutination |
| RASH | Rapid Surveillance Helper |
| RET | Reportable Events Table |
| RIA | Radioimmunoassay |
| SIDS | Sudden Infant Death Syndrome |
| SHC | State health coordinator |
| SPSS | Supplementary Pertussis Surveillance System |
| TIG | Tetanus immune globulin |
| TT | Tetanus toxoid |
| VAE | Vaccine adverse event |
| VAERS | Vaccine Adverse Event Reporting System |
| VAPP | Vaccine-associated paralytic poliomyelitis |
| VHSP | Viral Hepatitis Surveillance Program |
| VPD | Vaccine-preventable disease |
| VZIG | Varicella-zoster immune globulin |
| VZV | Varicella-zoster virus |
| WBC | White blood-cell count |
| WHO | World Health Organization |

# Definitions of Terms

| | |
|---|---|
| **Attenuated virus** | A strain of virus whose virulence has been lowered by physical or chemical processes or by repeated passage through the cells of another species. |
| **Breakthrough** | The appearance of clinical disease in an individual who has previously been vaccinated against the agent causing the disease. |
| **Clinically compatible case** | A case featuring a clinical syndrome generally compatible with the disease, but for which specific clinical criteria may not have been met unless they are noted in the case classification. |
| **Confirmed case** | A case that is classified as confirmed for reporting purposes. |
| **Contraindication** | A characteristic or attribute of an individual that may be temporary or permanent that prohibits the administration of a drug, vaccine, or other therapeutic intervention. |
| **Encephalitis** | An inflammatory condition of brain tissue caused by a variety of infectious and non-infectious diseases. In varicella, influenza, and measles, this is sometimes referred to as post-infectious encephalitis. |
| **Epidemiologically linked case** | A case in which the patient has or has had contact with one or more persons who have or have had the disease, and transmission of the agent by the usual modes of transmission is plausible. In general, a case may be considered epidemiologically linked to a laboratory-confirmed case if at least one case in the chain of transmission is laboratory confirmed. |
| **Erythema** | Redness (or inflammation) of the skin or mucous membranes that is the result of dilation and congestion of superficial capillaries. |
| **Exanthem** | A skin eruption or rash that may have specific diagnostic features of an infectious disease. Chickenpox, measles, roseola infantum, rubella, and smallpox are usually characterized by a particular type of exanthem. |
| **Immunocompromised** | A state in which an individual has either a decreased or absent ability to mount an antibody and/or cell-mediated immune response to infectious agents. |
| **Incubation period** | The period of time from exposure to an infecting agent to the onset of symptoms of disease. |
| **Laboratory confirmed case** | A case that is confirmed by one or more of the laboratory methods listed in the case definition under “Laboratory criteria.” Although other laboratory methods may be used in clinical diagnosis, only those listed are accepted for laboratory confirmation for reporting purposes. |
| **Line listing** | A tool used during epidemiologic investigations to allow investigators to record case information and to review and follow up case reports or conduct data analysis. |
| **Meets the clinical case definition** | Meets precisely the clinical case definition. Although in clinical practice the diagnosis may be made with the use of other criteria, for reporting purposes the stated criteria must be met. |
| **Primary vaccine failure** | The absence of seroconversion after vaccination. This is manifest as the occurrence of disease in a vaccinated individual in which the disease occurrence closely resembles that found in natural infection with wild-type virus, i.e., more commonly moderate or severe disease. |
| **Probable case** | A case that is classified as probable for reporting purposes. |
| **Secondary vaccine failure** | Loss of immunity acquired after vaccination. |
| **Sentinel event** | A preventable disease, disability, or untimely death that serves as a warning signal of a possible underlying problem. |
| **Sentinel surveillance** | Activities focused on monitoring key health indicators in the general population or in special populations. The primary intent is to obtain timely information needed for public health or medical action in a relatively inexpensive manner rather than to derive precise estimates of prevalence or incidence in the general population. |

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|---|---|
| **Supportive laboratory results** | Specified laboratory results consistent with the diagnosis but not meeting the criteria for laboratory confirmation. |
| **Susceptible** | Being sensitive to effects of an infectious disease, allergen, or other pathogenic agent; lacking immunity or resistance. |
| **Thermolability** | A characteristic of vaccines that cause them to lose potency when stored or held at temperatures other than that recommended by the manufacturer. |
| **Vaccine coverage** | The proportion or percentage of persons that have received a vaccine among all individuals in a particular group who are eligible to receive the vaccine. |
| **Vaccine effectiveness** | The ability of a vaccine to provide protection against disease when used under field conditions (e.g., use of the vaccine in routine practice). |
| **Vaccine efficacy** | The ability of a vaccine to provide protection against disease under ideal circumstances (e.g., during a clinical trial). |

# Chapter 1: Diphtheria

*Tejpratap S.P. Tiwari, M.D.*

## I. Disease Description

Diphtheria is an uncommon disease in the United States. It is caused by infection with toxigenic strains of gram-positive *Corynebacterium diphtheriae*. Important sites of infection are the respiratory mucosa (respiratory diphtheria) and the skin (cutaneous diphtheria). Rarely, extra-respiratory mucosal sites, e.g., the eye, ear, or genitals, may be affected. Humans are the only known reservoir of *C. diphtheriae*. The disease is transmitted from person to person by respiratory droplets or direct contact with respiratory secretions, discharges from skin lesions or, rarely, fomites.

The onset of respiratory diphtheria is insidious and begins after an incubation period of 2–5 days. Initial symptoms of illness include a sore throat, difficulty in swallowing, malaise, and low-grade fever. The hallmark of respiratory diphtheria is the presence of an exudate that organizes into a tough, grayish-white pseudomembrane over the tonsils, the pharynx, or larynx. The pseudomembrane is strongly adherent to the underlying tissue, and attempts to dislodge it usually result in bleeding. Accompanying inflammation of the cervical lymph nodes and surrounding soft-tissue swelling of the neck give rise to a "bull-neck" appearance and are signs of moderate to severe disease. The membrane may progressively extend into the larynx and trachea and cause airway obstruction, which, if left untreated, can be fatal. Absorption of diphtheria toxin from the site of infection can cause systemic complications, including damage to the myocardium, nervous system and kidneys. Untreated respiratory diphtheria usually lasts for one to 2 weeks, but complications can persist for months. The case-fatality rate is about 10%. Nontoxigenic strains of *C. diphtheriae* may cause a mild sore throat and, rarely, a membranous pharyngitis, but these strains can be invasive and cause bacteremia and endocarditis.[1] Isolation of nontoxigenic strains of *C. diphtheriae* from the throat does not necessarily indicate a pathogenic role in the illness. A small percentage of the population may carry nontoxigenic or toxigenic strains of *C. diphtheriae* without disease symptoms, but the frequency at which this occurs is unknown.

Cutaneous diphtheria, caused by either toxigenic or nontoxigenic strains of *C. diphtheriae*, is usually mild, typically consisting of nondistinctive sores or shallow ulcers, and rarely causes toxic complications (1%–2% of infections with toxigenic strains). Since 1980, cutaneous diphtheria has not been a nationally reportable disease.

Rarely, other *Corynebacterium* species (*C. ulcerans* or *C. pseudotuberculosis*) may produce diphtheria toxin. Toxigenic *C. ulcerans* may cause classic respiratory diphtheria-like illness.[2, 3] Both species may cause disease in animals.

## II. Background

Although diphtheria is now reported only infrequently in the United States, in the prevaccine era, the disease was one of the most common causes of illness and death among children. Since the introduction and widespread use of vaccines containing diphtheria toxoid (formalin-inactivated diphtheria toxin) beginning in the 1920s and 1930s and universal childhood immunization in the late 1940s, diphtheria has been well controlled in the United States. In the 1970s, diphtheria was endemic in the Southwest, the Northern Plains, and the Pacific Northwest. The last major outbreak was in Seattle, Washington, in the 1970s.[4] In recent years, some cases in the United States have been related to importation.[5–7] From 1980 to 2010, 55 cases of diphtheria were reported to CDC's National Notifiable Diseases Surveillance System. The majority of cases (77%) were among persons 15 years of age or older. Four of the five fatal cases occurred among unvaccinated children; the fifth fatal case was in a 75-year-old male returning to the United States from a country with endemic disease.[5, 6] Although few cases of respiratory diphtheria have been reported in the United States in the past 2 decades, enhanced surveillance in a previously endemic-disease area—a Northern Plains Indian community—has shown ongoing circulation of toxigenic *C. diphtheriae*.[8] Similarly, endemic circulation of toxigenic *C. diphtheriae* strains has also persisted in some communities in Canada.[9]

Diphtheria remains endemic in many parts of the developing world, including some countries of the Caribbean and Latin America, Eastern Europe, Southeast Asia, and Africa. In the 1990s, a large epidemic of diphtheria occurred in the former Soviet Union where diphtheria had previously been well controlled and this renewed interest in the factors associated with persistent circulation of toxigenic *C. diphtheriae*.[10, 11] During the past decade, many developing countries have achieved high childhood immunization coverage with DTP/DTaP vaccine resulting in significant reduction in diphtheria incidence.[12] However, sporadic cases and outbreaks still occur among population subgroups.[10–12] A feature of these outbreaks is that the majority of cases have occurred among adolescents and adults instead of children. Many of these adolescents and adults had not received routine childhood vaccination or booster doses of diphtheria toxoid. Rarely, outbreaks occur in well-vaccinated populations with intense exposure to toxigenic *C. diphtheriae*, but disease is usually mild and with fewer complications and no fatalities.[13]

## III. Importance of Rapid Identification

Prompt recognition and reporting of the disease is important to ensure early, appropriate treatment with diphtheria antitoxin; to obtain necessary laboratory specimens before antibiotic or antitoxin treatment; to identify and evaluate contacts; and to provide necessary antimicrobial prophylaxis to prevent further spread. The outcome of diphtheria infection improves with early, appropriate treatment.

## IV. Importance of Surveillance

About half of U.S. adults are estimated to have levels of diphtheria toxin antibodies below the lower limit of protection (0.01 IU/ml). This is because immunity to diphtheria wanes with time after vaccination, and many older adults may not have received either a primary vaccination series or a recommended tetanus-diphtheria toxoid (Td) booster every 10 years. In 1996, endemic transmission of *C. diphtheriae* was documented in a Northern Plains state.[8] Persons traveling to the United States from countries where diphtheria is endemic may import the disease. Therefore, continued awareness of diphtheria is needed and enhanced surveillance is particularly important in areas in which diphtheria was endemic in the 1970s.[8]

The source of infection for persons with diphtheria may be asymptomatic carriers (persons infected with *C. diphtheriae* bacteria in the nose and/or throat but who do not have disease symptoms). Carriers often augment the spread of the bacteria to other persons.

Surveillance, prompt investigation, and treatment of case-patients and close contacts help to halt the spread of disease. Information obtained through surveillance is used to characterize infected persons or areas so that additional intervention efforts can be focused to reduce disease incidence.

## V. Disease Reduction Goals

Since 2003, no case of diphtheria was reported in the United States and the *Healthy People 2010* goal to eliminate indigenous diphtheria among persons younger than 35 years of age in the U.S. was achieved.[14]

## VI. Case Definition

The following case definition for diphtheria was revised by the Council of State and Territorial Epidemiologists (CSTE) and published in 2010.[15]

**Probable:** In the absence of a more likely diagnosis, an upper respiratory tract illness with an adherent membrane of the nose, pharynx, tonsils, or larynx; and absence of laboratory confirmation; and lack of epidemiologic linkage to a laboratory-confirmed case of diphtheria.

**Confirmed:** An upper respiratory tract illness with an adherent membrane of the nose, pharynx, tonsils, or larynx; and any of the following: isolation of *Corynebacterium diphtheriae* from

the nose or throat; or histopathologic diagnosis of diphtheria; or epidemiologic linkage to a laboratory-confirmed case of diphtheria.

**Comment:** Cutaneous diphtheria should not be reported. Respiratory disease caused by nontoxigenic *C. diphtheriae* should be reported as diphtheria. All diphtheria isolates, regardless of association with disease, should be sent to the Diphtheria Laboratory, National Center for Immunization and Respiratory Diseases (NCIRD), CDC.

Rarely, respiratory diphtheria-like illness may result from infection with toxigenic *C. ulcerans*. *C. pseudotuberculosis* may also produce a diphtheria toxin but usually causes infection in non-respiratory sites. All Isolates of *C. diphtheriae*, *C. ulcerans*, and *C. pseudotuberculosis* should also be forwarded to CDC.

An epidemiologically linked case is one in which the patient has had contact with one or more persons who have or had the disease, and transmission of the agent by the usual modes of transmission is plausible. A case may be considered epidemiologically linked to a laboratory-confirmed case if at least one case in the chain of transmission is laboratory confirmed.

## VII. Laboratory Testing

Diagnostic tests used to confirm infection include isolation of *C. diphtheriae* by culture and toxigenicity testing. Although no other tests for diagnosing diphtheria are commercially available, CDC can perform a polymerase chain reaction (PCR) test on clinical specimens to confirm infection with a toxigenic strain. The PCR assay allows for detection of the regulatory gene for toxin production (dtxR) and the diphtheria toxin gene (tox).[16] PCR is particularly useful if nonviable *C. diphtheriae* organisms are present in clinical specimens that are obtained from a patient after antibiotic therapy has been initiated. The state health department should be contacted to report a suspected case and to arrange for laboratory testing.

Although, as performed by the CDC Diphtheria Laboratory, PCR provides supportive evidence for the diagnosis, data are not yet sufficient for PCR to be accepted as a criterion for laboratory confirmation. A case that is PCR positive without isolation of the organism or histopathologic diagnosis and without epidemiologic linkage to a laboratory-confirmed case should be classified as a probable case.

For additional information on laboratory testing for confirmation of diphtheria, see Chapter 22, "Laboratory Support for the Surveillance of Vaccine-Preventable Diseases."

***Note:*** *Other pathogens can cause a membrane in the throat and over the tonsils, including Streptococcus spp., Epstein-Barr virus and cytomegalovirus (both of which cause infectious mononucleosis syndrome), Arcanobacter hemolyticum, Candida albicans, fusiform bacteria (can cause Vincent's angina), and some viruses. The patient's healthcare provider should be encouraged to perform appropriate laboratory tests to rule out these conditions and organisms.*

### *Isolation of* C. diphtheriae *by culture*

Isolation of *C. diphtheriae* by culture is essential for confirming diphtheria. However, even if the patient's culture is negative, isolation of *C. diphtheriae* from close contacts may help confirm the diagnosis of the case. Clinical specimens for culture should be taken from the nose or nasopharynx, and throat from all persons with suspected cases and their close contacts. If possible, swabs also should be taken from beneath the membrane, or a piece of the membrane should be removed. Specimens for culture should be obtained as soon as diphtheria (involving any site) is suspected, even if treatment with antibiotics has already begun. For more information on collection of clinical specimens, see Appendix 1. The laboratory should be alerted to the suspicion of diphtheria because isolation of *C. diphtheriae* requires special culture media containing tellurite.

### *Toxigenicity testing and biotyping*

After *C. diphtheriae* has been isolated, biotyping should be performed to determine the biotype (intermedius, belfanti, mitis, or gravis), and toxigenicity testing using the Elek test should be done to determine whether the organisms produce diphtheria toxin. Demonstration of toxin

production confirms a case as diphtheria. Note that PCR does not demonstrate production of diphtheria toxin but only detection of the diphtheria toxin gene. A positive PCR test in the absence of a positive culture does not meet the laboratory criteria for classifying a case as confirmed diphtheria. Elek and PCR tests are not readily available in many clinical microbiology laboratories; isolates should be sent to a reference laboratory proficient in performing the tests.

### *Polymerase chain reaction (PCR) testing*

Isolation of *C. diphtheriae* may not always be possible because many patients will have received antibiotics before a diagnosis of diphtheria is considered. PCR allows for detection of the regulatory gene for toxin production (dtxR) and the diphtheria toxin gene (tox) on nonviable organisms. Additional clinical specimens for PCR testing at CDC should be collected when specimens are being collected for culture. Clinical specimens (nasal and throat swabs, pieces of membrane, biopsy tissue) can be transported to CDC with cold packs in a sterile empty container or in silica gel sachets. For detailed information on collection and shipping of specimens, and for arranging PCR testing, the state health department may contact the CDC Diphtheria Laboratory (404-639-1231).

### *Serologic testing*

Measurement of the patient's serum antibodies to diphtheria toxin before administration of antitoxin may help in assessing the probability of the diagnosis of diphtheria. The state health department or CDC can provide information on laboratories that offer this test (few laboratories have the capability to accurately test antibody levels). If antibody levels are less than 0.01 IU/ml, immunity is likely to be absent, but a level of greater than 0.1 IU/ml is considered protective and diphtheria is unlikely to be the cause of the patient's illness. Diphtheria antibody levels between 0.01 IU/ml and 0.09 IU/ml indicate the presence of some or limited immunity.

### *Submission of* C. diphtheriae *isolates*

All isolates of *C. diphtheriae*, whether toxigenic or nontoxigenic, regardless of association with disease, and from any anatomic site (respiratory, cutaneous, or other) should be sent to the CDC Diphtheria Laboratory, CDC, for reference testing. To arrange specimen shipping, the state health department should be contacted.

### *Submission of isolates of other* Corynebacterium *species*

Infrequently, other diphtheria toxin-producing *Corynebacterium* species (e.g., *C. ulcerans* or *C. pseudotuberculosis*) may be isolated from patients. Such isolates should also be sent to the CDC laboratory (404-639-1231).

## VIII. Reporting

Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[17] These regulations and laws list the diseases that are to be reported, and describe those persons or groups who are responsible for reporting, such as health-care providers, hospitals, laboratories, schools, daycare and childcare facilities, and other institutions. Persons reporting these conditions should contact their state health department for state-specific reporting requirements.

### *Reporting to CDC*

Suspected diphtheria cases should be reported promptly by telephone to the CDC Emergency Operations Center (770-488-7100) so that diphtheria antitoxin can be obtained for the patient. An FDA-licensed diphtheria antitoxin product is no longer available commercially in the United States. However, diphtheria antitoxin is available from CDC under an Investigational New Drug (IND) protocol[18] (See Section X, "Treatment," for contact information), additional epidemiologic and clinical data are needed as requirements under the IND.

The healthcare provider should notify the state health department promptly so that an epidemiologic investigation can be initiated. Reports of probable and confirmed cases should be forwarded by the state health department to the National Notifiable Disease Surveillance System (NNDSS) via the National Electronic Telecommunications System for Surveillance (NETSS)

or National Electronic Disease Surveillance System (NEDSS). Reporting should not be delayed because of incomplete information or lack of laboratory confirmation.

Respiratory disease caused by nontoxigenic *C. diphtheriae* should be reported as diphtheria. Rarely, respiratory diphtheria-like illness may result from infection with other *Corynebacterium* species (e.g., *C. ulcerans*, *C. pseudotuberculosis*). Such cases should also be reported to CDC.

Cutaneous diphtheria is no longer notifiable, and these cases should not be reported to NNDSS.

### *Information to collect*

The following data are epidemiologically important and should be collected in the course of case investigation. Additional information may also be collected at the direction of the state health department.

- Demographic information
  - Name
  - Address
  - Date of birth
  - Age
  - Sex
  - Ethnicity
  - Race
  - Country of birth
  - Length of time in United States
- Reporting Source
  - County
  - Earliest date reported
- Clinical
  - Hospitalizations: dates and duration of stay
  - Date of illness onset
  - Site of infection (e.g., nose, throat, larynx)
  - Symptoms (e.g., fever, sore throat)
  - Signs (e.g., neck edema, stridor, tachycardia)
  - Complications (e.g., myocarditis, neuritis)
  - Outcome (patient survived or died)
    - Date of death
    - Postmortem examination results
    - Death certificate diagnoses
- Treatment
  - Date of administration of antitoxin
  - Number of units of antitoxin given
  - Antibiotics given
  - Antibiotic dosage given
  - Duration of therapy
- Laboratory
  - Culture
  - Biotype and toxigenicity test
  - PCR
  - Molecular typing

- Vaccine information
  - Dates and types of diphtheria vaccination
  - Number of doses of diphtheria toxoid received
  - Manufacturer name
  - Vaccine lot number
  - If not vaccinated, reason
- Epidemiologic
  - Contact with a probable or confirmed case
  - Contact with immigrants or returning travelers from endemic-disease areas
  - Number of contacts cultured
  - Results of contact cultures
  - Local or international travel history: 6-week period before illness onset or date of presentation
  - Contact with domestic pets, horses, or dairy farm animals

## IX. Vaccination

Primary diphtheria immunization with diphtheria-tetanus toxoids-acellular pertussis vaccine (DTaP) is recommended for all persons at least 6 weeks old but less than 7 years of age and without a history of contraindications. DTaP is the preferred vaccine for all doses in the infant and childhood vaccination series (including completion of the series for children who have received one or more doses of whole-cell DTP). The primary vaccination with DTaP series consists of a three-dose series, administered at ages 2, 4, and 6 months, with a minimum interval of 4 weeks between doses. The fourth (first booster) dose is recommended at 15–18 months of age to maintain adequate immunity during preschool years. The fourth dose should be administered at least 6 months after the third. If the interval from the third dose is 6 months or greater and the child is unlikely to return for a visit at the recommended age, the fourth dose of DTaP may be administered as early as age 12 months. The fifth (second booster) dose is recommended for children aged 4–6 years to confer continued protection against disease during the early years of schooling. A fifth dose is not necessary if the fourth dose in the series is administered on or after the fourth birthday.[19]

Adolescents 11–18 years of age should receive a single dose of Tdap instead of Td for booster immunization against tetanus, diphtheria, and pertussis if they have completed the recommended childhood DTP/DTaP vaccination series. Thereafter, routine booster doses of Td vaccine should be given at 10-year intervals. Adolescents and adults who have never been vaccinated against diphtheria should receive a primary series of three doses of Td. The first two doses should be administered at least 4 weeks apart, and the third dose 6–12 months after the second dose. For added protection against pertussis, Tdap can substitute for any one dose in the 3-dose primary series. Td is preferred to TT for adults as part of wound management if the last dose of Td was received five or more years earlier. Up-to-date vaccination against diphtheria is especially important for travelers who will be living or working with local populations in countries where diphtheria is endemic.[20]

For added protection against pertussis, adults 19 years and older should receive a single dose of Tdap (ADACEL®, BOOSTRIX®) to replace a single routine booster dose of Td, if they received their last dose of Td 10 or more years earlier and have not previously received a dose of Tdap.[21, 22]

Healthcare providers should ensure that travelers to all countries with endemic or epidemic diphtheria are up-to-date with diphtheria vaccination. Information on countries with diphtheria is summarized in a recent publication by the World Health Organization[23] and updates can be found on the CDC website for travelers at http://www.cdc.gov/travel. Vaccine providers should carefully review the vaccine history of all travelers to areas with endemic and epidemic diphtheria to ensure that they are optimally protected according to the recommendations of the Advisory Committee on Immunization Practices.[19–23]

## X. Treatment

### *Diphtheria antitoxin*

The mainstay of treatment of a case of suspected diphtheria is prompt administration of diphtheria antitoxin. This should be given without waiting for laboratory confirmation of a diagnosis. The recommended dosage and route of administration depend on the extent and duration of disease. Diphtheria antitoxin is currently available for treatment of clinical cases of respiratory diphtheria in the United States only through CDC under an FDA-approved Investigational New Drug protocol. The healthcare provider should contact CDC Emergency Operations Center (770-488-7100) to obtain diphtheria antitoxin and assistance for its transport,[18] and notify the local and state health departments for public health investigation.

### *Antibiotics*

Persons with suspected diphtheria should also receive antibiotics to eradicate carriage of *C. diphtheriae*, to limit transmission, and to halt further production of diphtheria toxin.[24] Treatment with erythromycin or penicillin is administered as a 14-day course.

### *Vaccination*

Because diphtheria disease does not always confer immunity, an age-appropriate vaccine containing diphtheria toxoid should be administered during convalescence.

### *Contacting CDC*

Providers should contact the CDC Emergency Operations Center (770-488-7100) to request diphtheria antitoxin.

## XI. Enhancing Surveillance

Because diphtheria has occurred only rarely in the United States in recent years, many clinicians may not include diphtheria in their differential diagnoses. Clinicians are reminded to consider the diagnosis of respiratory diphtheria in patients with membranous pharyngitis and who are not up-to-date with vaccination against diphtheria. However, if diphtheria is suspected, appropriate laboratory confirmation may not be feasible locally because isolation of the organism requires selective media. Treatment with antibiotics before specimen collection may further decrease the probability of isolating the organism. Local health departments should assure the availability of laboratory capacity for isolation of *C. diphtheriae*, and at the state level, reference capacity for biotyping, and toxigenicity testing should be available. Laboratories should maintain proficiency in the necessary laboratory procedures.

In areas with endemic *C. diphtheriae* in the 1970s, public health officials should consider recommending routine screening for *C. diphtheriae* of clinical specimens obtained from patients in high-risk populations who have pharyngitis or ear drainage. High-risk populations are defined according to the epidemiology of diphtheria in the area. For consultation and assistance in deciding which populations may be at increased risk for *C. diphtheriae* infection, contact the state health department. See Chapter 19, "Enhancing Surveillance," for additional recommendations for enhancing surveillance of vaccine-preventable diseases.

## XII. Case Investigation

Guidelines for investigating a suspected case and for managing contacts are published and are included in Appendix 2 (Figure 1.23).

Management of contacts of persons with suspected cases should include screening for possible respiratory or cutaneous diphtheria, obtaining nasopharyngeal cultures for *C. diphtheriae*, administering prophylactic antibiotics, assessing diphtheria vaccination status, and administering any necessary vaccinations. The CDC Diphtheria Worksheet may be used for guidelines in conducting a case investigation (see Appendix 3).

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# Chapter 2: *Haemophilus influenzae* Type b Invasive Disease

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## I. Disease Description

*Haemophilus influenzae* (Hi) invasive disease is caused by the bacterium *Haemophilus influenzae*. *H. influenzae* may be either encapsulated (typeable) or unencapsulated (nontypeable). Six antigenically distinct capsular types of *H. influenzae* (types a–f) that can cause invasive disease in persons of any age have been identified. Nontypeable strains can also cause invasive disease but more commonly cause mucosal infections.

Invasive *H. influenzae* diseases include clinical syndromes of meningitis, bacteremia or sepsis, epiglottitis, pneumonia, septic arthritis, osteomyelitis, pericarditis, and cellulitis. In contrast, syndromes of mucosal infections such as bronchitis, sinusitis, and otitis media are considered noninvasive disease. The noninvasive syndromes are not nationally notifiable.

Before the introduction of effective vaccines, *H. influenzae* serotype b (Hib) was the cause of more than 95% of invasive *H. influenzae* diseases among children younger than 5 years of age. Hib was the leading cause of bacterial meningitis in the United States among children younger than 5 years of age and a major cause of other life-threatening invasive bacterial diseases in this age group. Meningitis occurred in approximately two-thirds of children with invasive Hib disease, resulting in hearing impairment or severe permanent neurologic sequelae, such as mental retardation, seizure disorder, cognitive and developmental delay, and paralysis in 15%–30% of survivors. Approximately 4% of all cases were fatal.[1]

## II. Background

Since the introduction of the Hib polysaccharide and conjugate vaccines in 1985 and 1990, the incidence of invasive Hib disease in children less than 5 years of age has decreased by 99%, to fewer than 1 case per 100,000 children younger than 5 years of age.[2–5] Continued monitoring of invasive *H. influenzae* disease through the Active Bacterial Core surveillance (ABCs) system, which includes serotype information on all invasive *H. influenzae* isolates, has demonstrated low rates of invasive Hib in children younger than 5 years of age; between 2005-2009, the average incidence was 0.16 cases per 100,000.[6–10]

In the post-Hib vaccine era, the epidemiology of invasive *H. influenzae* disease in the United States has changed. Studies suggest that the majority of invasive *H. influenzae* disease in all age groups is now caused by nontypable *H. influenzae*.[11, unpublished data]

## III. Importance of Rapid Case Identification

Rapid identification of cases is important to allow for early administration of chemoprophylaxis and Hib vaccine, if needed, to household and childcare classroom contacts of case-patients.[12] Early notification of *H. influenzae* invasive disease cases in children younger than 5 years is also important to ensure isolates are saved for serotyping. State health departments with questions about serotyping should contact the CDC Meningitis and Vaccine-Preventable Diseases Branch laboratory at 404-639-3158.

## IV. Importance of Surveillance

*H. influenzae* surveillance information is used to monitor the effectiveness of Hib immunization programs and vaccines, to assess progress toward Hib disease elimination, and to describe the epidemiology of non-b invasive *H. influenzae* disease.

## V. Disease Reduction Goals

Hib disease has declined rapidly because of widespread immunization of infants and young children with conjugate vaccines and because humans are the only known reservoir for Hib.

## VI. Case Definition

The following case definition for invasive *H. influenzae* disease has been approved by the Council of State and Territorial Epidemiologists (CSTE) and was published in 2009.[15]

### Clinical case definition

Invasive disease caused by *H. influenzae* can produce any of several clinical syndromes, including meningitis, bacteremia, epiglottitis, pneumonia, septic arthritis, cellulitis, or purulent pericarditis; endocarditis and osteomyelitis occur less commonly.

### Laboratory criteria for diagnosis

Isolation of *H. influenzae* from a normally sterile site (e.g., blood or cerebrospinal fluid [CSF] or, less commonly, joint, pleural, or pericardial fluid)

*[Detection of H. influenzae type b–specific antigen in CSF by latex agglutination can only be used as evidence of a probable case.]*

### Case classification

**Probable:** A clinically compatible case with detection of *H. influenzae* type b antigen in CSF.

**Confirmed:** A clinically compatible case that is laboratory confirmed by isolation of *H. influenzae* type b from a normally sterile site.

**Comment:** Positive antigen detection test results from urine or serum samples are unreliable for diagnosis of *H. influenzae* disease.

*[The positive antigen test results can occur from circulation of Hib antigen in urine or serum; this circulation can be caused by asymptomatic Hib carriage, recent vaccination, or fecal contamination of urine specimens. Cases identified exclusively by these methods should be considered suspect cases only.]*

## VII. Laboratory Testing

### Culture

Confirming a case of Hib disease requires culturing and isolating the bacteria from a normally sterile body site. Most hospital and commercial microbiologic laboratories have the ability to isolate *H. influenzae* from cultured specimens. Normally sterile-site specimens for isolation of invasive *H. influenzae* include CSF, blood, joint fluid, pleural effusion, pericardial effusion, peritoneal fluid, subcutaneous tissue fluid, placenta, and amniotic fluid. All *H. influenzae* isolates should be tested for antimicrobial susceptibility according to guidelines in M2-A9 Performance Standards for Antimicrobial Disk Susceptibility Tests (January 2006) from the Clinical Laboratory Standards Institute.[16]

### Serotype testing (serotyping)

Serotyping distinguishes encapsulated strains, including Hib, from unencapsulated strains, which cannot be serotyped. The six encapsulated serotypes (designated a–f) have distinct capsular polysaccharides that can be differentiated by slide agglutination with type-specific antisera.

To make public health decisions about chemoprophylaxis, microbiology laboratories should perform serotype testing of *H. influenzae* isolates[15] Even though Hib disease has declined, laboratories should continue routine serotyping. If serotyping is not available at a laboratory, laboratory personnel should contact the state health department. State health departments with questions about serotyping should contact the CDC Meningitis and Vaccine Preventable Diseases Branch laboratory at 404-639-3158.

### Antigen Detection

Because the type b capsular antigen can be detected in body fluids, including urine, blood, and CSF of patients, clinicians often request a rapid antigen detection test for diagnosis of Hib disease. Antigen detection may be used as an adjunct to culture, particularly in the diagnosis of

patients who have received antimicrobial agents before specimens are obtained for culture. The method for antigen detection is latex agglutination (LA). LA is a rapid and sensitive method used to detect Hib capsular polysaccharide antigen in CSF, serum, urine, pleural fluid, or joint fluid but false negative and false positive reactions can occur.

If the Hib antigen is detected in CSF but a positive result is not obtained from culture or sterile site, the patient should be considered as having a probable case of Hib disease and reported as such. Because antigen detection tests can be positive in urine and serum of persons without invasive Hib disease, persons who are identified exclusively by positive antigen tests in urine or serum should not be reported as cases. Real-time PCR detects DNA of all *H. influenzae* in blood, CSF, or other clinical specimens. A major advantage of PCR is that it allows for detection of *H. influenzae* from clinical samples in which the organism could not be detected by culture methods, such as when a patient has been treated with antibiotics before a clinical specimen is obtained for culture. Even when the organisms are nonviable following antimicrobial treatment, PCR can still detect *H. influenzae* DNA.[17] Isolation of the bacterium is needed to confirm *H. influenzae* invasive disease, determine the serotype, and test for antimicrobial susceptibility.

### Subtyping

Although not widely available, subtyping the Hib bacterium by pulsed field gel electrophoresis (PFGE),[18,19] and multilocus sequence typing (MLST) can be performed for epidemiologic purposes. Some subtyping methods such as outer membrane proteins, lipopolysaccharides, and enzyme electrophoresis are no longer recommended or performed because they were unreliable or too labor intensive. The state health department may direct questions about subtyping to the CDC Meningitis and Vaccine Preventable Diseases Branch laboratory at 404-639-3158.

For additional information on laboratory support for surveillance of vaccine-preventable diseases, see Chapter 22.

## VIII. Reporting

Invasive *H. influenzae* disease became nationally notifiable in 1991. Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[20] These regulations and laws list the diseases to be reported and describe those responsible for reporting, such as healthcare providers, hospitals, laboratories, schools, child care facilities, or other institutions. Vaccine failure information should be collected for case-patients who received all required doses of vaccines but still contracted Hib. CDC has a form for reporting vaccine failures, or a state form can be used if available. Persons reporting should contact their state health department for state-specific reporting requirements. The Meningitis and Vaccine-Preventable Diseases Branch, NCIRD, can be contacted during office hours, 8:00 a.m.–4:30 p.m. Eastern time, at 404-639-3158.

### Reporting to CDC

A provisional report of probable and confirmed cases should be sent to the National Notifiable Disease Surveillance System by the state health department via the National Electronic Telecommunications System for Surveillance (NETSS) or the National Electronic Disease Surveillance System (NEDSS), when available, within 14 days of the initial report to the state or local health department (Appendix 4). Reporting should not be delayed because of incomplete information or lack of confirmation. Cases of disease should be reported by the state in which the patient resides at the time of diagnosis.

The Expanded *Haemophilus influenzae* type b Surveillance Worksheet (Appendix 5) can be used to collect information on each case. Many state health departments have the technology available to send this detailed case report information to CDC through NETSS by using supplemental data entry screens. States that do not have access to supplemental data entry screens should contact CDC. The highest priority for completion of supplemental information forms should be given to cases of *H. influenzae* invasive disease in children younger than 5 years of age. The second highest priority for completion of forms should be cases of *H. influenzae* invasive disease in children 5–14 years of age.

### *Information to collect*

The following data are epidemiologically important and should be collected in the course of case investigation. Additional information may be collected at the direction of the state health department.

- Demographic information
  - Name
  - Address
  - Date of birth
  - Age
  - Sex
  - Ethnicity
  - Race
- Reporting source
  - County
  - Earliest date reported
  - Case ID
- Clinical
  - Date of illness onset
  - Type of disease syndrome (meningitis, bacteremia, epiglottitis, pneumonia, arthritis, osteomyelitis, pericarditis, cellulitis)
- Outcome (patient survived or died)
  - Date of death
- Laboratory
  - Serotype of isolate
  - Specimen source from which organism was isolated (blood, CSF, pleural fluid, peritoneal fluid, pericardial fluid, joint fluid, amniotic fluid, or other normally sterile site)
  - Date first positive culture identified as *H. influenzae*
  - Date of specimen collection
- Antibiotic susceptibility
- Vaccination status (for type b or unknown serotype infections only)
  - Dates of Hib immunization
  - Manufacturer name
  - Vaccine lot number
  - If not vaccinated, reason
- Epidemiologic
  - Attendance in child care

## IX. Vaccination

Table 1 and 2 list the Hib monovalent and combination conjugate vaccines that are currently available and the recommended vaccination regimens for each vaccine. The combination vaccines include the Hib monovalent vaccine and vaccines for other vaccine-preventable diseases in one vial, thus decreasing the number of injections needed for protection. Based on the recommended vaccination schedule, infants should receive three primary doses of Hib conjugate vaccine with PRP-T (monovalent or combination) at ages 2, 4, and 6 months, or two primary doses of PRP-OMP (monovalent or combination) at 2 and 4 months. A booster dose should be administered at age 12–15 months with any of the Hib vaccines. Any type of licensed Hib vaccine may be used interchangeably to complete the series. However, the PRP-T Hiberix vaccine is only licensed for use as a booster dose and should not be used for the primary series. The number of doses needed to complete the primary series is determined by the type of

vaccine used; if a PRP-OMP vaccine is not administered as both doses in the primary series, a third dose of Hib vaccine is needed to complete the series.[21–23] The recommended schedule for Hib vaccination of previously unvaccinated children is shown in Table 3.

**Table 1. Hib monovalent conjugate vaccines currently available and recommended regimens for routine vaccination of children in the United States**

| Licensed vaccine (Manufacturer) | Trade name | Primary Series | Booster Dose |
|---|---|---|---|
| PRP-T (Sanofi Pasteur) | ActHIB | 2, 4, 6 months | 12-15 months |
| PRP-OMP (Merck & Co., Inc) | PedvaxHIB | 2, 4 months | 12-15 months |
| PRP-T (GlaxoSmithKline) | Hiberix | Not licensed for primary series | 12-15 months |

**Table 2. Combination vaccines currently available and recommended regimens for routine vaccination of children in the United States**

| Licensed vaccine (Manufacturer) | Trade name | Primary Series | Booster Dose |
|---|---|---|---|
| PRP-OMP + HepB (Merck & Co., Inc) | COMVAX | 2, 4 months | 12-15 months |
| PRP-T + DTaP+IPV (sanofi Pasteur) | Pentacel | 2, 4, 6 months | 12-15 months |

**Table 3. Recommended schedule for Hib conjugate vaccine administration among previously unvaccinated children**

| Age at first dose | Primary Doses | Booster Dose |
|---|---|---|
| <12 months | 2-3* doses, 1 month apart | At 12-15 months** |
| 12-15 months | 2 doses, 2 months apart | NR |
| >15 – 72 months | 1 dose | NR |
| >72 months | NR | NR |

**Note: 2-3 doses depending on whether PRP-T or PRP-OMP vaccine was used*
***Only necessary if 3 primary doses received before age 12 months*

## X. Enhancing Surveillance

Elimination of childhood Hib disease requires participation by all levels of the healthcare system so that all cases are identified and assessed rapidly and reported promptly, and data on reported cases are used in an optimal manner to prevent disease among unvaccinated or undervaccinated populations. The activities listed here can improve the detection and reporting of cases as well as the completeness and quality of reporting. See Chapter 19, "Enhancing Surveillance," for additional recommendations for enhancing surveillance of vaccine-preventable diseases.

### *Ensuring that all isolates from children are serotyped*

Because of the need to make rapid decisions about chemoprophylaxis, serotype should be determined and reported for all *H. influenzae* isolates. It is particularly important that serotype be reported for cases in children younger than 5 years of age; the second highest priority is for cases among children 5–14 years of age. This information is also used to determine whether a case indicates a vaccine failure (i.e., a vaccinated person who gets the disease) or a failure to vaccinate. The state public health laboratory or another reference laboratory should be able to provide serotype testing of *H. influenzae* isolates. Hospital laboratories unable to perform serotype testing should forward all *H. influenzae* isolates for serotyping to one of these laboratories, or should contact the state health department for advice, if necessary.

### *Monitoring surveillance indicators*

Regular monitoring of surveillance indicators, including reporting dates, time intervals between diagnosis and reporting, and completeness of reporting may identify specific areas of the

surveillance system that need improvement. Important indicators to evaluate the completeness and overall quality of the surveillance system include the following:

- The proportion of *H. influenzae* cases reported to NNDSS with complete information (clinical case definition–species, specimen type; vaccine history; and serotype testing)
- Proportion of Hib cases among children younger than 5 years of age with complete vaccination history
- Proportion of Hib cases among children younger than 5 years of age with serotyped isolate

### *Monitoring the incidence of invasive disease due to non–type-b H. influenzae*

Data from active surveillance sites suggest an expected rate of invasive disease due to non–type-b *H. influenzae* to be 0.9 per 100,000 children younger than 5 years of age.[24] This rate may be used as a surveillance indicator for monitoring the completeness of invasive *H. influenzae* case reporting. Although limited data are available on temporal and geographic variability in incidence of non–type-b invasive diseases, use of this surveillance indicator is encouraged.

## XI. Case Investigation

Laboratory, hospital, and clinic records should be reviewed during case investigations by health department personnel in order to collect important information such as serotype, immunization status, dates of vaccination, vaccine lot numbers, and clinical illness description and outcome. The Expanded *Haemophilus influenzae* type b Surveillance Worksheet may be used as a guide for collecting demographic and epidemiologic information in a case investigation (see Appendix 5).

### *Investigating contacts*

Identification of young children who are household or childcare contacts of patients with Hib invasive disease and assessment of their vaccination status may help identify persons who should receive antimicrobial prophylaxis or who need to be immunized.

The Advisory Committee on Immunization Practices recommends that because children who attend child care are at increased risk for Hib disease, efforts should be made to ensure that all child care attendees younger than 5 years of age are fully vaccinated.[12] Children < 24 months of age who develop invasive Hib disease should repeat the Hib vaccine series because they can remain at risk of a second episode of disease; children >24 months of age who develop invasive Hib disease usually develop a protective immune response and do not need immunization. For household contacts of a person with invasive Hib disease, no rifampin chemoprophylaxis is indicated if all persons are 48 months of age or older, or if children younger than 48 months of age are fully vaccinated according to the schedule in Table 3. Rifampin chemoprophylaxis is recommended for the index case-patient and all household contacts in households with an infant younger than 12 months of age who has not received the primary series, a child 1–3 years of age who is inadequately vaccinated, or an immunocompromised child (regardless of vaccination status). The recommended rifampin dose is 20 mg/kg as a single daily dose (maximal daily dose 600 mg) for 4 days. A dose of 10 mg/kg once daily for 4 days is recommended for neonates (less than 1 month of age).[12] The risk of Hib invasive disease for child care center contacts of a patient with Hib invasive disease case is thought to be lower than that for a susceptible household contact. Public health officials should refer to the American Academy of Pediatrics (AAP) Red Book 2006 for information on chemoprophylaxis of child care center contacts.[12]

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# Chapter 3: Hepatitis A

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## I. Disease Description

Hepatitis A is caused by infection with hepatitis A virus (HAV), a non-enveloped RNA virus that is classified as a picornavirus. It was first isolated in 1979. Humans are the only natural host, although several nonhuman primates have been infected in laboratory conditions. Depending on conditions, HAV can be stable in the environment for months. The virus is relatively stable at low pH levels and moderate temperatures but can be inactivated by high temperature (185°F [85°C] or higher), formalin, and chlorine.[1]

HAV is acquired by mouth (through fecal-oral transmission) and reaches the liver, where it replicates. After 10–12 days, virus is present in blood and is excreted via the biliary system into the feces. The virus is present in stools during the 1-2 weeks before and for 1-3 weeks after onset of illness. Although virus is present in serum, its concentration is several orders of magnitude less than in feces. Children and infants may excrete virus longer than adults.[1]

The mean incubation period of hepatitis A is approximately 28 days (range 15–50 days). HAV infection occurs often without overt symptoms. Among persons presenting symptoms, hepatitis A is indistinguishable from other types of acute viral hepatitis, but is usually mild. The illness presentation varies widely: there may be flu-like symptoms, fever, malaise, anorexia, nausea, abdominal discomfort, dark urine and jaundice. Clinical illness usually resolves within 2 months among about 65% of cases and within 6 months for nearly all cases. Virus may be excreted during a relapse. The likelihood of symptomatic illness from HAV infection is directly related to age. In children younger than 6 years of age, most (70%) infections are asymptomatic. In older children and adults, infection is usually symptomatic, with jaundice occurring in more than 70% of patients. There is no specific treatment for hepatitis A virus infection. Disease is usually self-limiting and treatment and management of HAV infection are supportive; HAV infection does not result in chronic infection or chronic liver disease. However, HAV infection can complicate chronic liver disease among persons infected with hepatitis C virus; thus, susceptible persons should be vaccinated.[1]

## II. Background

Population-based seroprevalence surveys play a critical role in supplementing data systems for disease incidence, vaccination coverage, and vaccine adverse events in the development of vaccination policy. In the United States, seroprevalence is monitored by the National Health and Nutrition Examination Survey (NHANES). NHANES is conducted by the U.S. Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics and obtains nationally representative data on the health and nutritional status of the non-institutionalized, civilian U.S. population. During the 1999–2006 cycles of NHANES, 43,029 people ≥6 years of age were sampled, 34,338 were interviewed and 32,534 had physical examinations. Serum samples were available for anti-HAV testing for 29,858 of the examined individuals.[2]

Before the availability of vaccine in 1995, seroprevalence of antibody to hepatitis A virus (anti-HAV) in the population solely reflected prior infection. Currently, seroprevalence can reflect immunity due to either previous infection or to vaccination. In the U.S., during 1999–2006, the overall seroprevalence of anti-HAV was 34.9% (95% confidence interval (CI) 33.1-36.7). Seroprevalence among children increased from 8.0% (6.3–10.1) in NHANES 1988–1994 to 20.2% (16.0–24.8) in 1999–2006 ($p<0.001$). For U.S.-born children aged 6-19 years, the strongest predictor of immunity is residence in a state that implemented vaccination in 1999. During 1999-2006, U.S.-born children living in vaccinating states (33.8%, 26.2–42.4) had a higher seroprevalence of anti-HAV than children in non-vaccinating states (11.0%, 9.4–12.8; $p<0.001$).[2]

Among U.S.-born adults aged >19 years, the overall age-adjusted seroprevalence of anti-HAV was 29.9% (28.3, 31.5) during 1999–2006, not significantly different than during 1988–1994

(32.4%, 30.4–34.4). In multivariable models, older age and Mexican-American race/ethnicity are the factors most strongly associated with immunity. Age-adjusted seroprevalence of anti-HAV in 1999–2006 was significantly lower than that in 1988–1994 among adults in lower socio-economic subgroups including those living below poverty, living in more crowded households, having less than a high school education, and those having no health insurance. The risk of lower prevalence of immunity among adults is the susceptibility of population clusters of at-risk adults leading to outbreaks; examples of these are well documented in the European Union.[3] Prevention of secondary transmission of HAV in the United States comes at an enormous public health cost, largely due to the number of persons offered prophylaxis.

The distribution of risk behaviors and exposures among hepatitis A cases has changed dramatically in the U.S. since implementation of hepatitis vaccination. In sites conducting enhanced hepatitis surveillance during 2005–2007, the most frequent (46%) potential source of infection among persons reported with HAV disease was travel outside the U.S. and Canada. These cases mostly reflected persons who traveled, but also included some exposed to a traveler, but did not travel themselves. Other risk factors reported among cases, during the 2–6 week period before onset of symptoms, included contact with a case (15%), being an employee or child in a daycare center (7%), exposure during a common-source outbreak (7%), using illicit drugs (4%), or men who have sex with men (4%). In 37% of cases, the case denied all the above risk factors.[4]

## III. Importance of Rapid Identification

Rapid identification and prompt reporting of cases of hepatitis A are important because measures can be taken to prevent transmission to other persons. Contacts can be effectively identified and vaccinated post-exposure.

## IV. Importance of Surveillance

The main goals of surveillance are to:

1. detect and provide data to control outbreaks;
2. identify contacts of case-patients who require postexposure prophylaxis;
3. characterize changes in the epidemiology of infected populations, and risk factors/behaviors of their infections; and
4. use surveillance data to guide vaccination policies.

There is evidence that electronic medical records can yield more complete and timely identification of acute, symptomatic hepatitis A infections. These result from a combination of coded clinical and laboratory criteria (aminotransferase levels, jaundice, and positive IgM antibody test result).

Surveillance depends heavily on laboratory-initiated reporting of positive markers of hepatitis A. Persons with positive test results are then investigated using traditional, notifiable diseases methods in most health departments in the U.S. Investigations can be labor intensive; thus, providers should be discouraged from using IgM anti-HAV as a screening tool or as part of testing panels in workups of nonacute liver function abnormalities, because IgM screening of non acute liver function tests may result in high percentage of false-positive IgM results. This will limit the need for health departments to conduct investigations of persons who are unlikely to have acute HAV infection.

Surveillance can supplement case notifications using seroprevalence surveys and administrative data.

## V. Disease Reduction Goals

Healthy People 2020 disease reduction goals have been established for achieving the prevention of HAV transmission in the U.S.

**IID–23:** Reduce hepatitis A.

**Target:** to reduce the rate of incident hepatitis A disease to 0.3 cases per 100,000 population.

**Baseline:** 1.0 cases of hepatitis A virus per 100,000 population were reported in 2007.

## VI. Case Definition

The following surveillance case definition for hepatitis A was adopted by the Council of State and Territorial Epidemiologists (CSTE) in 2000; plans for updating this definition are ongoing in 2011. This and previous case definitions are available at:
http://www.cdc.gov/osels/ph_surveillance/nndss/casedef/case_definitions.htm

### *Clinical Criteria*

An acute illness with a) discrete onset of symptoms and b) jaundice, elevated serum aminotransferase levels (ALT or AST)

### *Laboratory criteria:*

Immunoglobulin M (IgM) antibody to hepatitis A virus (anti-HAV) positive

### *Case classification*

**Confirmed:** a case that meets the clinical case definition and is laboratory confirmed or

a case that meets the clinical case definition and occurs in a person who has an epidemiologic link with a person who has laboratory-confirmed hepatitis A (i.e., household or sexual contact with an infected person during the 15-50 days before the onset of symptoms).

## VII. Laboratory Testing

### *Serologic testing*

Serologic testing is required to distinguish hepatitis A from other types of viral hepatitis, since clinical or epidemiologic features overlap. Virtually all patients with acute hepatitis A have detectable IgM anti-HAV. Acute HAV infection is confirmed during the acute or early convalescent phase of infection by the presence of IgM anti-HAV in serum. IgM generally becomes detectable 5–10 days before the onset of symptoms and can persist for up to 6 months. IgG anti-HAV appears in the convalescent phase of infection, remains present in serum for the lifetime of the person, and confers enduring protection against disease.

The antibody test for total anti-HAV measures both IgG anti-HAV and IgM anti-HAV. Persons who are total anti-HAV positive and IgM anti-HAV negative are considered immune, whether from past infection or vaccination history.

### *CDC laboratory special studies*

Molecular epidemiologic methods have been useful in understanding HAV transmission within networks of persons with similar risk factors. When applied in combination with conventional epidemiologic methods, HAV sequencing has also been useful in the investigation and control of outbreaks. However, for routine surveillance purposes, collecting specimens and conducting molecular characterization of HAV strains does not provide actionable information.

Specimens collected as part of enhanced hepatitis surveillance from 2005–2009 were sequenced: 271 (77.4%) of 350 available were PCR positive. Genotypes among the 271 case specimens were: IA (87.8%), IB (11.4%), and IIIA (0.7%). Almost half (131 or 48%) of the PCR positive specimens were from cases reporting travel or exposure to a traveler; 58/131 reported travel to Mexico; and 53/58 grouped within a previously described US-IA1 cluster.[4]

Providers with questions about molecular virology methods should consult with their state health department and the CDC Division of Viral Hepatitis.

## VIII. Reporting

Hepatitis A became nationally reportable as a distinct entity in 1966. Incidence rates of hepatitis A disease were high in the 60's and 70's (>12 cases per 100,000 population). Since vaccine became available in 1995, rates have declined. In 2009, the rate overall was 0.6 per 100,000 population (1,987 cases). In 2009, rates were highest for persons aged 20–29 years (0.96 cases per 100,000 population); the lowest rates were among children <9 years (0.3 cases per 100,000 population). Infant and childhood immunization is thought to be responsible for this marked decrease in hepatitis A rates in the United States.

The CDC/CSTE surveillance case definition requires is a combination of clinical and laboratory characteristics. Thus, asymptomatic cases are not reportable (see case definition above). To estimate all new infections, case reports are adjusted for the proportion of asymptomatic cases and surveillance underreporting. In 2009 there were an estimated 21,000 new infections.

All states notify hepatitis A cases to CDC. However, each state determines who and how hepatitis A should be reported to their state or local jurisdictions. For a national summary of hepatitis A reporting requirements in the U.S., see the CSTE list available at: http://www.cste.org/dnn/ProgramsandActivities/PublicHealthInformatics/StateReportableConditionsQueryResults/tabid/261/Default.aspx

State health departments transmit case reports of hepatitis A along with other notifiable diseases weekly to the National Notifiable Diseases Surveillance System. Surveillance monitors basic demographic information (excluding personal identifiers)— age, race/ethnicity, sex, date of onset, date of report, and county of residence of individual cases. At CDC, the Division of Viral Hepatitis develops and disseminates an annual report available at: http://www.cdc.gov/hepatitis/Statistics/index.htm

## IX. Vaccination

Hepatitis A vaccines were licensed in the United States in 1995. Shortly thereafter the Advisory Committee on Immunization Practices (ACIP) made recommendations for routine vaccination of children aged 2–18 years, living in communities with the highest rates of infection and disease. By 1999, there was epidemiologic evidence that the strategy had a limited impact on national disease incidence; thus in 1999, ACIP recommended routine vaccination for children living in 11, mostly western states, with average incidence rates that were twice or greater than the 1987–1997 national average (i.e. ≥20 cases per 100,000 population). In an additional six states, where average incidence rates were greater than the national average, but less than twice that value (i.e., 10–19 cases per 100,000 population), ACIP recommended consideration of routine vaccination of children. This expansion had a dramatic impact: by 2003, acute hepatitis A disease had declined overall by 76% from a rate of 10.7 per 100,000 in 1990–1997 to 2.6 per 100,000 in 2003, and in 2007 was the lowest ever reported (1.0 per 100,000). In 2006, the ACIP recommended integration of hepatitis A virus (HAV) vaccine into the routine childhood vaccination schedule with HAV vaccine for all children at age 12 months.[5]

In August 2005, the youngest age for which hepatitis A vaccine was licensed was lowered from 24 months to 12 months, and in May 2006, the Advisory Committee for Immunization Practices (ACIP) recommended routine vaccination of all children aged 12–23 months, regardless of risk category or location.[5]

### *Vaccination of children*

All children should receive hepatitis A vaccine at age 1 year (i.e., 12–23 months). Vaccination should be completed according to the licensed schedules (Tables 1, 2) and integrated into the routine childhood vaccination schedule. Children who are not vaccinated by age 2 years can be vaccinated at subsequent visits. States, counties, and communities with existing hepatitis A

vaccination programs for children aged 2–18 years are encouraged to maintain these programs. In these areas, new efforts focused on routine vaccination of 12–23-month-old children should enhance, not replace, ongoing programs directed at a broader population of children. In areas without existing hepatitis A vaccination programs, catch-up vaccination of unvaccinated children <19 years of age can be considered. Such programs might especially be warranted in the context of rising incidence or ongoing outbreaks among children or adolescents.

### *Vaccination of persons at increased risk for HAV infection*

Persons at increased risk for hepatitis A should be identified and vaccinated. Hepatitis A vaccine should be strongly considered for persons aged 1 year and older who are traveling to or working in countries where they would have a high or intermediate risk of hepatitis A virus infection. These areas include all areas of the world except Canada, Western Europe and Scandinavia, Japan, New Zealand, and Australia. The first dose of hepatitis A vaccine should be administered as soon as travel is considered. For healthy persons 40 years of age or younger, 1 dose of single antigen vaccine administered at any time before departure can provide adequate protection. Unvaccinated adults older than 40 years of age, immunocompromised persons, and persons with chronic liver disease planning to travel in 2 weeks or sooner should receive the first dose of vaccine and also can receive immune globulin at the same visit with separate syringes and at different anatomic sites. Travelers who choose not to receive vaccine should receive a single dose of IG (0.02 mL/kg), which provides protection against HAV infection for up to 3 months. Persons whose travel period is more than 2 months should be administered IG at 0.06 mL/kg. IG should be repeated in 5 months for prolonged travel. Other groups that should be offered vaccine include men who have sex with men, persons who use or are in treatment for illegal drugs, contacts of newly arriving adoptees from countries with high or intermediate HAV endemicity, persons who have clotting factor disorders, and persons with occupational risk of infection. Persons with occupational risk include only those who work with hepatitis A-infected primates or with hepatitis A virus in a laboratory setting. No other groups have been shown to be at increased risk of hepatitis A infection due to occupational exposure.

Persons with chronic liver disease are not at increased risk for HAV infection because of their liver disease alone. However, these persons, including those with chronic hepatitis C infection, are at increased risk for fulminant hepatitis A should they become infected. Susceptible persons who have chronic liver disease should be vaccinated. Adults with chronic hepatitis C may be good candidates for vaccination with TWINRIX to prevent both hepatitis A and B. Susceptible persons who either are awaiting or have received liver transplants should also be vaccinated.

### *Prophylaxis*

**Pre-exposure:**
Currently, Advisory Committee on Immunization Practices (ACIP) recommends hepatitis A vaccination of all children at age 12–23 months, catch-up vaccination of older children in selected areas, and vaccination of persons at increased risk for hepatitis A (including travelers to endemic areas, users of illicit drugs, or men who have sex with men and contacts of newly arriving adoptees from countries with high or intermediate HAV endemicity). During 2007, the overall U.S. vaccination coverage, with at least 1 dose of HAV vaccine, among children 24–35 months was 47.4%.[5]

HAVRIX is available in two formulations: pediatric (720 ELISA units [EL.U.] per 0.5-mL dose) and adult (1,440 EL.U. per 1.0-mL dose) (Table 1). Children 1 through 18 years of age should receive a single primary dose of the pediatric formulation followed by a booster dose 6 to 12 months later. Adults 19 years of age and older receive one dose of the adult formulation followed by a booster 6 to 12 months later. The vaccine should be administered intramuscularly into the deltoid muscle. A needle length appropriate for the vaccinee's age and size (minimum of 1 inch) should be used.

VAQTA is quantified in units (U) of antigen and is available in pediatric and adult formulations (Table 2). Children 1 through 18 years of age should receive one dose of pediatric formulation (25 U per dose) with a booster dose 6 to 18 months later. Adults 19 years of age and older should

receive one dose of adult formulation (50 U per dose) with a booster dose 6 to 18 months after the first dose. The vaccine should be administered intramuscularly into the deltoid muscle. A needle length appropriate for the vaccinee's age and size should be used (minimum of 1 inch).

The hepatitis A component of TWINRIX consists of 720 ELISA units in a 1.0 mL dose (Table 3). It is approved for vaccination of persons aged >18 years in 2 schedules: a 3-dose schedule (0, 1, and 6 months) and alternate 4-dose schedule (0, 7, and 21–30 days, followed by a dose at 12 months). The alternative 4-dose schedule can be used where vaccination with TWINRIX or single antigen HAV vaccine has been initiated and travel or other potential exposure is anticipated before the second dose is due. A person 19 years of age or older who receives one dose of TWINRIX may complete the hepatitis A series with two doses of adult formulation hepatitis A vaccine separated by at least 5 months. A person who receives two doses of TWINRIX may complete the hepatitis A series with one dose of adult formulation hepatitis A vaccine or TWINRIX 5 months after the second dose. A person who begins the hepatitis A series with single-antigen hepatitis A vaccine may complete the series with two doses of TWINRIX or one dose of adult formulation hepatitis A vaccine. An 18-year-old should follow the same schedule using the pediatric formulation.

TWINRIX should be administered by intramuscular injection in the deltoid muscle. Injections in the gluteus can result in a lower response. When given with other vaccines or IG they should be given with different syringes and in different injection sites.

**Post-exposure:**
In the absence of post-exposure prophylaxis, secondary attack rates of 15%–30% have been reported in households, with higher rates of transmission occurring from infected young children than from infected adolescents and adults. Attack rates among persons exposed to HAV-infected food handlers are generally lower.

Vaccine (either HAVRIX or VAQTA) is recommended as post-exposure prophylaxis in healthy persons 12 months through 40 years of age as of 2007 because it induces active immunity providing longer protection, has higher acceptability and availability, and is easy to administer.

Immune globulin (IG) is typically used for post-exposure prophylaxis of hepatitis A in susceptible persons who are either older than 40 years of age, children younger than 12 months of age, immunocompromised persons, and persons with chronic liver disease.

## *Vaccination schedule*

See additional details above in immunization section.

**Table 1.** The dose of HAVRIX is quantified in enzyme-linked immunosorbent assay (ELISA) units (EL.U.). HAVRIX is currently licensed in a two-dose schedule of 720 EL.U. per dose (0.5 mL) for children and adolescents (12 months through 18 years of age), and 1440 EL.U. per dose (1.0 mL) for adults (older than 18 years of age).

**Table 1. Recommended doses of HAVRIX® (hepatitis A vaccine, inactivated)***

| Group | Age | Dose (EL.U.)† | Volume | No. doses | Schedule§ |
|---|---|---|---|---|---|
| Children and adolescents | 12 months–18 years | 720 | 0.5 mL | 2 | 0, 6–12 |
| Adults | >18 years | 1,440 | 1.0 mL | 2 | 0, 6–12 |

* *GlaxoSmithKline*

† *Enzyme-linked immunosorbent assay units*

§ *Months; 0 months represents timing of the initial dose; subsequent number(s) represent months after the initial dose.*

**Table 2.** The dose of VAQTA is quantified in units (U). The dose and schedule for children and adolescents (12 months through 18 years of age) is 25 U per dose in a two-dose schedule, and for adults (older than 18 years of age), 50 U per dose in a two-dose schedule.

**Table 2. Recommended doses of VAQTA® (hepatitis A vaccine, inactivated)***

| Group | Age | Dose (U)† | Volume | No. doses | Schedule§ |
|---|---|---|---|---|---|
| Children and adolescents | 12 months–18 years | 25 | 0.5 mL | 2 | 0, 6–18 |
| Adults | >18 years | 50 | 1.0 mL | 2 | 6–18 |

* *Merck & Co., Inc.*

† *Units*

§ *Months; 0 months represents timing of the initial dose; subsequent number(s) represent months after the initial dose.*

**Table 3.** The dose of Twinrix is quantified in ELISA units (EL.U.) and micrograms. Each dose of Twinrix contains at least 720 EL.U. of inactivated hepatitis A virus and 20 µg of recombinant hepatitis B surface antigen (HBsAg) protein. There is a three dose schedule, given at 0, 1, and 6 months (the same schedule as that used for single-antigen hepatitis B vaccine), and a four dose schedule to accommodate travelers with short notice.

**Table 3. Recommended doses of TWINRIX®***

*(combined hepatitis A and B vaccine for adults ≥18 years of age only)*

| Group | Age | Dose† | Volume | No. doses | Schedule§ |
|---|---|---|---|---|---|
| Adults | ≥18 years | 720 EL.U. and 20mcg of HBsAg | 1.0 mL | 3 | 0, 1, 6 |
| Adults | ≥18 years | 720 EL.U. and 20mcg of HBsAg | 1.0 mL | 4 | 0,7, 21-30 days, 12 months |

* *GlaxoSmithKline*

† *Enzyme-linked immunosorbent assay units*

§ *Months; 0 months represents timing of the initial dose; subsequent number(s) represent months after the initial dose.*

## X. Enhancing Surveillance

### *Provider education and case investigation*

Providers should be educated about the importance of reporting all cases of acute hepatitis A. A common risk factor for persons with acute infection is contact with a previously identified case-patient. Aggressive case investigations of persons with acute disease provide the best opportunity to administer post-exposure prophylaxis to contacts of case-patients and have the potential to significantly reduce missed opportunities to prevent disease.

Surveillance and epidemiology staff (often the same person) should routinely investigate suspected cases of viral hepatitis. Each state may have their own protocols for conducting these investigations, and CDC is available to provide support as needed (http://www.cdc.gov/hepatitis/ContactUs.htm).

Information necessary includes 1) determining a discrete onset of illness, 2) confirming evidence of acute liver disease (jaundice or elevated aminotransferase levels), 3) obtaining serologic laboratory results, and 4) risk factor information and determining the risk for secondary transmission.

### *Information to collect*

Additional information may also be collected at the direction of the state health department. A case report form that may be useful is available at:
http://www.cdc.gov/hepatitis/Statistics/index.htm

Basic information includes:

- Demographic information
- Clinical details, including
  - Date of onset of illness
  - Symptoms including abdominal pain and jaundice
- Laboratory results
- Vaccination status
- Risk factors
- Occupation, contacts for investigation and prophylaxis

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# Chapter 4: Hepatitis B

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## I. Disease Description

Hepatitis B is caused by infection with the hepatitis B virus (HBV), a double-stranded DNA virus of the family hepadnaviridae. HBV replicates in the liver and causes both acute and chronic hepatitis. Although the highest concentrations of virus are found in blood, other body fluids, such as semen and saliva, also have been demonstrated to contain HBV. Thus, HBV is predominantly a blood and sexually transmitted infection and is transmitted by percutaneous and mucosal exposure to infectious body fluids.

The incubation period for acute hepatitis B ranges from 45 to 160 days (average 120 days). The clinical manifestations of acute HBV infection are age dependent. Infants, young children (younger than 10 years of age), and immunosuppressed adults with newly acquired HBV infection are usually asymptomatic.[1] Older children and adults are symptomatic in 30%–50% of infections. When present, clinical symptoms and signs might include anorexia, malaise, nausea, vomiting, abdominal pain, jaundice, dark urine, and clay-colored or light stools. Occasionally, extrahepatic manifestations occur and include skin rashes, arthralgias, and arthritis. Fulminant hepatitis occurs with a case-fatality rate of 0.5%–1%.

From 2003-2008, there was an estimated 38,000–73,000 new HBV infections annually in the U.S.[2] Each year about 600,000 HBV-related deaths occur worldwide.[3] Among adults with normal immune status, most (94%–98%) recover completely from newly acquired HBV infections, eliminating virus from the blood and producing neutralizing antibody that creates immunity from future infection. In infants, young children, and immunosuppressed persons, most newly acquired HBV infections result in chronic infection.[4] Infants are at greatest risk, with a 90% chance of developing chronic infection if infected at birth. Although the consequences of acute hepatitis B can be severe, most of the serious sequelae occur in persons in whom chronic infection developed. Persons who acquire chronic HBV infection as infants or young children are often asymptomatic; however, chronic liver disease develops in two-thirds of these persons, and approximately 15%–25% die prematurely from cirrhosis or liver cancer. Persons with chronic HBV infection are often detected in screening programs, such as those for blood donors, pregnant women, and refugees. Persons with chronic HBV infection are a major reservoir for transmission of HBV infections. Any person testing positive for hepatitis B surface antigen (HBsAg) is potentially infectious to both household and sexual contacts.

## II. Background

Each year during the 1970s and 1980s, an estimated 200,000–300,000 persons worldwide were newly infected with HBV. Until recently, hepatitis B was one of the most frequently reported vaccine-preventable diseases in the United States, with 15,000–20,000 cases reported annually to the National Notifiable Diseases Surveillance System (NNDSS). Since 1985, a steady decline has occurred in the number of cases of acute hepatitis B reported to the NNDSS. In 2007, approximately 4,500 cases of acute hepatitis B were reported, which after correcting for underreporting and asymptomatic infections, represented an estimated 43,000 new cases.[2] Based on testing from the National Health and Nutrition Examination Survey, the age-adjusted prevalence of hepatitis B core antibody, which indicates past or present infection, in the US population decreased from 5.4% in 1988-1994 to 4.7% during 1999-2006 among persons aged 6 years and older. The age adjusted prevalence of hepatitis B core antibody and hepatitis B surface antigen together, which indicates chronic active HBV infection, decreased from 0.38% to 0.27% among persons aged 6 years and older during the same time periods.[3] An estimated 730,000 US adults had chronic active hepatitis B during 1999-2006.[3]

The extent to which children acquire HBV infection in the United States has not been appreciated, primarily because most infections in this age group are asymptomatic. In the United States, approximately 24,000 HBsAg-positive women gave birth in 2005. Without postexposure prophylaxis to prevent perinatal HBV infection, it is estimated that 12,000 infants

and children would be infected with HBV annually. Furthermore, before the implementation of universal infant hepatitis B immunization, an additional 16,000 children younger than 10 years old were infected annually in the United States through exposure to HBsAg-positive household members or community contacts. Populations with the highest rates of these early childhood infections included Alaska Natives, children of Pacific Islander parents, and children of first-generation immigrants from countries where HBV is of high or intermediate endemicity.[5-8]

Screening of all pregnant women for HBsAg to identify infants requiring postexposure prophylaxis has been recommended since 1988, universal childhood hepatitis B immunization since 1991, universal adolescent hepatitis B immunization since 1995,[9,10] and universal hepatitis B birth dose administration since 2005. In the United States, without postexposure prophylaxis, HBV would annually infect 12,000 infants; without routine childhood immunization, 16,000 children would be infected.

Among persons who reported risk behaviors/exposures in 2007, the most frequently reported risk behavior/exposure for acute, symptomatic hepatitis B was multiple sex partners (38%), followed by men who have sex with men (MSM) (11%) and sexual contact with a person known to have hepatitis B (6%). Injection drug use (IDU) was reported for 15% of persons.[11] Although up to 25% of persons with newly acquired hepatitis B do not report a source for their infection, many of these persons have had a past history of high-risk sex or drug behaviors. Furthermore, more than half of persons with newly acquired hepatitis B were previously seen in medical settings where hepatitis B vaccine is routinely recommended, such as sexually transmitted disease (STD) treatment clinics. Thus, programs to vaccinate older adolescents and adults at increased risk for HBV infection need to be strengthened nationwide in order to have a significant impact on reducing HBV transmission in the next 2 decades.

## III. Importance of Rapid Identification

Rapid identification and prompt reporting of cases of acute hepatitis B is important because measures such as postexposure prophylaxis can be taken to prevent transmission to other persons. Although outbreaks of hepatitis B are unusual, rapid recognition allows for identification of the source and prevention of further transmission. In addition, identification of risk behaviors/exposures for infection provides a means to assess the effectiveness of hepatitis B immunization activities in the community and identify missed opportunities for immunization.

In most states, HBsAg positivity is a laboratory reportable condition. Reporting of HBsAg-positive persons facilitates timely immunization of contacts. For HBsAg-positive pregnant women, reporting allows for initiation of case management to ensure prevention of perinatal HBV transmission (see "Postexposure prophylaxis" below). In 2003, chronic HBV infection became nationally notifiable and is reportable by state health departments to the NNDSS. All states are encouraged to report chronic hepatitis B infection. States should develop registries of persons with HBsAg-positive laboratory results to facilitate postexposure prophylaxis of contacts and reporting to NNDSS (see "Registries/databases for HBsAg-positive persons" below).

### *Postexposure prophylaxis*

Hepatitis B immune globulin (HBIG) is prepared from human plasma known to contain a high titer of antibody to HBsAg (anti-HBs). The plasma from which HBIG is prepared is screened for HBsAg, hepatitis C virus (HCV), and human immunodeficiency virus, and since 1999, all products available in the United States have been manufactured by methods that inactivate HCV and other viruses. A regimen combining HBIG and hepatitis B vaccine is 85%–95% effective in preventing HBV infection when administered at birth to infants born to HBsAg-positive mothers. Regimens involving either multiple doses of HBIG alone or the hepatitis B vaccine series alone are 70%–75% effective in preventing HBV infection. It is recommended that HBIG should be given as soon as possible, after exposure to hepatitis B. Although the postexposure efficacy of the combination of HBIG and the hepatitis B vaccine series has not been evaluated for occupational or sexual exposures, it can be presumed that the increased efficacy of this regimen observed in the perinatal setting compared with HBIG alone would apply to these exposures.

Postexposure prophylaxis with HBIG and hepatitis B vaccine should be given to infants born to HBsAg-positive mothers, unvaccinated infants whose mothers or primary caregivers have acute hepatitis B, sexual contacts of persons with hepatitis B, and healthcare workers after occupational exposure to HBsAg-positive blood depending on their vaccination and vaccine response status. Household and sexual contacts of persons with chronic HBV infection should be vaccinated.

## IV. Importance of Surveillance

Disease surveillance is used to 1) identify contacts of case-patients who require postexposure prophylaxis; 2) detect outbreaks; 3) identify infected persons who need counseling and referral for medical management; 4) monitor disease incidence and prevalence; and 5) determine the epidemiologic characteristics of infected persons, including the source of their infection, to assess and reduce missed opportunities for vaccination.

## V. Disease Reduction Goals

The primary goal of hepatitis B vaccination is to prevent chronic HBV infection. However, because such a high proportion of persons with chronic HBV infection are asymptomatic and the consequences are not seen for many years, monitoring the direct impact of prevention programs on the prevalence of chronic infection is difficult. Consequently, the disease reduction goals that have been established for hepatitis B are a combination of process and disease outcome measures. Because most HBV infections among children younger than 10 years of age are asymptomatic, programs targeting infants and children are best evaluated by measuring vaccination coverage and not by measuring reduction in acute infection. In older age groups, monitoring the incidence of acute disease as well as measuring vaccine coverage levels provides data useful for measuring the effectiveness of prevention programs.

*Healthy People 2020* disease reduction goals have been established for achieving the prevention of HBV transmission in the United States. Disease reduction goals for infants and children include reducing the estimated number of chronic HBV infections in infants and young children to 400 cases and the number of new hepatitis B cases reported among persons 2–18 years of age to zero cases. Healthy People 2020 vaccination goals for infants and children include setting a target coverage level for infants age 0–3 days receiving the initial birth dose of hepatitis B vaccine to 85% and for children age 19–35 months completing the three-dose hepatitis B vaccination series to 90%.[12]

Disease reduction goals for adults include reducing the rate of acute hepatitis B to 1.5 cases per 100,000 in persons age 19 years and older. Among adults in high-risk groups, disease reduction goals include reducing the number of cases of acute hepatitis B to 215 cases in injection-drug users and to 45 new infections among men who have sex with men.[12]

## VI. Case Definition

The following case definitions for acute hepatitis B, chronic hepatitis B virus infection and perinatal HBV infection have been adopted by the Council of State and Territorial Epidemiologists.[13]

### *Hepatitis B, acute (effective 2000)*

**Clinical case definition**

An acute illness with

a. a discrete onset of symptoms, and
b. jaundice or elevated serum aminotransferase levels.

**Laboratory criteria for diagnosis**

- IgM antibody to hepatitis B core antigen (anti-HBc) positive or hepatitis B surface antigen (HBsAg) positive
- IgM anti-HAV negative (if done)

**Case classification**

***Confirmed:*** *a case that meets the clinical case definition and is laboratory confirmed*

### *Chronic hepatitis B virus infection (effective 2007)*

**Clinical description**

Persons with chronic HBV infection may have no evidence of liver disease or may have a spectrum of disease ranging from chronic hepatitis to cirrhosis or liver cancer. Persons with chronic infection may be asymptomatic.

**Laboratory criteria for diagnosis**

- IgM anti-HBc negative AND a positive result on one of the following tests: HBsAg, HBeAg, or HBV DNA **OR**
- HBsAg positive or HBV DNA positive or HBeAg positive two times at least 6 months apart (Any combination of these tests performed 6 months apart is acceptable.)

**Case classification**

***Confirmed*:** a case that meets either laboratory criterion for diagnosis

***Probable:*** a case with a single HBsAg-positive or HBV DNA-positive or HBeAg-positive laboratory result when no IgM anti-HBc results are available

***Comment:*** Multiple laboratory tests indicative of chronic HBV infection may be performed simultaneously on the same patient specimen as part of a "hepatitis panel." Testing performed in this manner may lead to seemingly discordant results, e.g., HBsAg negative AND HBV DNA positive. For purposes of this case definition, any positive result among the three laboratory tests mentioned above is acceptable, regardless of other testing results. Negative HBeAg results and HBV DNA levels below positive cutoff level do not confirm the absence of HBV infection.

### *Perinatal hepatitis B virus infection (effective 1995)*

**Clinical description**

Perinatal hepatitis B in the newborn may range from asymptomatic to fulminant hepatitis.

**Laboratory criteria for diagnosis**

- Hepatitis B surface antigen (HBsAg) positive

**Case classification**

HBsAg positivity in any infant aged >1–24 months who was born in the United States or in U.S. territories to an HBsAg-positive mother

***Comment:*** Infants born to HBsAg-positive mothers should receive HBIG and the first dose of hepatitis B vaccine within 12 hours of birth, followed by the second and third doses of vaccine at 1 and 6 months of age, respectively, if receiving the single-antigen vaccine. Dosage and scheduling will be different if the infant received a combination vaccine (see Table 1). Postvaccination testing for HBsAg and anti-HBs (antibody to HBsAg) is recommended from 3 to 6 months following completion of the vaccine series. If HBIG and the initial dose of vaccine are delayed for more than 1 month after birth, testing for HBsAg may determine if the infant is already infected.

**Table 1. Hepatitis B combination vaccine schedule for newborn infants born to HBsAg positive mothers**

| Single antigen* combination vaccine | |
|---|---|
| **Dose** | **Age** |
| 1 | Birth (< 12 hrs) |
| HBIG | Birth (< 12 hrs) |
| 2 | 2 mos |
| 3 | 4 mos |
| 4 | 6 mos (Pediarix) or 12-15 mos (Comvax) |

** Recombivax HB or Engerix-B should be used for the birth dose. Comvax and Pediarix cannot be administered at birth or before age 6 weeks.*

*Source: CDC. A comprehensive strategy to eliminate transmission of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP); Part 1: Immunization of infants, children and adolescents. MMWR 2005; 54(No. RR-16).*

## VII. Laboratory Testing

Several specific and well-defined antigen–antibody systems are associated with HBV infection, including hepatitis B surface antigen (HBsAg) and antibody to HBsAg (anti-HBs); hepatitis B core antigen (HBcAg) and antibody to HBcAg (anti-HBc); and hepatitis B e antigen (HBeAg) and antibody to HBeAg (anti-HBe). Serologic assays are commercially available for all of these except HBcAg because no free HBcAg circulates in blood. One or more of these serologic markers are present in the blood during different phases of HBV infection (Table 2). Subtyping of HBsAg has occasionally been used to investigate outbreaks of hepatitis B, but this procedure is not routinely available in commercial laboratories.

**Table 2. Interpretation of serologic test results for hepatitis B virus infection**

| Serologic Markers | | | | |
|---|---|---|---|---|
| **HBsAg* Serologic Marker** | **Total Anti-HBc† Serologic Marker** | **IgM Anti-HBc§ Serologic Marker** | **Anti-HBs¶ Serologic Marker** | **Interpretation** |
| - | - | - | - | Susceptible, never infected |
| + | - | - | - | Early acute infection, transcient (up to 18 days) after vaccination ** |
| + | + | + | - | Acute infection |
| - | + | + | - | Acute resolving infection |
| - | + | - | + | Past infection, recovered and immune |
| + | + | - | - | Chronic infection |
| - | + | - | - | False positive (i.e., susceptible), past infection, or "low level" chronic infection |
| - | - | - | + | Immune (vaccination, prior infection) if titer is >10 mIU/mL |

** Hepatitis B surface antigen*
*† Antibody to hepatitis B core antigen*
*§ Immunoglobulin M*
*¶ Antibody to hepatitis B surface antigen*
*** Transient HBsAg positivity (lasting <18 days) might be detected in some patients after vaccination.*

The presence of HBsAg is an indication of ongoing HBV infection and the potential to spread the infection. In persons newly infected, HBsAg is present in serum 30–60 days after exposure to HBV and persists for variable periods. Anti-HBc develops in HBV infections, appearing at onset of symptoms or in liver test abnormalities in acute HBV infection, rising rapidly to high

levels, and persisting for life. The presence of the immunoglobulin M (IgM) class of anti-HBc, which persists for approximately 6 months, distinguishes acute or recently acquired infection. However, among infected infants, passively transferred maternal anti-HBc may persist beyond the age of 12 months, and IgM anti-HBc may not be present in newly infected children younger than 2 years of age, especially if they acquired their infection through perinatal transmission.

In persons who recover from HBV infection, HBsAg is eliminated from the blood system in 2–3 months, and anti-HBs develops during convalescence. The presence of anti-HBs indicates immunity from HBV infection. After recovery from natural infection, most persons will be positive for both anti-HBs and anti-HBc, whereas only anti-HBs develops in persons who are successfully vaccinated against hepatitis B. Additionally, anti-HBs can be present in persons who have received HBIG. Persons who do not recover from HBV infection and become chronically infected remain positive for HBsAg (and anti-HBc), although a small proportion (0.3% per year) eventually clear HBsAg and might develop anti-HBs.

### *Special laboratory studies*

Molecular virologic methods such as polymerase chain reaction (PCR)-based assays are often used to amplify and sequence viral genomes. In conjunction with epidemiologic studies, these assays may be helpful for investigating common-source outbreaks of hepatitis B. In addition, these assays are essential for detecting the emergence of potential vaccine-resistant strains. Healthcare professionals with questions about molecular virologic methods or those who identify HBsAg-positive events among vaccinated persons should consult with their state health department or the Epidemiology and Surveillance Branch, Division of Viral Hepatitis, CDC, 404-718-8500.

For additional information on laboratory support for surveillance of vaccine-preventable diseases, see Chapter 22.

## VIII. Reporting

In the United States, case reports of viral hepatitis are classified as hepatitis A, acute hepatitis B, acute hepatitis C, perinatal HBV infection, chronic HBV infection and hepatitis C, past or present. Serologic testing is necessary to determine the etiology of viral hepatitis, and case reports should be based on laboratory confirmation (see Section VII). Each state and territory has a list of reportable diseases and conditions of public health importance.[14] These diseases and conditions that are to be reported and describe those persons or groups who are responsible for reporting, such as healthcare providers, hospitals, laboratories, and other institutions. Persons reporting these conditions should contact their state health department for state-specific reporting requirements.

### *Reporting to CDC*

Case reports of acute hepatitis B, chronic HBV infection, perinatal HBV infection, and other reportable diseases are transmitted by the state health department weekly to CDC via the National Electronic Telecommunications System for Surveillance (NETSS). The NETSS core data elements include basic information (excluding personal identifiers)—age, race/ethnicity, sex, date of onset, date of report, county of residence. The NETSS extended data elements include clinical data, laboratory results, and exposure history. However, completeness of reporting of these extended data elements is often incomplete. In 2007, 52% of acute, symptomatic hepatitis B cases were reported in the United States with unavailable risk exposure/behavior information.[11] The Division of Viral Hepatitis has developed an extended Data Collection Worksheet to collect information about symptoms, risk behavior/exposures and serologic data (Appendix 6). This worksheet can be used for case investigation and data can be directly entered into the state's electronic reporting system. Sites reporting through the National Electronic Diseases Surveillance System (NEDSS)15 NEDSS-compatible, and Emerging Infections Program[16] (Enhanced Hepatitis Surveillance) infrastructure collect data elements using this worksheet.

## IX. Vaccination

Infants born to HBsAg-positive women should be administered by intramuscular injection hepatitis B immune globulin (HBIG; for hepatitis B postexposure prophylaxis) and the first dose of hepatitis B vaccine within 12 hours of birth. This combination also should be administered as soon as possible to unvaccinated infants whose primary caregivers have acute hepatitis B, unvaccinated healthcare personnel after occupational exposure, and sex partners of persons with acute hepatitis B . Studies are limited on the maximum interval after exposure during which postexposure prophylaxis is effective, but the interval is unlikely to exceed 7 days for percutaneous exposures and 14 days for sexual exposures. Exact treatment varies depending on source status and vaccination status. For infants born to women positive for HBsAg, the dose of HBIG is 0.5 mL. For all other applications, the dose is 0.06 mL/kg.[17]

### *Hepatitis B vaccine*

Two single-antigen recombinant hepatitis B vaccines are commercially available, Recombivax HB® (Merck & Company, Inc.) and Engerix-B® (GlaxoSmithKline). Recombivax HB contains 5–40 µg of HBsAg protein per milliliter, depending on the formulation, whereas Engerix-B contains 20 µg/mL. Both vaccines are licensed for persons of all ages (Table 3).

**Table 3. Recommended doses of currently licensed single-antigen hepatitis B vaccines**

| | Recombivax HB* | | Engerix-B* | |
|---|---|---|---|---|
| Group | Dose (µg) | Volume (mL) | Dose (µg) | Volume (mL) |
| Infants, children and adolescents younger than 20 years of age | 5 | (0.5) | | (0.5) |
| Adolescents 11–15 years† (adult formulation administered on 2-dose schedule) | 10 | (1.0) | | |
| Adults 20 years of age or older | 10 | (1.0) | 20 | (1.0) |
| Hemodialysis patients and other immunocompromised persons | 40 | (1.0)§ | 40 | (2.0)¶ |

** Both vaccines are routinely administered in three-dose series. Engerix-B also has been licensed for a four-dose series administered at 0, 1, 2, and 12 months.*

*† Two-dose schedule for adolescents using adult dose of Recombivax HB has been approved by ACIP, administered at 0, 4–6 months.*

*§ Special formulation administered on a 3-dose schedule at 0, 1, and 6 months.*

*¶ Two 1.0-mL doses administered at one site in a four-dose schedule at 0, 1, 2, and 6 months.*

Twinrix® (GlaxoSmithKline), a combination of hepatitis A and B vaccine, is also available for use in persons aged 18 years and older. Twinrix consists of the antigenic components used in HAVRIX® (hepatitis A vaccine) and Engerix-B. In addition, there are two combination vaccines (Comvax® [Merck] and Pediarix® [GlaxoSmithKline]) that are used for vaccination of infants and young children. Comvax contains recombinant HBsAg and Haemophilus influenzae type b (Hib) polyribosylribitol phosphate conjugated vaccine. Pediarix contains recombinant HBsAg, diphtheria and tetanus toxoids and acellular pertussis adsorbed (DTaP), and inactivated poliovirus (IPV). However, these combination vaccines may not be administered to infants younger than 6 weeks of age (with exception of Twinrix®); only single-antigen hepatitis B vaccine may be used for the birth dose. Administration of four-dose hepatitis B vaccine schedules, including schedules with a birth dose followed by a combination vaccine series, is permissible (Table 4).

**Table 4. Recommended doses of currently licensed combination hepatitis B vaccines***

| Group | COMVAX | | PEDIARIX | | TWINRIX† | |
|---|---|---|---|---|---|---|
| | Dose (µg)§, ¶ | Volume (mL) | Dose (µg)§, ** | Volume (mL) | Dose (µg)§, †† | Volume (mL) |
| **Infant (less than 1 year)—** Mother HBsAg negative | 5 | 0.5 | 10 | 0.5 | NA | NA |
| **Infant—** Mother HBsAg positive | 5 | 0.5 | 10 | 0.5 | NA | NA |
| **Children—** (1–10 years) | 5§§ | 0.5 | 10 | 0.5 | NA | NA |
| **Adolescents** 11–17 years | NA | NA | NA | NA | NA | NA |
| **Adults—** 18 years or older | NA | NA | NA | NA | 20 | 1.0 |

* *Hepatitis B vaccines are administered by intramuscular injection and may be given at the same time as other vaccines. Single-antigen vaccines may be administered with HBIG, but in a separate injection site.*

† *For persons ≥18 years of age at increased risk of both hepatitis B virus and hepatitis A virus infection*

§ *Recombinant HBsAg protein concentration*

¶ *Comvax also contains combined hepatitis B-Haemophilus influenzae type B conjugate vaccine. This vaccine cannot be administered at birth, before age 6 weeks, or after age 71 months.*

** *Pediarix also contains combined hepatitis B-25 Lf diphtheria toxoid, 10 Lf tetanus toxoid, 25 µg inactivated pertussis toxin, 25 µg filamentous hemagglutinin, 8 µg pertactin, 40 D-Wantigen Units (DU) Type 1 poliovirus, 8 DU Type 2 poliovirus, and 32 DU Type 3 poliovirus (cannot be administered at ages >7 years.*

†† *Twinrix also contains 720 ELISA Units (EL.U) inactivated hepatitis A virus.*

§§ *Maximum age at administration is 71 months.*

An infant born to a HBsAg-positive woman who has not received HBIG and the first dose of hepatitis B vaccine by 12 hours of age or who has not received the third dose of hepatitis B vaccine by the age of 6 months is not adequately vaccinated.[10] Infants born to HBsAg-positive mothers should be tested for HBsAg and antibody to HBsAg after completion of three or more doses in a licensed hepatitis B vaccination series, at age 9–18 months (generally at the next well-child visit). The testing should be done 1–2 months after the most recent hepatitis B vaccine dose to avoid a positive HBsAg result due to vaccine. Serologic testing can determine whether these infants are infected or have developed a protective antibody response after vaccination. Infants who do not respond to the primary vaccination series should be given three additional doses of hepatitis B vaccine on a 0, 1–2, 4–6–month schedule and re-tested 1–2 months after the final dose of vaccine.

The vaccination schedule for infants born to HBsAg-negative women includes three doses of vaccine in the first 18 months of life. The first dose should be given at birth with a minimum interval between doses 1 and 2 of 4 weeks; and a minimum interval of 8 weeks between doses 2 and 3.[10] Dose 3 of hepatitis B vaccine should not be given before 24 weeks of age (164 days). Any infant born to an HBsAg-negative woman who has not received the third dose of hepatitis B vaccine by the age of 19 months is considered not up-to-date (Table 5).

**Table 5. Hepatitis B vaccine schedules for newborn infants, by maternal hepatitis B surface antigen (HBsAg) status***

| Maternal HBsAg Status | Single-Antigen Vaccine | Single-Antigen + Combination Vaccine |
|---|---|---|
| Positive | **Dose:** 1† **Age:** Birth (12 hours or younger) | **Dose:** 1† **Age:** Birth (12 hours or younger) |
| Positive | **Dose:** HBIG§ **Age:** Birth (12 hours or younger) | **Dose:** HBIG§ **Age:** Birth (12 hours or younger) |
| Positive | **Dose:** 2 **Age:** 1-2 months | **Dose:** 2 **Age:** 2 months |
| Positive | **Dose:** 3¶ **Age:** 6 months | **Dose:** 3 **Age:** 4 months |
| Positive | | **Dose:** 4¶ **Age:** 6 months (Pediarix) or 12-15 months (Comvax) |

**Table 5. Hepatitis B vaccine schedules for newborn infants, by maternal hepatitis B surface antigen (HBsAg) status***

| Maternal HBsAg Status | Single-Antigen Vaccine | Single-Antigen + Combination Vaccine |
|---|---|---|
| Unknown** | **Dose:** 1† **Age:** Birth (less than or equal 12 hours) | **Dose:** 1† **Age:** Birth (less than or equal 12 hours) |
| Unknown** | **Dose:** 2 **Age:** 1-2 months | **Dose:** 2 **Age:** 2 months |
| Unknown** | **Dose:** 3¶ **Age:** 1-2 months | **Dose:** 3 **Age:** 4 months |
| Unknown** | | **Dose:** 4¶ **Age:** 6 months (Pediarix) or 12-15 months (Comvax) |
| Negative | **Dose:** 1†, †† **Age:** Birth (before discharge) | **Dose:** 1†, †† **Age:** Birth (before discharge) |
| Negative | **Dose:** 2 **Age:** 1-2 months | **Dose:** 2 **Age:** 2 months |
| Negative | **Dose:** 3¶ **Age:** 6 months | **Dose:** 3 **Age:** 4 months |
| Negative | | **Dose:** 4¶ **Age:** 6 months (Pediarix) or 12-15 months (Comvax) |

* *Centers for Disease Control and Prevention. A comprehensive strategy to eliminate transmission of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP); Part 1: Immunization of Infants, Children and Adolescents. MMWR 2005;54(No. RR-16) p.9.*

† *Recombivax HB or Engerix-B should be used for the birth dose. Comvax and Pediarix cannot be administered at birth or before age 6 weeks.*

§ *Hepatitis B immune globulin (0.5 mL) administered intramuscularly in a separate site from vaccine.*

¶ *The final dose in the vaccine series should not be administered before age 24 weeks (164 days).*

** *Mothers should have blood drawn and tested for HBsAg as soon as possible after admission for delivery; if the mother is found to be HBsAg positive, the infant should receive HBIG as soon as possible but no later than 7 days of age.*

†† *On a case-by-case basis and only in rare circumstances, the first dose may be delayed until after hospital discharge for an infant who weighs ≥2,000 g and whose mother is HBsAg negative. When such a decision is made, a physician's order to withhold the birth dose and a copy of the original laboratory report indicating that the mother was HBsAg negative during this pregnancy should be placed in the infant's medical record.*

Vaccination of pre-term infants should be delayed until they are 1 month old or at time of discharged from hospital, except for infants born to HBsAg-positive women and infants born to women with unknown HBsAg status. Infants born to HBsAg-positive women or women with unknown HBsAg status should be immunized with HBIG within 12 hours of birth regardless of birth weight.

### *Children and adolescents*

Vaccination is routinely given as three-dose series at 0, 1, and 6 months. Acceptable alternative schedules include 0, 1, 2, 12 months and 0, 2, 4 months.

### *Adolescents 11–15 years of age*

An alternative two-dose vaccination schedule has been developed for use in adolescents. The adult dose of Recombivax HB is administered to the adolescent, with the second dose given 4–6 months or 0, 1, 2, and 12 months after the first dose.

### *Adults (20 years of age or older)*

Routinely given as three-dose series at 0, 1, and 6 months. Acceptable alternative schedules are 0, 1, 4 months and 0, 2, 4 months, and 0, 1, 2, and 12 months.

### *Dialysis patients and other immunocompromised persons*

Either given as a three-dose series (0, 1, 6 months) or four-dose series (0, 1, 2, and 6 months), depending on formulation. Larger vaccine doses may be required to induce protective antibody levels in other immunocompromised persons (e.g., those taking immunosuppressive drugs, HIV infected), although few data are available concerning response to higher doses of vaccine in these patients and no data exist for children.

### *Combined hepatitis A and B vaccine*

Primary vaccination of persons aged 18 years and older consists of three doses, administered on a 0, 1, and 6-month schedule.

## X. Enhancing Surveillance

Establishing surveillance for acute hepatitis is difficult for several reasons. Five different viruses (A–E) cause viral hepatitis, and the clinical manifestations of the different types of acute hepatitis are similar. Infection with HBV, HCV and HDV can result in both acute and chronic infection. Therefore, serologic testing is necessary to establish an etiologic diagnosis for persons with symptoms of acute hepatitis and to evaluate case reports of persons who are reported with viral hepatitis. However, a lack of understanding about the epidemiology of these diseases and underutilization of serologic testing could result in significant misclassification in reporting of acute viral hepatitis.

### *Provider education*

Providers should be educated about the importance of performing appropriate serologic tests to determine the etiology of viral hepatitis and reporting all cases of acute hepatitis B, chronic hepatitis B, and perinatal HBV. Case investigations of infected persons provide the best opportunity for postexposure prophylaxis of contacts and for reducing transmission.

### *Case investigation*

Case investigation is essential for determining contacts who are eligible for prophylaxis and for collection of risk factor data. Analysis of risk factor data can identify populations where targeted interventions may be needed.

### *Laboratory reporting*

Laboratories should be encouraged to report all persons with serologic markers of acute or chronic hepatitis to the state or local health department. All IgM anti-HBc, and HBsAg positive results should be reported. To facilitate reporting, these laboratory results could be included in the state's list of laboratory-reportable conditions.

### *Monitoring surveillance indicators*

Regular monitoring of surveillance indicators, including date of report, timeliness, and completeness of reporting, may identify specific areas of the surveillance and reporting system that need improvement. Important program indicators that can be monitored through the surveillance, reporting and case investigation system include the following:

- Characteristics of cases of acute hepatitis B that occur in children and adolescents younger than 20 years of age and missed opportunities for vaccination.
- Characteristics of cases of acute hepatitis in which death has occurred.
- Characteristics of cases of acute hepatitis B in persons reporting a history of vaccination.
- Characteristics of cases of acute hepatitis B in persons over 70 years of age.
- Characteristics of cases of acute hepatitis B associated with healthcare transmission.
- Characteristics of cases of perinatal hepatitis B.

### *Registries/databases for HBsAg-positive persons*

Reporting of HBsAg-positive test results and establishment of databases/registries for HBsAg-positive persons is encouraged. When any type of database is established, the confidentiality of individual identifying information needs to be ensured according to applicable laws and regulations. Computerized databases of persons with HBsAg-positive results can be used to:

- Distinguish newly reported cases of infection from previously identified cases and facilitate reporting of chronic hepatitis B;
- Facilitate case investigation and follow-up of persons with chronic HBV infection;
- Provide local, state, and national estimates of the proportion of persons with chronic HBV infection who have been identified.

### *Hospital-based reporting*

Hospitals and infection control practitioners should be encouraged to report all persons with acute viral hepatitis (ICD-10 code B16), and all births to HBsAg-positive women.

## XI. Case Investigation

Guidelines for investigating a suspected case of acute viral hepatitis include

1. determining a discrete onset of illness,
2. confirming evidence of acute liver disease (jaundice or elevated aminotransferase levels), and
3. obtaining serologic laboratory results.

The minimum recommended elements for investigating cases of chronic HBV infection and perinatal HBV infection include obtaining the serologic laboratory results needed to establish the case. Further investigation to determine the clinical characteristics of these cases may also be considered although it is not required to confirm the case.

### *Information to collect for acute hepatitis B infection*

The following information is epidemiologically important to collect in a case investigation for acute hepatitis B.[18, 19] Additional information may also be collected at the direction of the state health department.

- Demographic information
  - Clinical details
  - Date of illness onset
- Symptoms, including jaundice
- Laboratory results
- Vaccination status
- Risk behaviors/exposures
- Contact investigation and prophylaxis

### *Information to collect for chronic hepatitis B infection*

The following information is epidemiologically important to collect in a case investigation for chronic hepatitis B virus infection. Additional information may also be collected at the direction of the state health department.[19]

- Demographic information
- Laboratory results
- Risk behaviors/exposures
- Pregnancy status. All HBsAg-positive pregnant women should be reported to the perinatal hepatitis B program manager so that they can be tracked and their infants can receive appropriate case management

The recommended elements of case investigation and follow-up of persons with chronic hepatitis B virus infection are detailed elsewhere.[20] The following should be included:

- Contact investigation and prophylaxis: Provision of hepatitis B vaccination for sexual, household, and other (needle-sharing) contacts of persons with hepatitis B, and counseling to prevent transmission to others
- Counseling and referral for medical management, including
  - assessing for biochemical evidence of chronic liver disease, and
  - evaluating eligibility for antiviral treatment.[18]

### *Information to collect for perinatal HBV infection*

The following information is epidemiologically important to collect in a case investigation for perinatal HBV infection:

- Demographic information about the child and mother
- Laboratory results
- Immunization history of the child, including date and doses of HBIG and hepatitis B vaccine

Case investigation and follow-up of infants with hepatitis B virus infection should include the following:

- Referral for medical management, including
  - Assessing for biochemical evidence of chronic liver disease, and
  - Evaluating eligibility for antiviral treatment
- Identification of other susceptible infants and children in the household who require vaccination

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# Chapter 5: Human Papillomavirus

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## I. Background

Genital human papillomavirus (HPV) is the most common sexually transmitted infection in the United States, with an estimated 6.2 million persons becoming newly infected every year.[1] More than 100 HPV types have been identified, over 40 of which can infect the genital area. HPV types are classified by their association with cancer.[2] Non-oncogenic, or low-risk HPV types, such as HPV 6 or 11, can cause (1) benign or low-grade abnormalities of the cervix, (2) anogenital warts, and (3) a disease of the respiratory tract called recurrent respiratory papillomatosis (RRP).[3] Oncogenic, or high-risk HPV types, including types 16 and 18, can cause intraepithelial neoplasia of the anogenital region, including cervical, vulvar, vaginal, penile, and anal cancers as well as some oropharyngeal cancers.[4–6]

Among the cancer-related outcomes of HPV infection, cervical cancer is the most important outcome, with over 500,000 new cases and 275,000 attributable deaths world-wide in 2008.[4, 7] High-risk HPV types are detected in almost all cervical cancers; approximately 70% of cervical cancers worldwide are due to types 16 and 18.[8] While persistent infection with high-risk types is considered necessary for the development of cervical cancer, it is not sufficient because the vast majority of women with high-risk HPV infection do not develop cancer.[9–11]

In addition to its association with cervical cancer, high-risk HPV infection is associated with cancer of the vulva, vagina, penis and anus[5] (see Appendix A). Each of these cancers is less common than cervical cancer and, unlike cervical cancer, not all cases of these less common anogenital cancers are related to HPV infection.[4, 12–16] High-risk types of HPV also play a role in the development of some oropharyngeal cancers.[5, 6]

Genital HPV infection is primarily transmitted by genital contact, usually (but not necessarily) through sexual intercourse.[17] Most HPV infections are transient and asymptomatic, causing no clinical manifestations. Studies have shown that more than 90% of new HPV infections, including those with high-risk types, clear or become undetectable within two years, and clearance usually occurs in the first 6 months after infection.[11, 18–20] Persistent infection with high-risk HPV is the most important risk factor for cervical cancer precursors and invasive cervical cancer.[11, 20–23]

Noncancer-related outcomes of HPV infection include anogenital warts and RRP. Almost all anogenital warts are due to infection with low-risk HPV types; approximately 90% are associated with two low-risk HPV types, types 6 and 11.[3] The prevalence of genital warts has been examined using nationally representative surveys and health-care claims data.[24, 25] An estimated 1% of sexually active adolescents and adults in the United States have clinically apparent genital warts at any given time.[26] In one national survey, 5.6% of males and females aged 14-59 reported having been diagnosed with genital warts in their lifetime.[25] RRP is a rare condition characterized by recurrent warts or papillomas in the upper respiratory tract, particularly the larynx. There are juvenile onset and adult onset forms. The juvenile onset (JORRP) form is believed to result from HPV infection transmitted perinatally from a mother to her baby during delivery. Estimates of the incidence of JORRP are relatively imprecise but range from 0.12 to 2.1 cases per 100,000 children aged <18 years.[27] Even less is known about the incidence of the adult form of RRP.

## II. Disease Description

Most instances of HPV infection are asymptomatic (no clinical manifestations). However, even asymptomatic cervical infection can result in cervical changes that can be detected as a result of cervical cancer screening with cytology (Pap test). Cervical cytology can detect changes in cervical epithelial cells (epithelial cells found on the external surface of the cervix are squamous and those in the endocervical canal are glandular).

Abnormal Pap test results are classified by increasing grade of abnormality. Since 2003, molecular tests that detect oncogenic HPV DNA have provided another screening method that may be used in conjunction with Pap tests for certain age groups or situations. Each year, approximately 50 million women in the United States undergo cervical cancer screening. Approximately 3.5–5 million will require further evaluation: 2–3 million atypical squamous cells of unknown significance (ASC-US), 1.25 million low-grade squamous intraepithelial lesions (LSIL) and 300,000 high-grade intraepithelial lesions (HSIL) Pap tests.[29–31] HPV types 16 and 18 are more commonly found in higher grade lesions than lower grade lesions. In one study, the prevalence of HPV 16 was 29.8% among women with LSIL compared to 57.8% among those with HSIL Pap tests.[28]

Regular screening for cervical cancer with the Pap test can detect cancer precursor lesions early. Abnormal Pap test results (repeated ASC-US, ASC-US with positive HPV test, or more severe abnormality) require the woman to be evaluated further with colposcopic examination of the cervix (i.e. under magnification).During colposcopy, a biopsy of the cervix may be taken for histologic examination to diagnose precancerous or invasive (either squamous cell carcinoma or adenocarcinoma) cancer lesions.Precancerous lesions include cervical intraepithelial neoplasias (CIN) grades 2 and 3 and adenocarcinoma in situ (AIS).

Cervical screening recommendations in the US differ by organization;[29] however, all recommendations state that screening should begin by age 21 years. Cervical cancer incidence rates have decreased approximately 75% and mortality rates approximately 70% since the 1950's, largely due to Pap testing.[30, 31] In 2007, cervical cancer incidence in the United States was 7.9 per 100,000 women[32], with approximately 12,200 new cases reported.[33] The median age at diagnosis for cervical cancer was 48 years.[34]

Anogenital warts typically develop approximately 2–3 months after HPV infection (typically types 6 and 11). However, not all persons infected with HPV types 6 and 11 develop genital warts. Anogenital warts can be treated, although many warts (20–30%) regress spontaneously. Recurrence of anogenital warts is common (approximately 30%), whether clearance occurs spontaneously or following treatment.[35] Juvenile-onset recurrent respiratory papillomatosis (JORRP), believed to be from vertical transmission of HPV from mother to infant during delivery, has a median age at diagnosis of 4 years. A multicenter registry of JORRP in the US collecting data between 1997 to 2002,[36] demonstrated that the clinical course of JORRP was associated with extensive morbidity, requiring a median of 13 lifetime surgeries to remove warts and maintain an open airway.

## III. Treatment of HPV-Associated Diseases

HPV infections are not treated; instead treatment is directed at the HPV-associated conditions. Current treatment options for anogenital warts and intraepithelial neoplasias vary by the severity of disease and the anatomical location as described below.

### *Anogenital warts*

The primary goal of treating visible anogenital warts is wart removal. In the majority of patients, treatment can induce wart-free periods. If left untreated, visible anogenital warts might resolve on their own, remain unchanged, or increase in size or number. It is unknown if treatment of anogenital warts affects genital transmission of HPV. No evidence indicates that the presence of genital warts or their treatment is associated with the development of cervical cancer. No single treatment is ideal for all patients. Most patients require a course of therapy rather than a single treatment.

Treatment regimens are classified into patient-applied and provider-applied modalities. Patient-applied modalities include: Podofilox solution or gel 0.5%, Imiquimod cream 5%, or sinecatechins ointment 15%; provider-administered modalities include cryotherapy, podophyllin resin 10%–25%, trichloroacetic acid (TCA) or bichloroacetic acid 80%-90%, or surgical removal. Other regimens include intralesional interferon or laser surgery.[37]

### *Cervical Cancer and Precancer*

Persistent HPV infection can result in precancerous cervical lesions as well as invasive cervical cancer. With regular cervical cancer screening and appropriate follow-up, most cervical cancer precursors can be identified and treated to interrupt progression to invasive disease. Precancerous cervical lesions and invasive cancer are diagnosed based on the histology of tissues obtained with biopsy or excision, and these samples guide further treatment decisions. Cervical cytology (Pap test) is a screening, not a diagnostic, test.

For low-grade precancerous cervical biopsy results (CIN 1), the recommended management may be to follow-up with further screening to detect persistence or progression of the lesion. For moderate to high grade precancerous cervical lesions CIN 2, CIN 3, or AIS, a woman has several treatment options including removal of the area of abnormality (laser, loop electrosurgical excisional procedure or LEEP, cold knife conization) or destruction of the area of abnormality (cryotherapy, laser vaporization).[38] Each of those have their indications, advantages and disadvantages, but, importantly, cure rates are comparable. More recently, observation is recommended over treatment for CIN 2 lesions in women of reproductive age.[38]

For invasive cervical and other HPV-associated cancers, several treatment options are available including surgery, radiation therapy, and chemotherapy, alone or in combination depending on stage of disease. For cervical cancer, depending on the stage of disease at diagnosis, a woman may have the option to preserve her fertility or keep her ovaries. The survival rate five years after diagnosis of cervical cancer varies depending upon the stage of cervical cancer. The risk of survival decreases with higher stages of disease.

## IV. Laboratory testing

HPV cannot be detected through culture methods. HPV detection requires molecular testing. As noted in the treatment section, HPV infection per se is not treated, rather treatment is directed at clinically detectable lesions associated with the infections. HPV testing has a clinical role in identifying individuals with an increased risk of an HPV-associated cervical precancer or cancer. Three tests are currently approved by the Food and Drug Administration (FDA) for detecting clinically significant levels of any of 13–14 high-risk HPV types: (1) the Digene HC2 High-Risk HPV DNA test (Qiagen, Gaithersburg, MD, http://www.qiagen.com/products/digenehpvtesthc2.aspx), (2) the Cervista™ HPV HR test (Hologics, Bedford, MA, http://www.cervistahpv.com), and (3) the cobas 4800 HPV test (Roche Molecular Systems, Pleasanton, CA, https://www.cobas-roche.co.uk). Cervista™ High-Risk and HC2 High-Risk tests indicate the presence of one or more of the high risk types but does not indicate a specific type. The cobas test also provides individual detection of HPV 16 and 18, as does another test, the CervistaTM 16/18 HPV test (Hologics, Bedford, MA, http://www.cervistahpv.com). None of the HPV tests are approved for use in men, adolescents, or detection of infection in partners.

HPV infection of epithelial cells is associated with characteristic morphologic changes, and the presence of HPV may be suggested on the basis of pathologic findings. However, definitive detection of HPV requires molecular testing. HPV testing is not used for screening of HPV associated lesions in anatomic sites other than the cervix, and it is not useful in diagnosis or clinical management of cancer, cancer precursors, or warts.

For epidemiologic and research questions using HPV as an endpoint, type-specific HPV tests have many advantages. There are many different formats, and results are dependent on the nature of the assay and the type of sample. The most common approach is to use a PCR that amplifies all mucosal HPV types (consensus PCR) with type(s) being determined by subsequent hybridization and/or sequencing of the products. These PCR tests are not useful clinically because their high analytic sensitivity detects low levels of HPV that is not predictive of disease requiring treatment.

Research tests such as serologic testing for HPV antibodies may be useful to monitor population exposure to HPV. As HPV infection is confined to the epithelium and infected cells are shed before cell death, natural HPV infection results in minimal host immune response and not all those infected have detectable antibodies. Serologic assays are currently available only in research settings.

## V. HPV Vaccine

Two HPV vaccines are licensed in the US: a quadrivalent vaccine (HPV4; Gardasil, Merck and Co, Inc.) and a bivalent vaccine (HPV2; Cervarix, GlaxoSmithKline).[39] Neither vaccine is a live vaccine; both vaccines are composed of virus-like particles (VLPs) prepared from recombinant L1 capsid protein of the targeted HPV types. HPV2 is directed against two oncogenic types (HPV 16 and 18). HPV4 is directed against two oncogenic types (HPV 16 and 18) and two non-oncogenic types (HPV 6 and 11). The vaccines are prophylactic and have no therapeutic effect on HPV-related disease, or on risk of progression to disease in persons who have HPV infection at the time of vaccination. HPV4 (Gardasil) was licensed by the Food and Drug Administration (FDA) in 2006 for use in females aged 9 through 26 years and in 2009 for use in males aged 9 through 26 years. HPV2 (Cervarix) was licensed by the FDA in 2009 for use in females aged 10 through 25 years.[40, 41]

Clinical trials in >18,000 females aged 15–25 years for HPV2 and >20,000 females aged 16–26 for HPV4 have demonstrated high levels of efficacy for both vaccines in preventing cervical precancers (CIN 2/3 and AIS) caused by the targeted HPV types in females naïve to vaccine type infection at the time of vaccination.[42, 43] HPV4 also has demonstrated high efficacy against HPV 6 and HPV 11-related genital warts (males and females), HPV 16 and 18-related vaginal and vulvar precancer lesions, and HPV 16 and 18 related anal precancers (males).[42] In post hoc analyses, HPV2 demonstrated partial efficacy against incident cervical precancers related to non-vaccine HPV types 31 and 45 and HPV4 showed partial efficacy against HPV 31.[43]

Immunogenicity and safety studies were conducted in females aged 9 to 15 (quadrivalent vaccine)[44] and females aged 10–14 years (bivalent vaccine)[45] of age to bridge the antibody titers to females in the efficacy trials. For both vaccines, over 99% of study participants developed antibodies after vaccination; titers were higher for young girls than for older females participating in the efficacy trials.

Data from clinical trials demonstrated high efficacy of the quadrivalent vaccine against HPV vaccine type-related genital warts and anal HPV vaccine type-related precancers among males aged 9–26 years.[46] These data supported FDA licensure of the quadrivalent vaccine for prevention of genital warts and anal cancers among males aged 9–26 years.

Each 0.5-mL dose of HPV4 contains 20 µg HPV 6 L1 protein, 40 µg HPV 11 L1 protein, 40 µg HPV 16 L1 protein, and 20 µg HPV 18 L1 protein. The VLPs are adsorbed on 225 ug amorphous aluminum hydroxyphosphate sulfate adjuvant (alum). Each 0.5-mL dose of HPV2 contains 20 µg HPV 16 L1 protein and 20 µg HPV 18 L1 protein. The VLPs are adsorbed on 500 µg aluminum hydroxide and 50 µg 3-O-desacyl-4' monophosphoryl lipid A adjuvant.

## VI. Recommendations for Use of HPV vaccines.[40, 46] *(see Appendix B)*

Both HPV vaccines are administered intramuscularly as 3 separate 0.5 ml doses. The second dose should be administered 1–2 months after the first dose, and the third dose is administered 6 months after the first dose.

### *Female vaccination*

The Advisory Committee on Immunization Practices (ACIP) recommends vaccination with HPV2 or HPV4 vaccine for prevention of cervical cancers and precancers. Both vaccines may also provide protection against other HPV-related cancers in addition to cervical cancer. HPV4 vaccine is also recommended for prevention of genital warts in females.

ACIP recommends routine vaccination of females 11 or 12 years of age with three doses of either HPV2 or HPV4 vaccine. The vaccination series can be started as young as 9 years of age. Catch up vaccination with either vaccine is also recommended for females 13 through 26 years of age who have not been previously vaccinated or who have not completed the full series. Sexually active females who have not been infected with any of the HPV vaccine types would receive full benefit from vaccination. However, the great majority of females who may have

already been exposed to one or more of the HPV vaccine types can benefit from vaccination, even though benefit would be less. Pap testing, screening for HPV DNA or HPV antibody are not needed prior to vaccination at any age.

Whenever feasible, the same HPV vaccine should be used for the complete vaccination series. However, in the absence of information on previous doses, either vaccine can be used to complete the series for protection against HPV types 16 and 18. A vaccination series with less than 3 doses of HPV4 may provide less protection against HPV 6 or 11-related genital warts.

### *Male vaccination*

ACIP provides guidance that HPV4 may be given to males aged 9 through 26 years; however, vaccine for males is not part of the routine immunization schedule.

### *Cervical cancer screening among vaccinated females*

At present, cervical cancer screening recommendations have not changed for females who receive HPV vaccine. Health care providers administering HPV vaccine should educate women about the importance of cervical cancer screening as recommended by national organizations.

### *Immunocompromised persons*

Because HPV2 and HPV4 vaccines are non infectious vaccines, they can be administered to females who are immunosuppressed as a result of disease or medications; however, the immune response and vaccine efficacy might be less than that in persons who are immunocompetent.

### *Vaccination during Pregnancy*

HPV2 and HPV4 vaccines are not recommended for use in pregnancy. If a woman is found to be pregnant after initiating the vaccination series, the remainder of the 3-dose regimen should be delayed until after completion of the pregnancy. If a vaccine dose has been administered during pregnancy, there is no indication for any intervention.

### *Precautions and Contraindications*

**1) Acute Illnesses**

HPV2 and HPV4 vaccines can be administered to persons with minor acute illnesses (e.g., diarrhea or mild upper respiratory track infections, with or without fever). Vaccination of persons with moderate or severe acute illnesses should be deferred until after the illness improves.

**2) Hypersensitivity or allergy to vaccine components**

HPV2 is contraindicated for persons with a history of immediate hypersensitivity to any vaccine component. The prefilled syringes of HPV2 should not be used in persons with anaphylactic latex allergy because syringes have latex in the rubber stopper. HPV2 single dose vials contain no latex. HPV4 is contraindicated for persons with a history of immediate hypersensitivity to yeast or to any vaccine component.

## VII. Importance of Surveillance

Identification of every instance of HPV infection is not necessary. This is because (1) most sexually active individuals will acquire HPV infection at some point in their lives and infections usually clear or become undetectable, and (2) most infections will not have any associated clinical disease. However, special studies to monitor HPV infection and HPV-associated diseases, especially cervical cancer, can help determine the impact of HPV vaccines. Existing and new systems are in place to monitor coverage and impact of HPV vaccine on short-, medium-, and long-term outcomes in the US (see Enhanced Surveillance section).

## VIII. Disease Reduction Goals

Since the quadrivalent HPV vaccine was licensed in 2006, Healthy People 2020 states a goal of 80% coverage of 3 doses of HPV vaccines for females by age 13 to 15 years.[47] It also states a goal to "Reduce the death rate from cancer of the uterine cervix below a target of

2.2 deaths/100,000 females (from a baseline of 2.4 per 100,000 in 2007)." There is also a stated goal to "increase the proportion of women who receive a cervical cancer screening based on the most recent guidelines" with a target of 90% of women aged 21 to 65 years receiving screening (from a baseline of 84.5 percent in 2008). There are currently no stated goals for reduction of anogenital warts, RRP or non-cervical HPV-associated cancers.

Another Healthy People 2020 objective addresses surveillance to "increase the number of central, population-based registries from the 50 States and the District of Columbia that capture case information on at least 95 percent of the expected number of reportable cancers".

## IX. Case Definitions

There are currently no case definitions approved by the Council of State and Territorial Epidemiologists (CSTE) for the National Notifiable Diseases Surveillance System for HPV infection or any HPV-associated conditions including anogenital warts, RRP, precancerous lesions, or invasive cancers. However, explanations provided below are intended to describe classification of HPV-associated endpoints where surveillance is possible:

**HPV Infection:** Routine testing for HPV infection is not recommended. Testing for high risk types is clinically indicated in two specific clinical situations: (1) in order to triage women with ASC-US Pap tests for further evaluation, and (2) as an adjunct to Pap testing for women age 30 years and older. Tests for low risk HPV infection are not recommended by any clinical or medical organization.

**Abnormal Pap tests and precancerous anogenital lesions:** Pap tests are based on the cytology of the cells and are collected by scraping or brushing cells from the surface of the cervix (exfoliated cytology). Abnormal Pap test categories are listed by increasing grade of severity for squamous lesions: ASC-US; atypical squamous cells-cannot rule out high grade squamous intraepithelial lesion (ASC-H); low grade intraepithelial lesions (LSIL); and high grade intraepithelial lesions (HSIL). Categories for glandular lesions include atypical glandular cells (AGC) and adenocarcinoma in situ (AIS). Precancerous lesions (CIN 2/3 and AIS) are diagnosed by pathologists on specimens from cervical biopsy prompted by an abnormal Pap tests. Precancerous lesions are also defined for grade 2 or 3 vaginal intraepithelial neoplasias (VAIN 2/3), vulvar intraepithelial neoplasias (VIN 2/3), and anal intraepithelial neoplasia (AIN 2/3) These are defined and used for clinical diagnostics and management.

**Anogenital and oropharyngeal cancers:** The primary site and pathologic diagnosis of the cancers are coded using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3).

**Anogenital warts:** A diagnosis of anogenital warts is made based on visual inspection of the lesion(s). There are no case definitions for anogenital warts used for surveillance purposes.

**Recurrent Respiratory Papillomatosis:** RRP is diagnosed by a specialist based upon clinical evaluation. No case definitions for RRP are currently in use for surveillance purposes.

## X. Reporting

In the US, disease burden from cervical and other HPV-related cancers are measured by population-based cancer registries participating in the Centers for Disease Control and Prevention's (CDC's) National Program of Cancer Registries (NPCR) and/or the Surveillance Epidemiology and End Results (SEER) program. Data are collected and analyzed at the state (central cancer registries) as well national (NPCR/SEER) levels (see Appendix C).

HPV infection and other HPV-associated clinical conditions are not nationally reportable or required by CDC. However, some states or jusisdictions have made some HPV-associated conditions reportable. Contact the state health department for reporting requirements in your state.

## XI. Enhancing Surveillance

The goal of HPV vaccination is to prevent clinical conditions associated with infection with vaccine HPV types, with the primary goal being prevention of cervical cancers. However, monitoring the impact of a vaccination program poses many challenges because infection with HPV is relatively common, a high proportion of infections are asymptomatic and the consequences are not seen for many years.

Cervical cancer surveillance data (as well as data on other HPV-associated cancers) are collected by the NPCR and SEER population-based cancer registries which cover over 99% of the US population. Data from the registries have been used to assess the pre-vaccine burden of HPV-associated cancers and will be the basis for monitoring relevant cancers post-vaccine introduction. However, the impact of vaccine on invasive cancers is not expected until several decades after widespread adoption of the vaccine.

The proximal measures of vaccine impact include outcomes such as cervical cancer precursors, anogenital warts, and HPV infection. Although these outcomes are not nationally notifiable, a variety of activities have been established to monitor these endpoints in the US48 as described below.

Projects have been initiated to determine the feasibility of monitoring HPV vaccine impact on high grade HPV-associated cervical lesions and include state wide or sentinel population monitoring of cervical precancers as well as HPV type specific CIN2/3 and AIS.

Methods for monitoring genital warts in the US include surveillance in a network of STD clinics and through self report of ever being diagnosed with genital warts in the National Health and Examination Survey (NHANES), a nationally representative survey of the US population. NHANES data are also used to monitor the prevalence of type specific HPV infection in US females.

Additional ongoing efforts include analysis of data from administrative claims and managed care organizations to monitor HPV-associated conditions and determine the impact of HPV vaccine on health care costs related to detection and treatment of these conditions. Finally, a pilot study was initiated in 5 cancer registries in areas with a high burden of cervical cancer to evaluate baseline HPV types in cervical and other relevant cancers, and typing may be repeated in similar special projects in the future.

Although CDC does not recommend collection of routine surveillance data with respect to HPV-associated conditions other than cancer, these data may be useful in sentinel projects with resources to collect data and and where rigorous methods are utilized within specific states and jurisdictions. Within these settings, making conditions reportable, such as CIN2/3, may facilitate complete collection of data and has been initiated in some states/jurisdictions.

## Appendix A.

### Cancers Attributable to High-Risk Human Papillomavirus Infection, US, 2004-2007

| Anatomic Area | Average annual number of cases* | HPV associated+ | HPV 16/18 associated+ |
|---|---|---|---|
| Cervix | 11,845 | 11,370 | 9 ,000 |
| Vagina | 714 | 460 | 400 |
| Vulva | 3062 | 1,560 | 1,350 |
| Anus & rectum (W) | 2977 | 2,770 | 2,590 |
| Oropharynx (W) | 2306 | 1,450 | 1,380 |
| **Total (Females)** | **20,903** | **17,610** | **14,720** |
| Penis | 1,000 | 360 | 310 |
| Anus & Rectum (M) | 1,618 | 1,500 | 1,410 |
| Oropharynx (M) | 8,936 | 5,630 | 5,360 |
| **Total (Males)** | **11,553** | **7,490** | **7,080** |

** Watson M et al. Cancer 2008*
*+ Gillison ML et al. Cancer 2008*

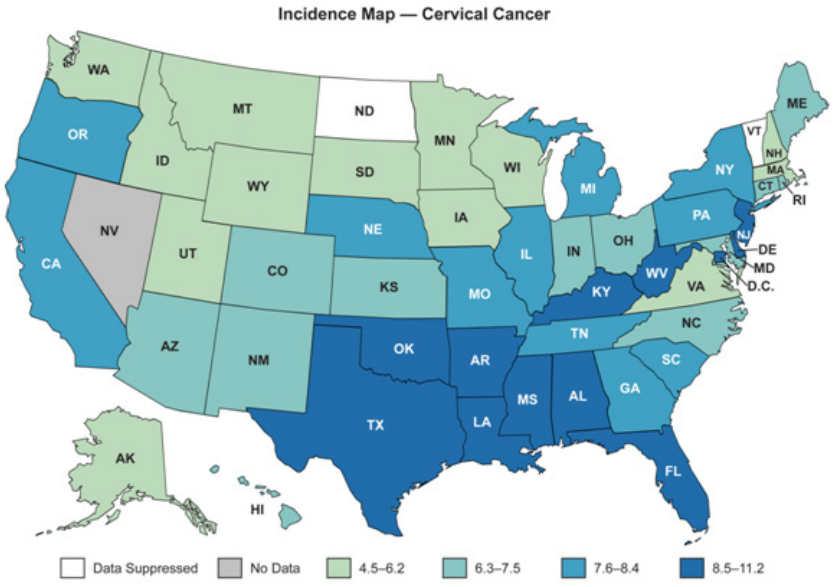
## Appendix B.

### ACIP Recommended Age Groups, Schedule, Dosages and Route of Administration for HPV vaccines

| Target population | ACIP Recommendation | Vaccine | Schedule | Dosage, Route |
|---|---|---|---|---|
| Females | Routine at ages 11 or 12 years and catch up through age 26 years | Quadrivalent or Bivalent vaccine | 0, 1-2, 6 months | 0.5 ml, Intramuscular injection |
| Males | May be given to males age 9 through 26 years | Quadrivalent | | |

## Appendix C.

### United States Cervical Cancer* Incidence Rates by State, 2007†




** Rates are per 100,000 and are age-adjusted to the 2000 US standard population.*
*† Source: US Cancer Statistics Working Group. United States Cancer Statistics: 2003 Incidence and Mortality (preliminary data). Atlanta (GA): US Department of Health and Human Services, Centers for Disease Control and Prevention, and National Cancer Institute; 2006.*

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# Chapter 6: Influenza

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## I. Disease Description

Influenza is an acute respiratory disease caused by infection with influenza viruses. The incubation period ranges from 1 to 4 days. Peak virus shedding usually occurs from 1 day before onset of symptoms to 3 days after. Typical features of influenza include abrupt onset of fever and respiratory symptoms such as cough (usually nonproductive), sore throat, and coryza, as well as systemic symptoms such as headache, muscle aches, and fatigue. The clinical severity of infection can range from asymptomatic illness to primary viral pneumonia and death. Acute symptoms generally last 2–7 days, although malaise and cough may continue for 2 weeks or longer. Complications of influenza infection include secondary bacterial pneumonia and exacerbation of underlying chronic health conditions. Complications occurring in children can include otitis media, febrile seizures, encephalopathy, transverse myelitis, myositis, myocarditis, pericarditis, and Reye syndrome.[1–5] Aspirin and other salicylate-containing medications are contraindicated for children and adolescents with influenza like illness, as their use during influenza infection has been associated with the development of Reye syndrome.

The sharp rise in influenza-associated acute respiratory illnesses that occurs during annual seasonal epidemics results in increased numbers of visits to physicians' offices, walk-in clinics, and emergency departments. Hospitalizations for pneumonia and other complications also increase. Persons 65 years of age and older, young children, and persons of any age with certain underlying health problems are at increased risk for complications of influenza and hospitalization. Because influenza seasons are unpredictable and often fluctuate in length and severity, the number of seasonal influenza-associated deaths varies from year to year. It is estimated that from the 1976-1977 season to the 2006-2007 influenza season, influenza-associated deaths ranged from 3,000 to 49,000 people.[6] More than 90% of influenza-associated deaths occur among persons age 65 years and older.

## II. Background

Influenza viruses can be divided into three types; A, B, and C. Influenza type C viruses are not associated with severe disease, epidemics or pandemics and will not be discussed further. Influenza type A viruses are divided into subtypes based on surface proteins called hemagglutinin (HA) and neuraminidase (NA).[7] There are 16 known hemagglutinin and 9 known neuraminidase subtypes. Influenza viruses can infect a wide range of animals, such as pigs, birds, horses, cats, ferrets, dogs, and whales. While influenza A viruses of only a few HA subtypes have been isolated from mammals, all of the known HA and NA subtypes have been isolated from avian species. The two influenza A virus subtypes that have cocirculated in human populations since 1977 are influenza A (H1N1) and A (H3N2). A reassortment of the influenza A (H1N1) and A (H3N2) viruses resulted in the circulation of A (H1N2) virus during the 2001–02 and 2002–03 influenza seasons. In April 2009, a novel influenza A (H1N1) virus, 2009 influenza A (H1N1), which was different from currently circulating influenza A (H1N1) viruses, emerged and its subsequent spread resulted in the first pandemic of the 21st century.

Influenza A and B viruses both undergo gradual, continuous change in the HA and NA proteins, known as antigenic drift. As a result of these antigenic changes, antibodies produced to influenza viruses as a result of infection or vaccination with earlier strains may not be protective against viruses circulating in later years. Consequently, yearly epidemics usually occur in populations, and multiple infections can occur over a person's lifetime. Antigenic changes also necessitate frequent updating of influenza vaccine components to ensure that the vaccine is matched to circulating viruses. In addition to antigenic drift, influenza type A viruses can undergo a more dramatic and abrupt type of antigenic change called an antigenic shift, which occurs when viruses belonging to a new influenza A subtype bearing either a novel HA protein or novel HA and NA proteins infect humans. A novel HA protein can include a virus of the same subtype but be dramatically antigenically different, as was seen during the

2009 H1N1 pandemic, where the HA likely came from a swine reservoir. While antigenic drift occurs continuously, antigenic shift occurs infrequently. When antigenic shift does occur, a large proportion, or even all, of the world's population has no antibody against the new virus. If the novel influenza A virus causes disease and is transmissible among humans, a worldwide epidemic called a pandemic may result. Novel influenza A viruses, but not influenza B viruses can cause influenza pandemics. During the 20th century, pandemics occurred in 1918 (A[H1N1]), 1957 (A[H2N2]), and 1968 (A[H3N2]). In April 2009, 2009 influenza A (H1N1) virus emerged to cause the first influenza pandemic in more than 40 years.

## III. Vaccination

Annual influenza vaccination is recommended for all persons 6 months of age and older.[8] Protection of persons at higher risk for influenza-related complications should continue to be a focus of vaccination efforts. When vaccine supply is limited, efforts should focus on delivering vaccination to protect persons at higher risk for severe influenza related complications, including the following groups:

- Children aged 6 months through 4 years (59 months)[8–12]
- Persons 50 years of age and older
- Women who are or will be pregnant during the influenza season
- Residents of nursing homes and other long-term care facilities that house persons of any age with chronic medical conditions
- Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus)
- Persons who are immunosuppressed, including immunosuppression caused by medications or by human immunodeficiency virus
- Children and adolescents (6 months–18 years of age) who are receiving long-term aspirin therapy and therefore might be at risk for developing Reye syndrome after influenza
- American Indians and Alaska Natives
- Persons who are morbidly obese (body-mass index ≥ 40)
- Health-care personnel
- Household contacts and caregivers of children aged <5 years and adults aged ≥ 50 years, particularly contacts of children aged < 6 months. (The pediatric group at greatest risk of complications is children younger than six months old. Influenza vaccines are not approved by the Food and Drug Administration [FDA] for use among children younger than six months.)[8]
- Household contacts and caregivers of persons with medical conditions that put them at higher risk for severe complications of influenza

In the United States, both inactivated and live attenuated influenza vaccines are available. The live attenuated influenza vaccine (LAIV), which is administered intranasally, is approved for use in healthy persons age 2 through 49 years. Inactivated vaccine (also called trivalent inactivated vaccine, or TIV) is administered by injection. Inactivated vaccines are available for use in persons 6 months of age and older. However, inactivated vaccines are available from several different manufacturers, and the recommended ages for individual brands of vaccines vary. For the 2010-11 influenza season, a newly approved inactivated TIV containing 60 mcg of HA per influenza vaccine virus strain (Fluzone High-Dose [Sanofi Pasteur]) was approved as an alternative inactivated vaccine for persons aged ≥ 65 years.[8] An intradermal vaccine was licensed by the Food and Drug Administration (FDA) for use in adults 18-64 years beginning in the 2011-2012 influenza season. Information regarding the age group for whom a given vaccines is recommended can be found in the package insert.

Both LAIV and TIV are trivalent vaccines, containing three different influenza virus strains: influenza A (H3N2), influenza A (H1N1), and influenza B. Each year, vaccine strains are selected to represent the strains judged most likely to circulate during the influenza season in the United States. Typically, one or two of the three vaccine components are updated each year to provide a better antigenic match with circulating viruses.

The effectiveness of influenza vaccines varies from season to season, and depends upon a number of factors. One factor is how well the vaccine strains match the viruses that actually circulate during the season. In addition, vaccine effectiveness is affected by the recipient's age, immunocompetence, and previous exposure to influenza viruses.

The best estimates of influenza vaccine efficacy come from randomized controlled trials (RCTs) that compare the rates of laboratory-confirmed influenza or an influenza-related outcome in persons who receive vaccine as with those who receive a placebo. It is not always feasible to perform randomized trials, however. For example, once a vaccine is recommended for use in a certain group, it is considered unethical to perform studies in which some people receive placebo, particularly among people who are recommended to receive vaccine (such as pregnant women, high risk individuals or people 65 years of age and older), because withholding vaccine from these groups could place them at risk for serious complications from influenza. For this reason, estimates of vaccine efficacy are usually derived from observational studies of vaccine effectiveness.

Historically, many studies of influenza vaccine efficacy and effectiveness have used nonspecific outcomes, such as influenza-like illness (ILI), hospitalizations, and all-cause mortality. Serologic evidence of influenza virus infection is also commonly used. The most accurate influenza vaccine efficacy and effectiveness estimates come from studies that use influenza-specific outcomes, such as laboratory-confirmed (e.g., by serology or RT-PCR) influenza virus infection. Such tests can be costly and take time to perform. As more and better diagnostic tests become available, more accurate and consistent assessments of influenza vaccine efficacy and effectiveness may be possible.

Recent RCTs of inactivated influenza vaccine among adults under 65 years of age have estimated 50-70% efficacy during seasons in which the vaccines' influenza A strains were well-matched to circulating influenza A viruses[13-15] which is the usual situation. The benefits of vaccination may be reduced during seasons in which the vaccine strains are poorly matched to the circulating strains. For example, in a case-control study among persons during the 2004-2005 influenza season, where the predominant virus recovered from study patients was a drift variant of the influenza H3N2 vaccine strain, inactivated influenza vaccine effectiveness against laboratory confirmed influenza was 5% among study participants.[16]

Only one large randomized controlled trial of influenza vaccine has been conducted among an elderly population. During the 1991-1992 influenza season, a study of Dutch community dwelling people aged 60 years of age and older reported a vaccine efficacy of 58% (95% CI = 26% - 77%) against laboratory-confirmed influenza illness during a season which the vaccine strains were considered to be well-matched to circulating strains.[17] There are no published studies of the efficacy or effectiveness of influenza vaccines in preventing laboratory-confirmed, serious outcomes of influenza such as hospitalization in the elderly.

Estimates of vaccine efficacy among children aged ≥ 6 months have varied by season and study design. In a randomized controlled trial among children aged 1–15 years, inactivated influenza vaccine efficacy was determined to be 77% against influenza A (H3N2) and 91% again influenza A (H1N1) virus infection.[18] A randomized, double-blind, placebo-controlled trial conducted during two influenza seasons among children aged 6-24 months indicated that inactivated influenza vaccine had 66% efficacy against culture-confirmed influenza illness during the 1999-2000 influenza season but did not reduce culture-confirmed influenza illness substantially during the 2000-2001 influenza season.[19]

In a randomized, double-blind, placebo-controlled experimental influenza virus challenge study among 92 healthy adults aged 18–41 years, the efficacy of inactivated and live attenuated influenza vaccines in preventing laboratory-confirmed influenza was 71% and 85%, respectively. The difference in efficacy between the two types of vaccines was not statistically significant.[20]

## IV. Antiviral Drugs

Antiviral medications with activity against influenza viruses are an important adjunct to influenza vaccine in the control of influenza. Antiviral treatment can reduce the risk of complications from influenza and is recommended as early as possible for any patient with confirmed or suspected influenza who is hospitalized, has severe, complicated, or progressive illness, or is at higher risk for influenza complications. The benefits of antiviral treatment are likely to be greatest if treatment is started as soon as possible after illness onset, and evidence for benefit is strongest in studies in which treatment was started within 48 hours of illness onset.[21] Antiviral treatment might still be beneficial in patients with severe, complicated, or progressive illness and in hospitalized patients when administered >48 hours from illness onset.[21] In such cases, decisions on starting antiviral treatment should not wait for laboratory confirmation of influenza.

Four antiviral medications in two drug classes are currently approved for use in the United States: the adamantanes—amantadine and rimantadine—and the neuraminidase inhibitors—zanamivir and oseltamivir. However, only zanamivir and oseltamivir are currently recommended for use to prevent or treat influenza, due to high levels of influenza virus resistance to adamantanes among circulating influenza virus A strains.

Resistance of influenza A viruses to adamantanes can occur spontaneously or emerge rapidly during treatment.[22] After the 2005–06 influenza season, resistance of influenza A (H3N2) viruses to amantadine and rimantadine increased dramatically and currently viruses of this subtype are resistant to these drugs. Almost all 2009 influenza A (H1N1) viruses are also resistant to amantadine and rimantadine. Because of this, CDC has recommended that the adamantanes not be used for treatment or chemoprophylaxis of influenza A virus infections.[23-24] The adamantanes have no activity against influenza B virus infections.

Zanamivir and oseltamivir are active against both influenza A and B viruses. Zanamivir is approved for treatment of uncomplicated influenza in person 7 years of age and older and for chemoprophylaxis in persons 5 years of age and older. Oseltamivir is approved for treatment or chemoprophylaxis of influenza in persons 1 year of age and older. Antiviral medications are not currently approved by the Food and Drug Administration (FDA) for use in children aged <1 year.[21] However, oseltamivir may be used for treatment or chemoprophylaxis of influenza among infants aged <1 year when indicated at the discretion of the treating physician.[21] When administered prophylactically to healthy adults or children, oseltamivir and zanamivir are 70%–90% effective in preventing illness from influenza A or B virus infection.[25–29] Resistance of influenza viruses to oseltamivir and zanamivir is being monitored, and as of March 2011-low levels of resistance among influenza A and influenza B viruses have been reported.[30]

Persons at higher risk for influenza-associated complications recommended for antiviral treatment include:

- children aged <5 years (especially those aged <2 years);
- adults aged ≥65 years;
- persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematologic (including sickle cell disease), metabolic disorders (including diabetes mellitus) or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy (seizure disorders), stroke, intellectual disability (mental retardation), moderate to severe developmental delay, muscular dystrophy, or spinal cord injury) (8);
- persons with immunosuppression, including that caused by medications or by HIV infection;
- women who are pregnant or postpartum (within 2 weeks after delivery);
- persons aged ≤18 years who are receiving long-term aspirin therapy;
- American Indians/Alaska Natives;
- persons who are morbidly obese (i.e., BMI ≥40); and
- residents of nursing homes and other chronic-care facilities.

## V. Importance of Rapid Case Identification

Rapid identification of influenza virus infection can assist healthcare providers in determining optimal strategies for preventing or treating influenza. In an institutional setting this may include the administration of antiviral drugs to reduce the spread of influenza. Rapid diagnosis of influenza illness occurring early in the season can be used to prompt members of target groups to receive vaccine before illness becomes widespread in the community.

## VI. Importance of Surveillance

Because influenza viruses undergo constant antigenic change, both virologic surveillance (in which influenza viruses are isolated and used for antigenic and genetic analysis as well as for antiviral resistance testing) and disease surveillance are necessary to identify influenza new virus variants, to monitor their health impact in populations, and to provide data necessary for selection of influenza vaccine components each year. Knowledge of the prevalent circulating virus type/subtype can also assist healthcare providers in making treatment decisions. For example, if influenza activity has been confirmed in a community, antiviral drugs may be used to treat patients with influenza-like illness within 48 hours of onset of symptoms to reduce the length and severity of illness. With the increased use of antiviral drugs, virologic surveillance also is important to determine the level of drug-resistance among circulating influenza viruses. Finally, disease surveillance allows for identification of high-risk persons, determination of the effectiveness of current prevention strategies, and refinement of vaccine and antiviral recommendations each year.

## VII. Importance of Vaccination

### *Annual vaccination of persons at high risk for influenza*

Vaccination against influenza is the most important method of prevention. Annual vaccination against influenza is recommended for all persons aged 6 months or older. Previous vaccination may offer little or no protection against viruses that have undergone substantial antigenic drift. Even when a vaccine component remains the same, immunity induced by the vaccine declines over time and may not be protective during the next season. Finally, while antiviral agents can be a useful adjunct to vaccination, treatment with licensed drugs is not a substitute for influenza vaccination.

### *Disease reduction goals*

The U.S. Department of Health and Human Services has established the following *Healthy People 2020* goals:

- Increase the proportion of children and adults who are vaccinated against seasonal influenza each year, including institutionalized adults aged 18 years and older in long-term or nursing homes, health care personnel, and pregnant women.[31]
- Increase the number of public health laboratories monitoring influenza-virus resistance to antiviral agents.[31]

## VIII. Case Definitions

Definitive diagnosis of influenza requires laboratory confirmation in addition to signs and symptoms. Case definitions for influenza-like illness are non specific for influenza and vary depending on the purpose for which they are used. A case definition of fever 100°F or greater, oral or equivalent, and cough and/or sore throat is used by CDC in its U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet), in which healthcare providers report the total number of patient visits and the number of patients seen for influenza-like illness each week.

## IX. Laboratory Testing

Influenza virus infection cannot be diagnosed accurately based on signs and symptoms alone. Laboratory testing is necessary to confirm the diagnosis.

Although influenza virus infection generally leads to more severe illness among adults than other respiratory viruses, individual cases of influenza cannot be distinguished from other respiratory virus infections based on clinical information alone. Methods available for the diagnosis of influenza include virus isolation (standard methods and rapid culture assays), molecular detection (reverse transcription polymerase chain reaction [RT-PCR]), detection of viral antigens (enzyme immunoassays [EIA] and immunoflourescence [DFA/IFA] testing), detection by commercially available rapid influenza diagnostic tests, and less frequently, by use of immunohistochemistry [IHC], and serologic testing.[32-33] The state health department should be contacted for information regarding the availability of testing and the methods used.

For additional information on laboratory support for surveillance, see Chapter 22, "Laboratory Support for Surveillance of Vaccine-Preventable Diseases."

### *Virus isolation and rapid culture assays*

Virus isolation is essential for virologic surveillance. Appropriate clinical specimens used for virus isolation include nasal washes, nasopharyngeal aspirates, nasal and throat swabs, tracheal aspirates, and bronchoalveolar lavages. Specimens should be taken within 72 hours of onset of illness. Influenza viruses can be isolated in fertilized chicken eggs or in tissue cell culture. The Madin-Darby canine kidney (MDCK) cell line and primary rhesus or cynomolgus monkey kidney cells support the growth of influenza viruses. Virus isolation has the advantage of producing quantities of virus sufficient for full antigenic characterization, which is required for determining vaccine match, and conducting testing for antiviral resistance. Standard isolation procedures have the disadvantage of requiring several days to obtain results, thereby making them less useful to the clinician.

Rapid culture assays that use immunologic methods to detect viral antigens in cell culture are available. The results of these assays can be obtained in 18–40 hours compared with an average of 4.5 days to obtain positive results from standard virus culture.[33]

### *Molecular testing methods*

RT-PCR is the most sensitive method for the detection of influenza virus and the gold standard for influenza diagnosis. The use of molecular techniques to directly detect virus in respiratory samples can provide rapid identification of viruses. RT-PCR is a powerful technique for identifying influenza virus genomes even when they are present at very low levels. RT-PCR can be used for detection of influenza viruses in original respiratory samples taken from patients with influenza-like illness, or for the characterization of viruses grown in tissue culture or embryonated eggs. RT-PCR testing with use of original clinical respiratory samples can be performed under biosafety level 2 conditions even for highly pathogenic viruses such as avian influenza A (H5N1) virus, which requires biosafety level 3 with enhancements for viral culture.

### *Antigen detection assays*

Several methods exist for the diagnosis of influenza infection directly from clinical material. Cells from the clinical specimen can be stained using an immunofluorescent antibody that reveals the presence of viral antigen. Nasal washes, nasopharyngeal aspirates, nasal and throat swabs, transtracheal aspirates, and bronchoalveolar lavages are suitable clinical specimens. Commercially available rapid diagnostic kits test for the presence of viral antigens, although these tests are usually less sensitive than RT-PCR testing. Currently available rapid influenza diagnostic tests fall into two groups tests that detect both influenza type A and B viruses but do not differentiate between virus types, and those that detect both influenza type A and B viruses and distinguish between the two. Results of these rapid influenza antigen detection tests can be available in 15 minutes or less. Another less frequently used antigen detection method is immunoflourescence using staining of respiratory specimens with monoclonal antibodies and visualization of viral antigens using a fluorescent microscope. This method and RT-PCR methods may also be used for detection of influenza antigens and nucleic acids, respectively, in postmortem respiratory tissue samples.

When direct antigen detection or molecular detection methods are used for the diagnosis of influenza, it is important to collect and save an aliquot of the clinical sample for possible further

testing. These samples may be used for culture confirmation of direct test results and isolation for subtyping of influenza A isolates by the state public health laboratory. For some rapid testing methods the medium used to store the specimen is inappropriate for viral culture; in this case, it is necessary to collect two separate specimens.

Full antigenic characterization of the virus may be performed by the U.S. World Health Organization (WHO) Collaborating Center for Surveillance, Epidemiology, and Control of Influenza, Influenza Division, CDC. Characterization of isolates is necessary for the detection and tracking of antigenic variants, an essential part of the selection of optimal influenza vaccine components.

### *Serologic testing*

While serologic testing can be useful in certain situations where viral culture is not possible or in special studies, serologic diagnosis of seasonal influenza using a single serum specimen is not accepted for the purposes of clinical diagnosis or national surveillance because of a lack of standardized methods for testing and interpretation. Paired serum specimens are required for serologic diagnosis of influenza virus infection. The acute-phase specimen should be collected within 1 week of the onset of illness, and preferably within 2–3 days. The convalescent-phase sample should be collected approximately 2–3 weeks later. Hemagglutination inhibition tests are most commonly used for serodiagnosis. A positive result is a fourfold or greater rise in titer between the acute- and convalescent-phase samples to one type or subtype of virus. For example, if the initial serum dilution is 1:10, twofold serial dilutions would result in serum concentrations of 1:10, 1:20, 1:40, 1:80, etc. A fourfold or higher increase in titer between the acute- and convalescent-phase sera (e.g., from 1:20 to 1:80 or higher) is considered positive. A twofold increase between the two sera (e.g., from 1:20 to 1:40) is within the variability of the test and is not considered a positive finding. Vaccination history of the patient must also be taken into account to ensure that a rise in titer reflects infection rather than a recent influenza vaccination. Because most human sera contain antibodies to influenza viruses, diagnosis of influenza cannot be made from a single serum sample.

## X. Reporting

Influenza-associated deaths among children younger than 18 years of age and human infection with a novel influenza A virus are reported through the National Notifiable Diseases Surveillance System (NNDSS). Other influenza virus infections are not nationally notifiable but may be reported in some states. Local health departments should contact the state health department for guidelines on reporting individual cases or outbreaks of influenza.

Influenza surveillance in the United States consists of five categories of information collected from nine data sources:

- Viral surveillance
  - U.S. WHO collaborating laboratories
  - National Respiratory and Enteric Virus Surveillance System (NREVSS)
  - Novel influenza A reporting
- Outpatient illness surveillance
  - U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet)
- Mortality surveillance
  - 122 Cities Mortality Reporting System
  - Influenza-associated pediatric mortality reporting
- Hospitalization surveillance
  - Influenza Hospitalization Network (FluSurv-NET)
  - Aggregate Hospitalization and Death Reporting Activity (AHDRA)
- Summary of the geographic spread of influenza
  - State and territorial epidemiologists' reports of influenza activity level

In addition, outbreaks of influenza or influenza like illness may be reported to CDC from other sources, such as a state health department, a collaborating hospital or university laboratory, or an institution experiencing an outbreak.

### *WHO and NREVSS collaborating laboratories*

Approximately 80 U.S. **World Health Organization (WHO) Collaborating Laboratories** and 60 **National Respiratory and Enteric Virus Surveillance System (NREVSS)** laboratories located throughout the United States participate in virologic surveillance for influenza viruses. All state public health laboratories participate as U.S. WHO collaborating laboratories along with some county public health laboratories and some large tertiary care or academic medical centers. Most NREVSS laboratories participating in influenza surveillance are hospital laboratories. The U.S. WHO and NREVSS collaborating laboratories report the total number of respiratory specimens tested and the number positive for influenza virus types A and B each week to CDC. Most of the U.S. WHO collaborating laboratories also report the influenza A subtype (H1 or H3) of the viruses they have isolated and the ages of the persons from whom the specimens were collected. The majority of NREVSS laboratories do not report the influenza A virus subtype. Reports from both sources are combined and the weekly total number of positive influenza tests, by virus type/subtype, and the percent of specimens testing positive for influenza are presented in the weekly influenza update, FluView (http://www.cdc.gov/flu/weekly/). A subset of the influenza viruses collected by U.S. WHO collaborating laboratories are sent to CDC for further characterization, including gene sequencing, antiviral resistance testing and antigenic characterization.

### *Novel influenza A reporting*

In 2007, human infection with a novel influenza A virus became a nationally notifiable condition. Novel influenza A virus infections include all human infections with influenza A viruses that are different from currently circulating human influenza H1 and H3 viruses. These viruses include those that are subtyped as nonhuman in origin and those that are unsubtypable with standard laboratory methods and reagents. Rapid reporting of human infections with novel influenza A viruses will facilitate prompt detection and characterization of influenza A viruses and accelerate the implementation of effective public health responses.

### *U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet)*

Information on patient visits to health care providers for influenza-like illness is collected through the **U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet)**. ILINet consists of more than 3,000 healthcare providers in all 50 states, the District of Columbia and the U.S. Virgin Islands reporting over 25 million patient visits each year. Each week, approximately 1,800 outpatient care sites around the country report data to CDC on the total number of patients seen and the number of those patients with influenza-like illness (ILI) by age group (0-4 years, 5-24 years, 25-49 years, 50-64 years, and ≥ 65 years). For this system, ILI is defined as fever (temperature of 100°F [37.8°C] or greater) and a cough and/or a sore throat in the absence of a KNOWN cause other than influenza. Sites with electronic records use an equivalent definition as determined by state public health authorities.

Additionally, data reports collected in ILINet are used to produce a measure of ILI activity by state. Activity levels range from minimal to intense and are arranged on a scale of 1-10 with 1 being the least intense and 10 being the most intense. The activity levels correspond with the given proportion of visits to outpatient clinics due to ILI, and the number of standard deviations from the mean proportion during non-influenza weeks the given value is. An activity level of 1 corresponds to values that are below the mean and an activity level of 10 corresponds with values that are 8 or more standard deviations above the mean. Because data at the state or jurisdiction level are variable, baselines are adjusted on a weekly basis based on which sites within each state or jurisdiction provide data. To perform this adjustment, provider level baseline ratios are calculated for providers that have a sufficient reporting history, and for providers that do not have the required reporting history they are assigned the baseline ratio for their practice type. The state level baseline is then calculated using a weighted sum of the baseline ratios for each contributing provider.

### *Influenza Hospitalization Network (FluSurv-NET)*

FluSurv-NET conducts surveillance for population-based, laboratory-confirmed influenza related hospitalizations in children (persons less than 18 years) and adults. The network covers over 80 counties in the 10 Emerging Infections Program (EIP) states (CA, CO, CT, GA, MD, MN, NM, NY, OR, and TN) and six additional states (ID, MI, OH, OK, RI and UT). Cases are identified by reviewing hospital laboratory and admission databases and infection control logs for children and adults with a documented positive influenza test (viral culture, direct/indirect fluorescent antibody assay (DFA/IFA), reverse transcription-polymerase chain reaction (RT-PCR), or a rapid influenza diagnostic test (RIDT)) conducted as a part of routine patient care. FluSurv-NET estimated hospitalization rates are reported every two weeks during the influenza season.

### *Aggregate Hospitalization and Death Reporting Activity (AHDRA)*

States and territories collecting reports of laboratory-confirmed influenza-associated hospitalizations and deaths in their jurisdictions voluntarily share the reports with the Influenza Division at CDC. AHDRA reporting by state health departments allows tracking of detailed data and trends in severe disease with greater geographic representativeness than is possible with existing systems alone and informs decision-making at the state and national levels. States report laboratory-confirmed hospitalizations and deaths as aggregate weekly counts to a secure website with the following age groups: 0-4 years, 5-17 years, 18-49 years, 50-64 years, and ≥ 65 years.

### *122 Cities mortality reporting system*

Each week, the vital statistics offices of 122 cities across the United States report the total number of death certificates received and the number of those for which pneumonia or influenza was listed as the underlying or contributing cause of death by age group (under 28 days, 28 days –1 year, 1-14 years, 15-24 years, 25-44 years, 45-64 years, 65-74 years, 75-84 years, and ≥ 85 years). The percentage of deaths due to pneumonia and influenza (P&I) are compared with a seasonal baseline and epidemic threshold value calculated for each week. The seasonal baseline of P&I deaths is calculated using a periodic regression model that incorporates a robust regression procedure applied to data from the previous five years. An increase of 1.645 standard deviations above the seasonal baseline of P&I deaths is considered the "epidemic threshold," i.e., the point at which the observed proportion of deaths attributed to pneumonia or influenza was significantly higher than would be expected at that time of the year in the absence of substantial influenza-related mortality.

### *Influenza-associated pediatric mortality reporting*

Influenza-associated deaths in children (persons less than 18 years) were added as a nationally notifiable condition in 2004. Any laboratory-confirmed influenza-associated death in a child is reported through this system. Demographic and clinical information are collected on each case and are transmitted to CDC.

### *State and territorial epidemiologists' reports*

State health departments report the estimated level of spread of influenza activity in their states each week through the **State and Territorial Epidemiologists Reports**. States report influenza activity as no activity, sporadic, local, regional, or widespread. These levels are defined as follows:

- **No Activity:** No laboratory-confirmed cases of influenza and no reported increase in the number of cases of ILI.
- **Sporadic:** Small numbers of laboratory-confirmed influenza cases or a single laboratory-confirmed influenza outbreak has been reported, but there is no increase in cases of ILI.
- **Local:** Outbreaks of influenza or increases in ILI cases and recent laboratory-confirmed influenza in a single region of the state.

- **Regional:** Outbreaks of influenza or increases in ILI and recent laboratory confirmed influenza in at least two but less than half the regions of the state with recent laboratory evidence of influenza in those regions.
- **Widespread:** Outbreaks of influenza or increases in ILI cases and recent laboratory-confirmed influenza in at least half the regions of the state with recent laboratory evidence of influenza in the state.

Together, the five categories of influenza surveillance are designed to provide a national assessment of influenza activity. Human infections with novel influenza A viruses, pneumonia and influenza mortality from the 122 Cities Mortality System, influenza-associated pediatric deaths and AHDRA are reported on a national level only. FluSurv-NET data provides population-based, laboratory-confirmed estimates of influenza-related hospitalizations but are reported from limited geographic areas. Outpatient influenza-like illness and laboratory data are reported on a national level and by region. Outpatient influenza-like illness activity levels are reported by state. The state and territorial epidemiologists' reports of the geographic spread of influenza activity and the ILI activity indicator display state-level information. Local health departments should contact their state health department for state surveillance and reporting procedures.

## XI. Enhancing Surveillance

A number of activities can improve the detection and reporting of influenza virus infections as well as the comprehensiveness, timeliness, and quality of reporting.

### *Expanding reporting period*

Healthcare providers should be made aware that influenza cases can occur during any month of the year and that collecting and testing respiratory specimens during the summer months may provide valuable information about viruses likely to circulate during the upcoming influenza season.

### *Promoting awareness*

Healthcare providers should also be aware of the methods, accuracy, and limitations of laboratory testing for influenza virus infection and of the importance of reporting influenza surveillance information at local, state, and national levels. They should also know about the sources for influenza surveillance information.

Influenza surveillance information is available through the Internet at: http://www.cdc.gov/flu/weekly/overview.htm.

Influenza activity updates are also published periodically in the Morbidity and Mortality Weekly Report (*MMWR*).

### *Expanding sources of surveillance*

Efforts should be made by state health departments to explore the inclusion of electronic records in ILINet and to increase the number of ILINet providers reporting influenza-like illness data each week to one participating physician per 250,000 population. Efforts should also be made to ensure that surveillance sites are geographically representative and cover all age groups.

### *Increasing awareness of local surveillance practices*

State health departments should invite local health departments and healthcare providers to participate in existing surveillance systems. In addition, healthcare providers and surveillance personnel may be reminded of the importance of prompt reporting and reserving aliquots of clinical specimens used for rapid influenza antigen testing for possible additional confirmation, including by RT-PCR or virus isolation.

## XII. Case Investigation

Any influenza A virus that cannot be subtyped using standard methods and reagents should be sent by the state health department to the CDC Influenza Division immediately.

Individual cases of influenza typically are not investigated. Exceptions to this are severe or fatal illnesses from unusual complications of influenza virus infection (e.g., encephalitis, myocarditis, rhabdomyolysis). Individual cases should also be investigated when the infecting virus is suspected or confirmed to be of animal origin (most frequently swine or avian), and the state health department and CDC should be notified immediately. In such cases, investigators should attempt to identify exposure to animals and determine if the virus has been transmitted from human-to-human. Generally, animal influenza viruses are identified as influenza A viruses that cannot be subtyped by hemagglutination inhibition testing using the standard H3N2 or H1N1 antisera included in the influenza reagent kit distributed by CDC or by CDC RT-PCR. Any influenza A virus that cannot be subtyped or that tests positive for a subtype other than H1N1 or H3N2 should be sent through the state health department to the CDC Influenza Division immediately. At the direction of the state health department, the Influenza Division may be contacted at 404-639-3591 during business hours. After hours, please contact the CDC emergency response hotline at 770-488-7100.

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# Chapter 7: Measles

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## I. Disease Description

Measles is an acute viral illness caused by a virus in the family paramyxovirus, genus *Morbillivirus*. Measles is characterized by a prodrome of fever and malaise, cough, coryza, and conjunctivitis, followed by a maculopapular rash. Measles is usually a mild or moderately severe illness. However, measles can result in complications such as pneumonia, encephalitis and death. From 1987–2000, in the United States, nearly one third of measles cases (29%) had some complication, with 6% of cases complicated by pneumonia, and 19% being hospitalized. During that period, measles resulted in encephalitis in 1 per 1000 reported cases and death was reported in 0.3% of the cases.[1] The most severe sequela of measles virus infection is subacute sclerosing panencephalitis (SSPE), a fatal disease of the central nervous system that generally develops 7–10 years after infection. Among persons who contracted measles during the resurgence in the U.S. in 1989–1991, the risk of SSPE was estimated to be 6.5–11 cases/100,000 cases of measles. The risk of developing SSPE may be higher when measles occurs prior to the second year of life.[2]

The average incubation period for measles is 14 days, with a range of 7–21 days.[3] Persons with measles are usually considered infectious from 4 days before until 4 days after onset of rash.[4]

## II. Background

Before the introduction of measles vaccine in 1963, roughly one-half million cases were reported each year in the United States. In 1989, a second-dose vaccination schedule was recommended[5] and in 1998, the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP) jointly recommended that States ensure second-dose coverage of children in all grades by 2001.[6] The current elimination strategy has led to a dramatic decline in measles cases.[7, 8] Fewer than 150 cases were reported each year during 1997–2004[7, 8] and measles incidence decreased to a record low of 37 reported cases in 2004.[8] In recent years, outbreaks of measles have been small, with < 35 cases reported.[8–10] Recent outbreaks do not have one predominant transmission setting but mostly involve people who are exposed to imported measles cases and who are unvaccinated or have received only 1 dose of measles vaccine. Moreover, recent outbreaks have been typically related to lack of adherence to existing recommendations for measles prevention among high risk groups such as travelers, health-care workers, and groups who routinely refuse vaccination.[9, 10]

While measles is now rare in many industrialized countries, it remains a common illness in many developing countries. Globally more than 30 million people are affected each year by measles. In 2004, it was estimated that there were 454,000 measles deaths globally: this translates to more than 1200 deaths every day or 50 people dying every hour from measles. The overwhelming majority (> 95%) of measles deaths occur in countries with per capita Gross National Income of less than U.S. $1000. In countries where measles has been largely eliminated, cases imported from other countries remain an important source of infection.[11]

In May 2003, the 56th World Health Assembly unanimously adopted a resolution[12] to reduce measles deaths by 50% by the end of 2005 compared to 1999 levels. This goal was established a year earlier by the United Nations General Assembly Special Session on Children, "World Fit for Children". In May 2005, the 58th World Health Assembly adopted the WHO/UNICEF Global Immunization Vision and Strategy (GIVS). GIVS calls on countries to reduce global measles deaths by 90% by 2010 compared to 2000 estimates. In the Americas, under the leadership of the Pan American Health Organization (PAHO), Ministries of Health implemented an aggressive measles elimination program. Based on the success in the Americas using PAHO's strategies, measles elimination targets have been established in the European and Eastern Mediterranean regions for the year 2010, and the Western Pacific region for 2012. The African and South East Asian regions have set goals for sustainable reductions in measles mortality. These initiatives will have direct benefits in the United States.

The WHO/UNICEF Comprehensive Strategy for Sustainable Measles Mortality Reduction includes the following.[11]

- Strong routine immunization, assuring that at least 90% of children are reached by routine immunization services every year, in every district.
- A 'second opportunity' for measles immunization is provided to all children, given either through routine immunization services (if high coverage can be achieved and maintained over time) or through periodic Supplementary Immunization Activities (SIAs). SIAs target large populations (entire nations or large regions) and aim to achieve immunization coverage of over 90%.
- Enhancing surveillance, ensuring prompt recognition and investigation of measles outbreaks and assuring the implementation of appropriate outbreak response activities.
- Improving clinical management of measles cases, including vitamin A supplementation and adequate treatment of complications, if needed, with antibiotics.

To advocate for reduction of measles mortality, the Measles Initiative was launched in February 2001. The Measles Initiative is a long-term commitment to control measles deaths starting in Africa by vaccinating at-risk children 15 years of age and younger. Leading this effort are the American Red Cross, United Nations Foundation, the United States Centers for Disease Control and Prevention (CDC), United Nations Children's Fund (UNICEF), and the World Health Organization (WHO). Other key players in the fight against measles include the International Federation of Red Cross and Red Crescent Societies and countries and governments affected by measles. As of the end of 2005, the Measles Initiative helped to decrease related mortality by 60% by vaccinating 213 million children in more than 40 African countries, saving more than 1.2 million lives. Because of the Measles Initiative's success in Africa, the program has expanded into Asia, where the measles burden remains high.[13]

## III. Importance of Rapid Identification

Prompt recognition, reporting, and investigation of measles are important because the spread of the disease can be limited with early case identification and vaccination of susceptible contacts.

## IV. Importance of Surveillance

The highly contagious measles virus is frequently imported into the United States by persons from other countries. Each imported measles case could start an outbreak, especially if under-vaccinated groups are exposed. Surveillance and prompt investigation of cases and contacts help to halt the spread of disease.

Information obtained through surveillance is also used to assess progress towards disease elimination goals. Surveillance data are used to characterize persons, groups, or areas in which additional efforts are required to reduce disease incidence.

## V. Disease Reduction Goals

The United States has established the goal of eliminating the transmission of endemic measles.[14] Current surveillance data indicate this goal has been achieved, and endemic measles was declared eliminated in the U.S. in 2000.[15] To prevent imported strains of measles virus from establishing endemic chains of transmission, rapid detection of cases is necessary so that appropriate control measures can be quickly implemented. The major challenges to sustaining the elimination of measles from the United States are a) continuing to vaccinate all children aged 12–15 months with a first dose of MMR, b) ensuring that all school-aged children receive a second dose of MMR vaccine, and c) working with other countries to set and achieve national measles elimination goals.[6]

## VI. Case Definition

The following case definition for case classification for measles including case classifications for importation status has been approved by the Council of State and Territorial Epidemiologists (CSTE) and was published in 2009.[16]

**Case classification**

Narrative description of criteria to determine whether a case should be classified as confirmed, probable (presumptive), or suspected (possible).

**Suspected:** any febrile illness that is accompanied by rash and that does not meet the criteria for probable or confirmed measles or any other illness.

**Probable:**

- In the absence of a more likely diagnosis, an illness characterized by
  - Generalized rash lasting ≥3 days; and
  - Temperature ≥101°F or 38.3°C; and
  - Cough, coryza, or conjunctivitis; and
- No epidemiologic linkage to a confirmed case of measles; and
- Noncontributory or no serologic or virologic testing.

**Confirmed:**

- Laboratory confirmation by any of the following
  - Positive serologic test for measles immunoglobulin M antibody;
  - Significant rise in measles antibody level by any standard serologic assay;
  - Isolation of measles virus from a clinical specimen; or
  - Detection of measles-virus specific nucleic acid by polymerase chain reaction
  - Note: A laboratory-confirmed case does not have to have generalized rash lasting ≥3 days; temperature ≥101°F or 38.3°C; cough, coryza, or conjunctivitis.

OR

- An illness characterized by
  - Generalized rash lasting ≥3 days; and
  - Temperature ≥101°F or 38.3°C; and
  - Cough, coryza, or conjunctivitis; and
  - Epidemiologic linkage to a confirmed case of measles.

**Comment:** Confirmed cases should be reported to CDC via the National Notifiable Diseases Surveillance System (NNDSS). All confirmed cases should be classified as one of the following:

**International importation:** An internationally imported case is defined as a case in which measles results from exposure to measles virus outside the United States as evidenced by at least some of the exposure period (7–21 days before rash onset) occurring outside the United States and rash onset occurring within 21 days of entering the United States and there is no known exposure to measles in the U.S. during that time. All other cases are considered U.S.-acquired.

**U.S.-acquired case:** An U.S.-acquired case is defined as a case in which the patient had not been outside the United States during the 21 days before rash onset or was known to have been exposed to measles within the United States.

U.S.-acquired cases are subclassified into four mutually exclusive groups:

**Import-linked case:** Any case in a chain of transmission that is epidemiologically linked to an internationally imported case.

**Imported-virus case:** a case for which an epidemiologic link to an internationally imported case was not identified, but for which viral genetic evidence indicates an imported

measles genotype, i.e., a genotype that is not occurring within the United States in a pattern indicative of endemic transmission. An endemic genotype is the genotype of any measles virus that occurs in an endemic chain of transmission (i.e., lasting ≥12 months). Any genotype that is found repeatedly in U.S.-acquired cases should be thoroughly investigated as a potential endemic genotype, especially if the cases are closely related in time or location.

**Endemic case:** a case for which epidemiological or virological evidence indicates an endemic chain of transmission. Endemic transmission is defined as a chain of measles virus transmission that is continuous for ≥12 months within the United States.

**Unknown source case:** a case for which an epidemiological or virological link to importation or to endemic transmission within the U.S. cannot be established after a thorough investigation. These cases must be carefully assessed epidemiologically to assure that they do not represent a sustained U.S.-acquired chain of transmission or an endemic chain of transmission within the U.S.

**Note:** *Internationally imported, import-linked, and imported-virus cases are considered collectively to be import-associated cases.*

States may also choose to classify cases as "out-of-state-imported" when imported from another state within the United States. The possibility that a patient was exposed within his or her state of residence should be excluded; therefore, the patient either must have been out of state continuously for the entire period of possible exposure (at least 7–21 days before onset of rash) or have had one of the following types of exposure while out of state: a) face-to-face contact with a person who had probable or confirmed measles, or b) attendance in the same institution as a person with measles (e.g., in a school, classroom, or childcare center). Out of State importations are uncommon.

For national reporting, cases will be classified as either internationally imported or U.S.-acquired.

## VII. Laboratory Testing

Because measles is an extremely rare disease in the United States, clinical evidence is not sufficient to confirm a case of measles. Many clinicians have never seen a case of measles, and most patients who present with measles-like illness today do not have measles. Because measles is such a highly contagious disease, with the potential for explosive spread following importation of the virus, it is critical to rapidly identify the few measles cases that do occur. For these reasons, it is crucial to use laboratory diagnosis to confirm the few actual measles cases among the thousands of patients with suspected measles.

Because measles is so rare, even with the excellent laboratory tests available, there will be some false positive results. (The positive predictive value of a test [PPV] is the proportion of people with positive results who actually have the disease. The PPV decreases when the disease becomes rare.) Some false positive results are expected, so it is preferable to misclassify a few false positive cases than to miss cases that are measles.

To minimize the problem of false positive laboratory results, it is important to restrict case investigation and laboratory tests to patients most likely to have measles: those with fever and generalized maculopapular rash. Testing for measles in patients with no rash, no fever, a vesicular rash, or a rash limited to the diaper area leads to false positive results.

For additional information on laboratory support for surveillance of vaccine-preventable diseases, see Chapter 22, "Laboratory Support for Surveillance of Vaccine-Preventable Diseases", and visit the CDC measles laboratory website: http://www.cdc.gov/measles/lab-tools/measles-virus-lab.html.

### Serologic testing

Serologic testing for antibodies to measles is widely available. Generally, in a previously susceptible person exposed to wild-type measles virus, the IgM response starts around the time of rash onset and may be detected for 1–2 months. The IgG response starts more slowly, at about 5–10 days after rash onset, but typically persists for a lifetime. The diagnosis of acute measles infection can be made by detecting IgM antibody to measles in a single serum specimen or by detecting a rise in the titer of IgG antibody in two serum specimens drawn roughly two weeks apart.

The serologic response following vaccination is slower; IgM and IgG may not be detectable until 8–21 days post vaccination.

### Recommendations for serologic testing for measles

- An enzyme immunoassay (EIA) test for IgM antibody to measles in a single serum specimen, drawn at the first contact with the suspected measles case, is the recommended method for diagnosing acute measles.
- A single specimen test for IgG is the most commonly used test for immunity to measles because IgG antibody is long lasting.
- Testing for IgG along with IgM is recommended for suspected measles cases.
- Paired sera (acute and convalescent) may be tested for a rise in IgG antibody to measles to confirm acute measles infection.
- When a patient with suspected measles has been recently vaccinated (6–45 days prior to blood collection) neither IgM nor IgG antibody responses can distinguish measles disease from the response to vaccination.

### Tests for IgM antibody

Although there are multiple possible methods for testing for IgM antibody, EIAs are the most consistently accurate tests and are therefore the recommended method. There are two formats for IgM tests. The first and most widely available is the indirect format; IgM tests based on the indirect format require a specific step to remove IgG antibodies. Removal of IgG antibodies can sometimes lead to false positive tests[17] or, less commonly, false negative results.

The second format, IgM capture, does not require the removal of IgG antibodies. CDC has developed a capture IgM test for measles and has trained personnel from every state public health laboratory. Although the IgM capture format is the preferred reference test for measles, there are several commercially available indirect measles IgM tests that perform equally well. In contrast, only one capture IgM EIA is commercially available. This is the preferred reference test for measles.

EIA tests for measles are often positive on the day of rash onset. However, 30% of serum samples obtained in the first 72 hours after rash onset may give false negative results. Negative results from serum collected in the first 72 hours after rash onset should be confirmed (Table 1) with a second serum obtained ≥ 72 hours after rash onset. IgM is detectable for at least 30 days after rash onset and frequently longer.[18]

When a laboratory IgM result is suspected of being a false positive (Table 1), additional testing may be performed. False positive IgM results for measles may be due to the presence of rheumatoid factor in serum specimens. In addition, false positives have been documented as a result of testing serum from patients with a rash illness caused by parvovirus B19, rubella, roseola or dengue. False positive tests may be suspected when thorough surveillance reveals no source or spread cases or when the case does not meet the clinical case definition. In these situations, confirmatory tests may be done at the state public health laboratory or at CDC.

### *Tests for IgG antibody*

Because tests for IgG require two serum specimens and because a confirmed diagnosis cannot be made until the second specimen is obtained, IgM tests are generally preferred. However, if the IgM tests remain inconclusive, a second (convalescent) serum specimen, collected 14–30 days after the first (acute) specimen, can be used to test for an increase in the IgG titer. These tests can be performed in the state laboratory or at CDC. A variety of tests for IgG antibodies to measles are available and include EIA, hemagglutination inhibition, indirect fluorescent antibody tests, and plaque reduction neutralization. Complement fixation, although widely used in the past, is no longer recommended. The gold standard test for serologic evidence of recent measles virus infection is a four-fold rise in a measles virus plaque reduction neutralization test of IgG between acute and convalescent paired sera.

Paired IgG testing for laboratory confirmation of measles requires the demonstration of a four-fold rise in the titer of antibody against measles. The tests for IgG antibody should be conducted on both acute and convalescent specimens at the same time. The same type of test should be used on both specimens. The specific criteria for documenting an increase in titer depend on the test. EIA values are not titers and increases in EIA values do not directly correspond to titer rises.

### *Virus isolation*

Isolation of measles virus in culture or detection of measles virus by reverse transcription polymerase chain reaction (RT-PCR) in clinical specimens confirms the diagnosis of measles. However, a negative culture or RT-PCR does not rule out measles because both methods are much affected by the timing of specimen collection and the quality and handling of the clinical specimens. If virus is isolated or detected by RT-PCR, the results can confirm the diagnosis of measles when serology results are inconclusive. Also, determination of the measles genotype provides the only means to distinguish between wild-type virus infection and a rash caused from a recent measles vaccination.[19]

The collection of viral samples is extremely important for molecular epidemiologic surveillance to identify the genotypes associated with imported cases of measles. This information is used to document the absence of endemic circulation of measles in the U.S. Isolation of measles virus is technically difficult and is generally performed in research laboratories. Nevertheless, the introduction of recombinant cell lines bearing the receptor(s) for measles virus has vastly improved the measles isolation in cell culture.

Specimens (urine, nasopharyngeal aspirates, heparinized blood, or throat swabs) for virus culture obtained from clinically suspected cases of measles should be shipped to the state public health laboratory or to the CDC at the direction of the state health department as soon as measles is confirmed. Specimens should be properly stored while awaiting case confirmation (see Appendix 6). Clinical specimens for virus isolation should be collected at the same time as samples taken for serologic testing. Because virus is more likely to be isolated when the specimens are collected within 3 days of rash onset, collection of specimens for virus isolation should not be delayed until laboratory confirmation is obtained. Clinical specimens should ideally be obtained within 7 days of rash onset and should not be collected more than 10 days after rash onset.

## VIII. Reporting

Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[20] These regulations and laws list the diseases to be reported and describe those persons or groups responsible for reporting, such as health-care providers, hospitals, laboratories, schools, daycare and childcare facilities, and other institutions. Contact your local or state health department for reporting requirements in your state.

### *Reporting to CDC*

Provisional reports of suspected measles should be reported within 24 hours to the CDC by the state health department or directly to Al Barskey at NCIRD, CDC by telephone at 404-639-3012 or by e-mail (ABarskey@cdc.gov). Information on confirmed cases should then also be electronically reported by the state health department to the National Notifiable Diseases Surveillance System (NNDSS) with the next regularly scheduled electronic transmission. Although only data from confirmed cases are published in the *Morbidity and Mortality Weekly Report (MMWR)*, states are encouraged to notify CDC of all suspected cases by phone as soon as possible.

### *Information to collect*

The following data are epidemiologically important and should be collected in the course of case investigation. Additional information also may be collected at the direction of the state health department.

- **Demographic information**
  - Name
  - Address
  - Date of birth
  - Age
  - Sex
  - Ethnicity
  - Race
- **Reporting source**
  - County
  - Earliest date reported
- **Clinical**
  - Date of rash onset
  - Duration of rash
  - Rash presentation
  - Symptoms
  - Date of onset of symptoms
  - Hospitalizations
  - Complications
- **Outcome (case survived or died)**
  - Date of death
- **Laboratory**
  - Serological test results
  - Date of collection of specimen for virus isolation

- **Vaccination status**
  - Number of doses of measles vaccine received
  - Dates of measles vaccinations
  - Manufacturer name
  - Vaccine lot number
  - If not vaccinated, reason
- **Epidemiological**
  - Transmission setting
  - Source of infection (e.g., age, vaccination status, relationship to case)
  - Source of exposure (contact with probable or confirmed case, or contact with immigrants or travelers)
  - Import status (indigenous, international import, or out-of-state import, linked or traceable to an international importations)
  - Residency (Did the case reside in the U.S.?)
  - Travel history

## IX. Vaccination

- Measles vaccine is incorporated with mumps and rubella vaccine as a combined vaccine (MMR). The Advisory Committee on Immunization Practices (ACIP) recommends a first dose at 12–15 months of age with a second dose at school entry (4–6 years) for routine vaccination.[6]
- Measles vaccine is also now available incorporated with mumps, rubella and varicella vaccines as a combined vaccine (MMRV). The Advisory Committee on Immunization Practices (ACIP) recommends a first dose of MMRV for children aged 12 months to 12 years who need a first dose of measles, mumps, rubella (MMR), and *varicella* vaccine, or children aged 12 months to 12 years who need a second dose of MMR and either a first or second dose (as indicated) of varicella vaccine.[21]

## X. Enhancing Surveillance

As measles incidence declines, additional effort may be required to ensure that appropriate and timely diagnosis of rash illnesses and reporting of suspected cases continues. In addition, the rapid investigation and reporting of all suspected cases and recording of vaccination history and import status for all cases will become increasingly important.

The activities listed below can improve the detection and reporting of measles cases and improve the comprehensiveness and quality of reporting. Additional guidelines for enhancing surveillance are given in Chapter 19, "Enhancing Surveillance."

### *Obtaining accurate and complete immunization histories*

Measles case investigations should include complete immunization histories that document any doses of measles-containing vaccine. Acceptable proof of vaccination is documented administration of live measles vaccine virus. Vaccination histories may be obtained from schools, medical providers or on immunization records provided by the case-patient. Verbal history of receipt of measles vaccine is not considered adequate proof of vaccination.

### *Laboratory testing*

If measles is suspected, laboratory testing should be performed in order to confirm or rule out the case. If a case is confirmed, a case investigation should be conducted. Measles specimens may be sent to CDC for testing if this resource is needed.

### *Investigating contacts*

Determining the source or chain of disease transmission, identifying all contacts (household, childcare, and other close contacts), and following up with susceptible persons may reveal previously undiagnosed and unreported cases.

### *Active surveillance*

Active surveillance for measles disease should be conducted for every confirmed measles case. In the case of an outbreak, local or state health departments should contact health-care providers in outbreak areas to inform them of the outbreak and request reporting of any suspected cases. These activities are especially important in large cities and in cities with large numbers of international visitors.

### *Special projects*

Special projects such as reviewing hospital and managed care administrative databases and emergency department logs to identify rash illnesses that may have been unreported cases of measles can be used to evaluate surveillance sensitivity and completeness of reporting.[22]

### *Monitering surveillance indicators*

Regular monitoring of surveillance indicators, including time intervals between diagnosis and reporting and completeness of reporting, may identify specific areas of the surveillance and reporting system that need improvement. These indicators should be monitored:

- The proportion of confirmed cases reported to the NNDSS with complete information
- The median interval between rash onset and notification of a public health authority, for confirmed cases
- The proportion of confirmed cases that are laboratory confirmed
- The proportion of cases that have an imported source
- The proportion of cases for which least one clinical specimen for virus isolation was collected

Another important indicator of the adequacy of the measles surveillance system is the detection of importations. In the absence of measles endemic transmission, imported cases or cases linked to importations should be detected. A program which reports no imported cases in settings where endemic measles has been eliminated cannot be assumed to have adequate measles surveillance. For more information on surveillance indicators, see Chapter 18, "Surveillance Indicators."

## XI. Case Investigation

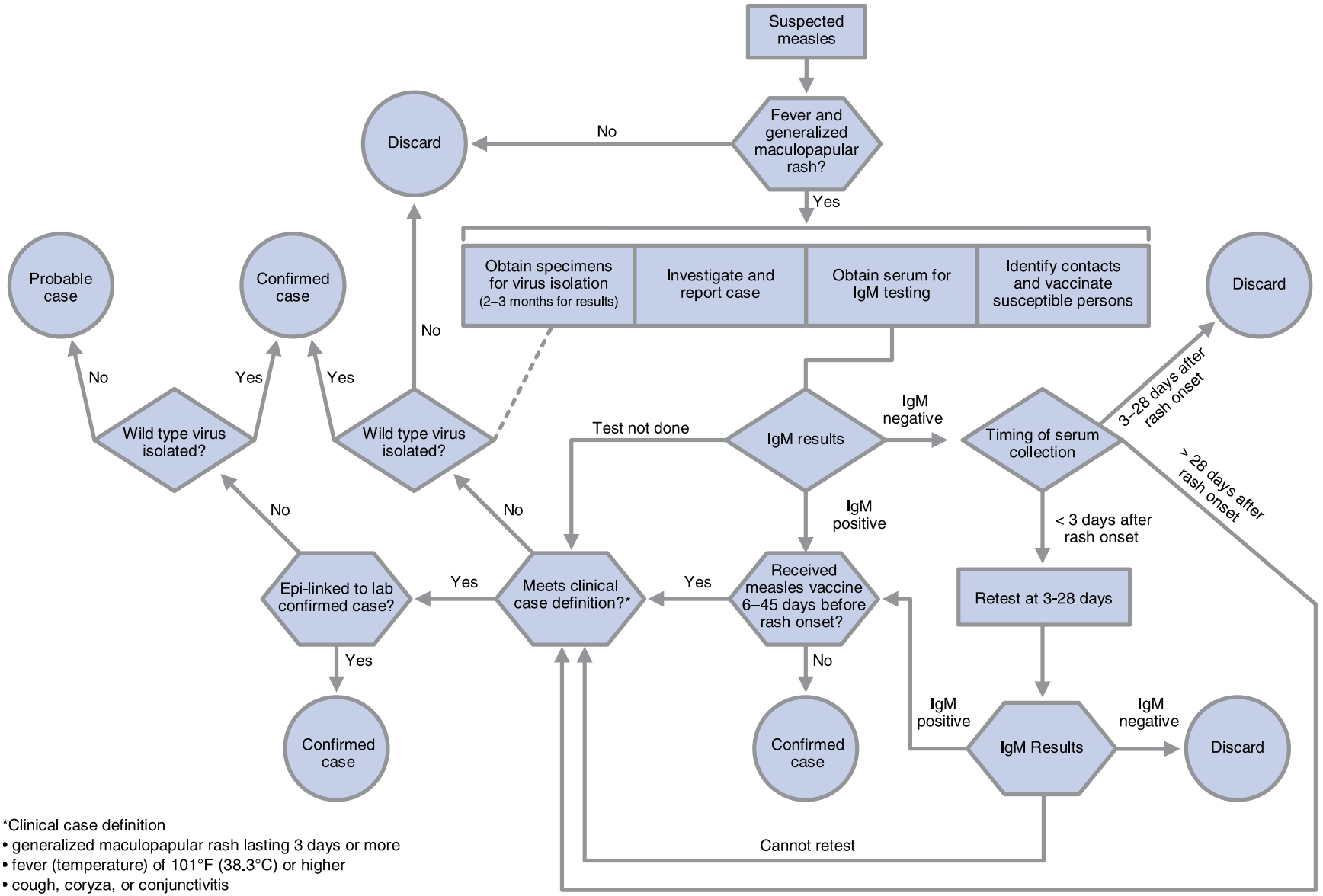
All reports of suspected measles cases should be investigated immediately. The measles surveillance worksheet (see Appendix 8) may be used as a guideline for collecting demographic and epidemiologic data during case investigation. Essential components of case investigation include establishing a diagnosis of measles, obtaining immunization histories for confirmed cases, identifying sources of infection, assessing potential for transmission, and obtaining specimens for viral isolation.

### *Establishing a diagnosis of measles (Figure 1)*

Necessary clinical information must be obtained to establish whether a reported case meets the clinical case definition (see "Case definitions"). If the case was reported within 3 days of onset of rash, appropriate follow-up is necessary to establish a rash duration of at least 3 days.

Laboratory confirmation is essential for all outbreaks and all isolated (sporadic) cases (those cases that are not part of a known outbreak). In an area of low measles incidence, most cases that meet the clinical case definition are not measles.[25] Even in outbreaks, laboratory confirmation should be obtained for as many cases as possible. Once community awareness is increased, many cases of febrile rash illness may be reported as suspected measles, and the magnitude of the outbreak may be exaggerated if these cases are included without laboratory confirmation. This is particularly important as the outbreak is ending; at that point, laboratory confirmation should be sought for all suspected cases.

**Figure 1. Establishing a Diagnosis of Measles Flow Chart**




*Clinical case definition
- generalized maculopapular rash lasting 3 days or more
- fever (temperature) of 101°F (38.3°C) or higher
- cough, coryza, or conjunctivitis

**Table 1. Classifying Suspected Measles Cases Based on Results of Case Investigation**

| IgM result | Optimal time for specimen collection?* | Recent vaccination?† | Meets clinical case definition?§ | Epidemiologic linkage?¶ | Wild-type measles virus identified? | Case classification |
|---|---|---|---|---|---|---|
| + | Yes or No | No | Yes or No | Yes or No | Yes or No | Confirmed** |
| + | Yes or No | Yes | Yes | Yes | Yes or No | Confirmed |
| + or - | Yes or No | Yes or No | Yes or No | Yes or No | Yes | Confirmed |
| + | Yes or No | Yes | Yes | No | No | Probable |
| + | Yes or No | Yes | No | Yes or No | No | Discard |
| - | Yes | Yes or No | Yes or No | Yes or No | No | Discard |
| - | No‡ | Yes or No | Yes | Yes | No | Confirmed |
| - | No‡ | Yes or No | Yes | No | No | Probable |
| - | No‡ | Yes or No | No | Yes or No | No | Discard |

***Note:*** *Cells with "Yes or No" values do not affect the case classification.*

* *Optimal time for collection of IgM serum specimen is 3–28 days after rash onset.*

† *Receipt of measles-containing vaccine 6–45 days before rash onset.*

§ *Generalized maculopapular rash lasting ≥3 days and fever (>101° F or 38.3° C) and cough, coryza, or conjunctivitis.*

¶ *Contact with a laboratory-confirmed case (source or spread case) during the appropriate period for transmission.*

** *The possibility of a false-positive IgM test is increased when 1) the IgM test was not an EIA, 2) the case did not meet clinical case definition, 3) the case is an isolated indigenous case (no epidemiologic link to another confirmed case and no international travel), or 4) measles IgG was detected within 7 days of rash onset. Consider confirmatory testing for these cases.*

‡ *Whenever possible, collect another serum specimen 3–28 days after rash onset, conduct an IgM test, and interpret the result according to this table*

The occurrence of measles-like illness in recently vaccinated persons can pose particular difficulties in an outbreak setting. Ten percent of recipients of measles-containing vaccine may develop fever and rash approximately 1 week after vaccination, and vaccination of susceptible persons results in production of IgM antibody that cannot be distinguished from the antibody resulting from natural infection. A positive measles IgM test cannot be used to confirm the diagnosis of measles in persons with measles-like illness who received measles vaccine 6–45 days before onset of rash. A negative test would exclude the diagnosis. Cases in persons with measles-like illness who received measles vaccine 6–45 days before onset of rash should be classified as confirmed cases only if: a) they meet the clinical case definition, and b) they are epidemiologically linked to a laboratory-confirmed case. For persons receiving vaccine 6–14 days prior to rash onset, specimens for viral isolation should be obtained in addition to serologic testing (see "Laboratory testing"); isolation of wild-type measles virus would allow confirmation of the case (Table 1).

Currently, very few of the suspected and probable cases investigated are confirmed as measles. However, case investigation and vaccination of susceptible household contacts should not be delayed pending the return of laboratory results. Initial preparation for major control activities also may need to be started before the laboratory results are known. However, it is reasonable to delay major control activities, such as vaccinating an entire school, pending the return of laboratory results, which should be obtained as quickly as possible (within 24 hours).

### *Obtaining accurate and complete immunization histories on all confirmed cases*

Measles case investigations should include complete immunization histories that document all doses of measles-containing vaccine. All confirmed case-patients should then be classified as recipients of one dose of measles-containing vaccine (as MMR, MMRV, MR or M), two doses, three doses, or no doses of vaccine. The age of vaccination for each dose and the interval between doses should be noted. Written or electronic records with dates of vaccine administration are the only acceptable evidence of vaccination.

Case-patients or their caregivers may have personal copies of immunization records available

that include dates of administration; these are acceptable for reporting purposes. Usually immunization records must be sought from review of childcare or school records (generally available for children attending licensed childcare centers or kindergarten through high school), or from providers. Immunization registries, if available, can readily provide vaccination histories. In the absence of a registry, immunization records should be reviewed at providers' clinics or offices. As part of the initial case investigation, case-patients or their parents should be asked where **all** vaccines were received, including the names of private physicians and out-of-town or out-of-state providers. Records at public health departments and health centers should be reviewed, and private physicians should be contacted and asked to review patient records for this information. With careful planning in an outbreak setting, it is possible to contact providers with a list of all case-patients reported to date for whom data are needed, and to call back at a prearranged time, rather than repeatedly contacting providers for records on individual children.

### *Identifying the source of infection*

Efforts should be made to identify the source of infection for every confirmed case of measles. Case-patients or their caregivers should be asked about contact with other known cases. In outbreak settings, such histories can often be obtained. When no history of contact with a known case can be found, opportunities for exposure to unknown cases should be sought. Such exposures may occur in schools (especially high schools with foreign exchange students), during air travel, through other contact with foreign visitors, while visiting tourist locations (casinos, resorts, theme parks), or in health-care settings. Unless a history of exposure to a known case within 7–21 days prior to onset of rash in the case is confirmed, case-patients or their caregivers should be closely queried about all these possibilities.

### *Assessing potential for transmission and identifying contacts*

Transmission is particularly likely in households, schools, health-care settings and other institutions (colleges, prisons, etc.). As part of the case investigation, the potential for further transmission should be assessed, and exposed contacts of the case-patient during the infectious period (4 days before to 4 days after onset of rash) should be identified. If the case-patient was traveling by plane or ship during the infectious period, the CDC Quarantine Station (operated by the Division of Global Migration and Quarantine) with jurisdiction for the reporting state should be contacted for assistance in the investigation and contact tracing of potentially exposed passengers and crew: http://www.cdc.gov/ncidod/dq/quarantine_stations.htm. If unable to contact the QS, call the DGMQ 24-hour number at 866-694-4867 for assistance.

Susceptible contacts are at risk for infection and further transmission to others so they should be vaccinated as quickly as possible. In general, contacts who have not received two doses of measles-containing vaccine on or after the first birthday (doses should be given at least 1 month apart) are considered susceptible. One dose of measles containing vaccine can be used as evidence of immunity for preschool-aged children and adults not at high risk.[6]

### *Obtaining specimens for viral isolation.*

Efforts should be made to obtain specimens (urine or nasopharyngeal mucus) for virus isolation from all cases at the time of the initial investigation; do not wait until serologic test results are received (see Appendix 7). These isolates are essential for tracking the epidemiology of measles in the United States now that measles is not endemic in this country.[19] By comparing isolates from new case-patients to other virus samples, the origin of particular virus types in this country can be tracked. For more information on obtaining and shipping these specimens, see "Laboratory testing."

## XII. Outbreak Investigation

Although a complete description of activities to be undertaken in an investigation of a measles outbreak is beyond the scope of this manual, the following guidance may be useful to local health department personnel responsible for outbreak investigations.

## Organizing for outbreak investigation

Because investigating an outbreak requires many person-days of work, personnel are frequently transferred to the activity from other areas in the health department or from other health departments and may only be involved in outbreak investigation for a few days before they are replaced by others. This turnover in personnel can cause problems unless activities are organized so that the status of the investigation is documented at all times. Some practical suggestions for organizing this activity are listed here.

- Identify a team leader for case investigators so that at least one person knows about all the new cases called in that day and what still needs to be done. Daily briefings are a good way of keeping the whole staff informed of the status of the investigation.
- Use a logbook (electronic spreadsheet preferred) to record all suspected cases as they are received. The person who receives the initial telephone call should attempt to obtain the information needed to fill in the line listing (see Table 2).
- Create a column in the logbook for actions needed for each suspected case ("draw blood," "call pediatrician for vaccination history," "notify contacts").
- Keep the logbook in one well defined location, preferably with folders containing the case investigations of all the cases that have been reported. It is useful to have one stack of all confirmed cases, one stack of suspected or probable cases awaiting further investigation or lab results, and a separate stack of discarded cases.
- Establish protocols for control measures necessary for all likely situations (exposure in a childcare center, school, doctor's office, workplace, etc.) and clearly define who (local health officer, immunization program manager) will make the decision to proceed when a case investigator identifies a situation that might require major investments of health department resources (such as vaccinating an entire school).

**Table 2. Example of line listing for recording data in a measles outbreak investigation**

| Case ID | Name (Last, First) | Age | Rash onset date | Source of exposure | Blood draw date | IgM result | MMR-1 date | MMR-2 date | Case status |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Doe, Jane | 15 yr | 12/31/1999 | id #2 | 1/3/2000 | | 9/16/1985 | — | — |
| 2 | Smith, Stacey | 13 mo | 12/16/1999 | | 12/27/1999 | + | — | — | lab confirmed |
| 3 | Doe, Henry | 11 yr | 12/26/1999 | id #2 | 1/3/2000 | | — | — | — |
| 4 | Smith, Joe | 26 yr | 12/30/1999 | id #2 | 1/3/2000 | | ? | — | — |

## General guidelines for outbreak investigation

**Tracking what information is collected and what still needs to be collected.** Tracking is easily accomplished by constructing a line listing of cases, allowing ready identification of known and unknown data and ensuring complete case investigation. A line listing can be maintained on a computer using database management or spreadsheet software but often is most useful when filled in by hand on a form such as shown in Table 2. Such a line listing provides a current summary of the outbreak and of ongoing case investigations. The line listing is an essential component of every outbreak investigation.

**Identifying the population affected by the outbreak.** In the course of the outbreak investigation, every suspected case (whether reported through active or passive surveillance or identified through contact investigation) should be investigated thoroughly, as described above. In very large outbreaks, it may not be possible to investigate each reported case thoroughly.

Based on the findings of individual case investigations, the population affected by the outbreak should be characterized in terms of person (who is getting measles and how many case-patients have had zero, one, and two doses of measles vaccine?), place (where are the cases?), and time (when did it start and is it still going on?). (For more information on data analysis, see

Chapter 20, "Analysis of Surveillance Data.") These essential data elements allow public health officials to identify the population at risk of infection (unvaccinated preschool-age children, high school students who have only received one dose of measles vaccine, persons who visited the emergency room of Hospital A on a certain day, etc.), determine where transmission is occurring (childcare centers, high schools, health-care settings), and identify persons who are at potential risk of infection (other unvaccinated preschool-age children, students attending other schools, etc.) In general, the most effective outbreak control efforts are those that are targeted based upon epidemiologic data, rather than those that are directed at the entire community. Neither susceptibility nor risk of exposure is uniformly distributed throughout the community, and resources available for outbreak control are always limited. Therefore, it is essential that data be used to determine the scope of the current outbreak and the potential for spread and that interventions be based on those determinations

**Enhancing surveillance for measles.** Many of the activities outlined in the section "Enhancing surveillance" are applicable in the outbreak setting. Previously unreported cases may be identified by reviewing emergency room logs or laboratory records. As part of outbreak response, active surveillance for measles should be established to assure timely reporting of suspected cases in the population known to be affected by the outbreak, as well as other segments of the community that may be at high risk of exposure or in whom vaccination coverage is known to be low. Hospital emergency rooms and physicians serving affected communities are usually recruited to participate in active surveillance. Active surveillance should be maintained until at least 2 incubation periods after the last confirmed case is reported.

## XIII. Outbreak Control

The primary strategy for control of measles outbreaks is achieving a high level of immunity (2 doses) in the population affected by the outbreak. In practice, the population affected is usually rather narrowly defined such as one or more schools. Persons who cannot readily document measles immunity should be vaccinated or excluded from the setting (school, hospital, day-care etc.). Only doses of vaccine with written documentation of the date of receipt should be accepted as valid. Verbal reports of vaccination without written documentation should not be accepted. Persons who have been exempted from measles vaccination for medical, religious, or other reasons should be excluded from affected institutions in the outbreak area until 21 days after the onset of rash in the last case of measles.

If many cases are occurring among infants < 12 months of age, measles vaccination of infants as young as 6 months of age may be undertaken as an outbreak control measure. MMR vaccine may be administered to children before the first birthday in this situation. Note that children vaccinated before the first birthday should be revaccinated when they are 12–15 months old and again when they are 4–6 years of age.

### *Postexposure vaccination and use of immunoglobulin to prevent measles in exposed persons*

If given within 72 hours of exposure to measles, measles vaccine may provide some protection. In most settings, post-exposure vaccination is preferable to use of immune globulin. Immune globulin can be administered within 6 days of exposure.[3] Immune globulin is indicated for susceptible household or other close contacts of patients with measles, particularly contacts younger than 1 year of age, pregnant women and immunocompromised people for whom risk of complications is highest.

### *Use of quarantine in control of measles outbreaks*

Imposing quarantine measures for outbreak control is both difficult and disruptive to schools and other institutions. Under special circumstances, such as during outbreaks in schools attended by large numbers of persons who refuse vaccination, restriction of an event or other quarantine measures might be warranted.

### *Control of outbreaks in schools and other institutions*

During outbreaks in elementary, junior, and senior high schools, and colleges and other institutions of higher education, as well as other institutions where young adults may have close contact (such as prisons), a program of vaccination with 2 doses of MMR vaccine is recommended in the affected schools or institutions. Past experience has indicated that measles outbreaks do not occur in schools in which all students are subject to a school requirement for two doses of measles vaccine.

In a school with a measles outbreak, all students and their siblings and all school personnel born in or after 1957 who cannot provide documentation that they have received two doses of measles-containing vaccine on or after their first birthday or cannot provide other evidence of measles immunity (such as serologic testing) should be vaccinated. Persons who cannot readily provide documentation of measles immunity should be vaccinated or excluded from the school or other institution. Persons receiving 2nd doses, as well as previously unvaccinated persons receiving their 1st dose as part of the outbreak control program, may be immediately readmitted to school provided all persons without documentation of immunity have been excluded. All persons, including those vaccinated as part of the outbreak control program, should immediately report the onset of symptoms consistent with measles or its prodrome. Persons who continue to be exempted from or who refuse measles vaccination should be excluded from the school, childcare, or other institution until 21 days after the onset of rash in the last case of measles.

### *Control of outbreaks in medical settings*

Persons who work in health-care facilities (including volunteers, trainees, nurses, physicians, technicians, receptionists, and other clerical and support staff) are at increased risk of exposure to measles, and all persons who work in such facilities in any capacity should have evidence of immunity to measles to prevent any potential outbreak. If a measles case or an outbreak occurs within or in the areas served by a hospital, clinic, or other medical or nursing facility, all personnel irrespective of birth year should receive two doses of MMR vaccine, unless they have other documentation of measles immunity. Serologic screening of health-care workers during an outbreak to determine measles immunity is not recommended, because stopping measles transmission requires the rapid vaccination of susceptible health-care workers without evidence of immunity, which can be impeded by the need to screen, wait for results, and then contact and vaccinate susceptible persons.

Healthcare personnel without evidence of immunity who have been exposed to measles should be relieved from patient contact and excluded from the facility from the 5th day after the first exposure to the 21st day after the last exposure, regardless of whether they received vaccine or immune globulin (Ig) after the exposure. Personnel who develop measles should be relieved from all patient contact and excluded from the facility for 4 days after they develop rash.

### *Role of community-wide vaccination efforts in outbreak control*

Mass revaccination of entire communities is not of demonstrated benefit in control of measles outbreaks. Such activities may sometimes have to be undertaken because of political or other community demands for “action” and concerns about the acceptability of targeted interventions directed toward selected high-risk populations, but there is no epidemiological evidence that they are feasible or useful in controlling measles outbreaks.

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# Chapter 8: Meningococcal Disease

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## I. Disease Description

Meningococcal disease is a serious and potentially life-threatening infection caused by the bacterium *Neisseria meningitidis*. Common symptoms of meningococcal disease include high fever, neck stiffness, confusion, nausea, vomiting, lethargy, and/or petechial or purpuric rash. Without appropriate and urgent treatment, the infection can progress rapidly and result in death.

## II. Background

Approximately 800–1,500 cases of meningococcal disease occur annually in the United States, a rate of 0.3–0.5/100,000 population.[1,2] *N. meningitidis* is one of the leading causes of bacterial meningitis in the United States. Dramatic declines in the incidence of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b have been achieved as a result of using conjugate vaccines.[3,4]

*N. meningitidis* can be classified into 13 serogroups based on the immunologic reactivity of their capsular polysaccharides.5 Serogroups B, C, and Y each cause approximately one-third of meningococcal disease cases in the United States. The proportion of cases caused by each serogroup varies by age; serogroup B causes over 50% of cases in infants younger than 1 year of age, while serogroups C, Y, and W135 cause 75% of meningococcal disease in those 11 years and older.[6] There is currently no vaccine available for serogroup B.

Humans are the only natural reservoir for *N. meningitidis*. *N. meningitidis* organisms are gram-negative, aerobic diplococci that can attach to the surface of mucosal cells of the nasopharynx. There they multiply, bind to specific receptors, and are taken up by epithelial cells, which then transport the meningococci across the mucosal epithelium. In a small number of persons, the bacteria penetrate the mucosa and gain access to the bloodstream, resulting in systemic disease. Once colonized on the mucosal surfaces, meningococci can be transmitted from human to human through direct contact with large droplet respiratory secretions.

### *Carriage*

Five to ten percent of adults are asymptomatic nasopharyngeal carriers of *N. meningitidis*. The frequency of carriage, like that of invasive disease, also varies by age. Adolescents and young adults have the highest rates of meningococcal carriage. Although asymptomatic carriage of both pathogenic and nonpathogenic strains is common, few carriers develop invasive disease. For the majority of people, carriage is an immunizing process that results in a systemic, serogroup-specific protective antibody response.[5]

### *Epidemiology*

The epidemiology of meningococcal disease in the United States has changed dramatically over the past hundred years. Large outbreaks of meningococcal disease caused by serogroup A were common during the first half of the twentieth century, with primary attack rates as high as 310 per 100,000 population and case-fatality ratios of 70%.[7] Currently, serogroup A disease is exceedingly uncommon in the United States, while serogroup Y disease has emerged in importance. The proportion of meningococcal disease caused by serogroup Y increased from 2% during 1989–1991 to 37% during 1997–2002.[6]

Meningococcal disease occurs year-round but has a seasonal pattern with peak incidence occurring in later winter and early spring.[5] There is a natural cyclical pattern of meningococcal disease with peaks of disease occurring every 7–10 years (CDC, unpublished data). Current rates of meningococcal disease are at historic lows; the disease pattern of the past 10 years is outside the previously observed periodicity of disease.[1]

### Risk factors

Risk factors for meningococcal disease include organism, host, and environmental factors. Persons with persistent complement component deficiencies (e.g., C5—C9, properidin, factor H, or factor D) or functional or anatomic asplenia are at increased risk for invasive meningococcal disease.[8]

Crowded living conditions can facilitate respiratory droplet transmission of meningococci. College freshman residing in dormitories are at greater risk of acquiring meningococcal disease than are college students not living in dormitories.[9] Active or passive smoking and recent upper respiratory tract infections also increase risk of disease.[7] Historically, blacks and persons of low socioeconomic status have been found to be at higher risk for meningococcal disease than whites and persons of high socioeconomic status, however in recent years these differences have diminished.[1,10] Race and socioeconomic status are likely markers for differences in risk factors such as household crowding, exposure to tobacco smoke, and urban residence.

Meningococcal disease rates in children younger than 1 year peak at 0-6 months.[1,11] More than 50% of meningococcal disease in children 0-6 months is caused by serogroup B; serogroup Y is also more prevalent in this age group.[1] In time, children gradually become exposed to meningococci and develop bactericidal antibodies. By the time they reach adulthood, 65%–85% of persons possess bactericidal antibody against meningococcal disease.[12]

Those who have close contact with case-patients, such as household members, are at a substantially increased risk for acquiring carriage and disease.[13] Rates of secondary disease are also elevated among daycare workers and attendees as well as among schoolchildren.[14,15]

### Clinical

Diagnosing meningococcal disease is often challenging because its initial clinical manifestations are similar to more common but less serious illnesses. In addition, it can progress rapidly.

The common clinical manifestations of invasive meningococcal disease include meningitis, bacteremia, and pneumonia. Meningitis is observed in approximately 50% of invasive cases[1] and is characterized by abrupt onset of fever, headache, and stiff neck. Sometimes these clinical features are accompanied by nausea, vomiting, photophobia, and altered mental status. In infants, symptoms may have a slower onset, signs may be nonspecific, and neck stiffness may be absent. Approximately 40% of meningococcal disease cases present as bacteremia.[1] A portion of these cases will present as meningococcemia, the most severe manifestation of meningococcal bacteremia.[10] Signs of meningococcemia include sudden onset of fever and a characteristic petechial or purpuric rash, which may progress to purpura fulminans. The clinical course can include hypotension, acute adrenal hemorrhage, multiorgan failure, shock, and death. Patients with severe meningococcemia often respond poorly to treatment, and death can occur within hours of onset. Pneumonia occurs in approximately 10% of cases and occurs most frequently in older persons.[1,10] Diagnosing meningococcal pneumonia is difficult because isolation of the organism from sputum does not distinguish persons who are carriers from those with pneumonia caused by the organism.[16]

Much less common manifestations of meningococcal disease include myocarditis, endocarditis or pericarditis, arthritis, conjunctivitis, urethritis, pharyngitis, and cervicitis.

Of those who survive invasive disease, 10%–20% experience sequelae, including limb loss from gangrene, extensive skin scarring, or cerebral infarction. Persons with meningococcal meningitis who do not develop septic shock are less likely to die or experience these sequelae but are at risk of developing neurosensory hearing loss, mild to moderate cognitive defects, or seizure disorders.[17]

## Treatment

The use of antibiotics has dramatically reduced mortality due to meningococcal disease. Before antibiotics were available, the case-fatality ratio for meningococcal disease was between 70% and 85%. Now with the widespread use of antibiotics, the case-fatality ratio for meningococcal disease is 10%–14%, although mortality may be as high as 40% among patients with meningococcemia.[5] Even with prompt treatment the case-fatality ratio for this condition remains high.

Because of the risks of severe morbidity and death, effective antibiotics should be administered promptly to patients suspected of having meningococcal disease. Multiple antimicrobial agents, including penicillins, are effective against *N. meningitidis*.[5] For patients who receive penicillin, eradication of nasopharyngeal carriage with rifampin, ciprofloxacin, or ceftriaxone is recommended prior to discharge from the hospital.

## Chemoprophylaxis

Persons who have had close contact with patients who have meningococcal disease are at greatly increased risk for contracting the disease. The primary means of preventing the spread of meningococcal disease is antimicrobial chemoprophylaxis. Secondary cases are rare as a result of effective chemoprophylaxis for household members, contacts at daycare centers, and anyone else directly exposed to an infected patient's oral secretions (e.g., kissing, mouth-to-mouth resuscitation). Risk of secondary disease among close contacts is highest during the first few days after the onset of disease, which requires that chemoprophylaxis be administered as soon as possible. If given more than 14 days after the onset of disease, chemoprophylaxis is probably of limited or no benefit.[6] Oropharyngeal or nasopharyngeal cultures are not useful in determining the need for chemoprophylaxis and may unnecessarily delay the use of effective preventive measures (Table 1).

In areas of the United States where ciprofloxacin-resistant strains of *N. meningitidis* have been detected, ciprofloxacin should not be used for chemoprophylaxis. Use of azithromycin as a single oral dose has been shown to be effective for eradication of nasopharyngeal carriage and can be used on a limited basis where ciprofloxacin resistance has been detected.[18]

**Table 1. Recommended chemoprophylaxis regimens for high-risk contacts and persons with invasive meningococcal disease**

| Drug | Age | Dose | Duration | Efficacy (%) | Cautions |
|---|---|---|---|---|---|
| **Rifampin** | <1 mo | 5 mg/kg, orally, every 12 h | 2 days | | |
| | ≥1 mo | 10 mg/kg (maximum 600 mg), orally, every 12 h | 2 days | 90–95 | Can interfere with efficacy of oral contraceptives and some seizure prevention and anticoagulant medications; may stain soft contact lenses.<br>Not recommended for pregnant women. |
| **Ceftriaxone** | <15 y | 125 mg, intramuscularly | Single dose | 90–95 | To decrease pain at injection site, dilute with 1% lidocaine. |
| | ≥15 y | 250 mg, intramuscularly | Single dose | 90–95 | |
| **Ciprofloxacin** | ≥18 y | 500 mg, orally | Single dose | 90–95 | Not recommended for persons <18 years of age.<br>Not recommended for pregnant women. |

**Table 1. Recommended chemoprophylaxis regimens for high-risk contacts and persons with invasive meningococcal disease**

| Drug | Age | Dose | Duration | Efficacy (%) | Cautions |
|---|---|---|---|---|---|
| **Azithromycin**[a] | | *10 mg/kg (maximum 500 mg)* | *Single dose* | *90* | Not recommended routinely. Equivalent to rifampin for eradication of *Neisseria meningitidis* from nasopharynx in one study. |

*Source: American Academy of Pediatrics. Meningococcal Infections. In: Pickering LK, Baker CJ, Long SS, McMillan JA, eds. Red Book: 2006 Report of the Committee on Infectious Diseases, 27th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2006:456.*

*[a]Use only if fluoroquinolone-resistant strains of N meningitidis have not been identified in the community.[18]*

## III. Importance of Rapid Identification

Immediate recognition and treatment of meningococcal disease is critical. Persons with suspected cases should be treated promptly without waiting for laboratory confirmation. Reporting of cases is also crucial so that the proper control measures can be quickly implemented for prevention of secondary cases.

## IV. Importance of Surveillance

Passive and active surveillance systems are used to monitor meningococcal disease, which is a reportable disease in the United States. Through a national passive reporting system, state health departments collect and transmit weekly reports of cases to CDC through the National Electronic Telecommunications System for Surveillance (NETSS).

The goals of meningococcal surveillance are

1. to detect outbreaks of meningococcal disease so that appropriate control measures can be promptly instituted, and
2. to assess changes in the epidemiology of meningococcal disease over time to permit the most efficient allocation of resources and formulation of the most effective disease control and prevention policies.[19]

Meningococcal serogroup surveillance data are important to monitor the impact of quadrivalent meningococcal conjugate vaccine (MCV4; Menactra®,sanofi pasteur; Menveo®, Novartis). Meningococcal serogroup data also help to determine the epidemiologic link between cases in cluster or outbreak situations.[19]

## V. Disease Reduction Goals

The *Healthy People 2020* goal is to reduce incidence of meningococcal disease to 0.3 cases/100,000 population.[20] The first evidence of vaccine impact on rates of meningococcal disease in adolescents was observed in 2008-2009. Rates of serogroup C, Y, and W-135 meningococcal disease in adolescents declined by 50% from 2006-2007 to 2008-2009. These same decreases were not observed in infants less than one year of age or adults. These decreases were also not observed for serogorup B disease in adolescents.[21]

There is currently no vaccine in the United States to protect against serogroup B disease. Approximately one-third of meningococcal cases in the United States are caused by this serogroup; development of a vaccine against group B disease would further reduce the meningococcal disease rates.

## VI. Case Definition

The following definitions can be used to describe a case of meningococcal disease:

**Confirmed case:** A confirmed case of meningococcal disease is defined by isolation of *N. meningitidis* from a normally sterile site (e.g., blood or cerebrospinal fluid [CSF]) from a person with clinically compatible illness.

**Probable case:** A probable case of meningococcal disease is defined by detection of *N. meningitidis* DNA by polymerase chain reaction or polysaccharide antigen in CSF (e.g., by latex agglutination or immunohistochemistry), or the presence of clinical purpura fulminans in the absence of diagnostic culture from a person with clinically compatible disease.

**Primary case:** A primary case of meningococcal disease is one that occurs in the absence of previous known close contact with another patient with meningococcal disease.

**Secondary case:** A secondary case of meningococcal disease is one that occurs among close contacts of a primary case-patient 24 hours or more after onset of illness in the primary patient.

**Co-primary case:** Co-primary cases are two or more cases that occur among a group of close contacts with onset of illness separated by less than 24 hours.

**Close contacts:** Close contacts of a patient who has meningococcal disease include

1. household members (including dormitory room, barracks),
2. child care center contacts, and
3. persons directly exposed to the patient's oral secretions (e.g., by kissing, mouth-to-mouth resuscitation, endotracheal intubation, or endotracheal tube management).[6]

## VII. Laboratory Testing

*N. meningitidis* is a gram-negative, encapsulated, aerobic diplococcus. Thirteen different meningococcal serologic groups have been defined, five of which cause the great majority of disease (A, B, C, Y, and W135). The distinction between serogroups is based on the immunochemistry of the capsular polysaccharide, but more recently PCR of capsule biosynthesis genes has been used for determining the serogroup of isolates.[22] Serogroup A, C, Y and W135 polysaccharides all elicit a serogroup-specific immune response, which allows for a successful quadrivalent vaccine. The serogroup B capsular polysaccharide is poorly immunogenic, thus making it challenging to develop a vaccine to protect against this serogroup. Vaccine development efforts for serogroup B are focusing on outer membrane proteins (OMPs) or other surface molecules rather than the capsular polysaccharide.

### *Identification of N. meningitidis*

The case definition for confirmed meningococcal disease requires isolation of *N. meningitidis* from a normally sterile site. Typically, the isolate comes from blood or CSF, but it can also be from joint, pleural, or pericardial fluid. Aspirates or skin biopsies of purpura or petechiae can yield meningococci in cases of meningococcemia. The typical medium used to grow the organism is chocolate agar or Mueller-Hinton medium in an atmosphere containing 5% carbon dioxide.[23] Gram staining is commonly used for identification of *N. meningitidis* and continues to be a reliable and rapid method for presumptive identification. If proper quality assurance/quality control is performed, intracellular gram-negative diplococci in CSF can be considered meningococci until proven otherwise.

In addition to bacteriology for definitive detection and identification, latex agglutination can be used for rapid detection of meningococcal capsular polysaccharides in CSF, although false-negative and false-positive results can occur. Antigen agglutination tests on serum or urine samples are unreliable for diagnosis of meningococcal disease.[5]

Real-time PCR detects DNA of meningococci in blood, CSF, or other clinical specimens. A major advantage of PCR is that it allows for detection of *N. meningitidis* from clinical samples in which the organism could not be detected by culture methods, such as when a patient has been treated with antibiotics before obtaining a clinical specimen for culture. Even when the

organisms are nonviable following antimicrobial treatment, PCR can still detect *N. meningitidis* DNA.[22] Because of the severity of meningococcal disease, it is critical to treat the patient as soon as infection is suspected, and not to delay to obtain culture or laboratory results first.

### *Susceptibility testing*

Routine antimicrobial susceptibility testing of meningococcal isolates is not currently recommended. Surveillance of susceptibility patterns in populations should be conducted in order to monitor trends in *N. meningitidis* susceptibility. State and local health departments should notify the Centers for Disease Control and Prevention (CDC) if resistance to ciprofloxacin or other agents used for treatment or prophylaxis is detected.

### *Public health impact*

Rapid and reliable results are crucial in determining the meningococcal serogroup in an outbreak because public health response will differ for vaccine-preventable or non-vaccine-preventable disease. Outbreaks of meningococcal disease are usually caused by the same or closely related strains.[6] Molecular genotyping techniques such as pulsed-field gel electrophoresis, 16S rRNA gene sequencing, or multilocus sequence typing are used for subtype characterization of an outbreak clone.[24,25] This subtyping helps to better define the extent of the outbreak but is not necessary for determining response during the outbreak.

## VIII. Reporting

Cases of meningococcal disease should be promptly reported to the appropriate local or state health department. Case information should be reported to CDC through the National Notifiable Diseases Surveillance System (NNDSS), through the National Electronic Telecommunications System for Surveillance (NETSS), or the National Electronic Disease Surveillance System (NEDSS) within 14 days of the initial report to the state or local health department (see Appendix 9).

## IX. Vaccination

Two quadrivalent meningococcal conjugate vaccines, MCV4 (Menactra®, Sanofi Pasteur; Menveo®, Novartis) are licensed for use in the United States. Both vaccines are licensed for persons aged 2–55 years. MCV4 is the preferred vaccine for people aged 2–55 years; meningococcal polysaccharide vaccine should be used for people >55 years. Approximately 7–10 days are required after vaccination for development of protective antibody levels.

The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of persons with MCV4 at age 11 or 12 years, with a booster dose at age 16 years. For adolescents who receive the first dose at age 13 through 15 years, a one-time booster dose should be administered preferably at age 16 through 18 years. Persons who receive their first dose of MCV4 at or after age 16 years do not need a booster dose, unless they remain at increased risk for meningococcal disease. Routine vaccination of healthy persons who are not at increased risk for exposure to *N. meningitidis* is not recommended after age 21 years.[26]

Vaccination is also recommended for certain persons who have an increased risk for meningococcal disease, including 1) college freshman living in dormitories, 2) microbiologists who are routinely exposed to isolates of *N. meningitidis*, 3) military recruits, 4) persons who travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic, particularly if contact with the local population will be prolonged, 5) persons who have persistent complement component deficiencies (e.g., C5-C9, properidin, factor H, or factor D), and 6) persons who have anatomic or functional asplenia.[5]

Persons previously vaccinated with either MCV4 or MPSV4 who are at prolonged increased risk for meningococcal disease should be revaccinated with MCV4. Persons at prolonged increased risk include 1) persons who have persistent complement component deficiencies, 2) persons with anatomic or functional asplenia, and 3) persons who have prolonged exposure (e.g., microbiologists routinely working with *N. meningitidis*, or travelers to or residents of countries where meningococcal disease is hyperendemic or epidemic).[27]

Data indicate that the immune response to a single dose of MCV4 is not sufficient in persons with certain medical conditions. Persons with persistent complement component deficiencies or asplenia should receive a 2-dose primary series administered 2 months apart and then receive a booster dose every 5 years. Adolescents aged 11 through 18 years with HIV infection should be routinely vaccinated with a 2-dose primary series. Other persons with HIV who are vaccinated should receive a 2-dose primary series administered 2 months apart. All other other persons at increased risk for meningococcal disease (e.g. microbiologists or travelers to an epidemic or highly endemic country) should receive a single dose. Persons previously vaccinated with a single dose at age ≥7 years and who are at prolonged increased risk should be revaccinated 5 years after their previous meningococcal vaccine, and persons who previously were vaccinated with a single dose at ages 2-6 years and are at prolonged increased risk should be revaccinated 3 years after their previous meningococcal vaccine.[26]

**Summary of meningococcal conjugate vaccine recommendations, by risk group—Advisory Committee on Immunization Practices (ACIP), 2010**

| Risk group | Primary series | Booster dose |
|---|---|---|
| Persons aged 11 through 18 years | 1 dose, preferably at age 11 or 12 years | At age 16 years if primary dose at age 11 or 12 years |
| | | At age 16 through 18 years if primary dose at age 13 through 15 years |
| | | No booster needed if primary dose on or after age 16 years |
| HIV-infected persons in this age group | 2 doses, 2 months apart | At age 16 years if primary dose at age 11 or 12 years |
| | | At age 16 through 18 years if primary dose at age 13 through 15 years |
| | | No booster needed if primary dose on or after age 16 years |
| Persons aged 2 through 55 years with persistent complement component deficiency* or functional or anatomical asplenia | 2 doses, 2 months apart | Every 5 years |
| | | At the earliest opportunity if a 1-dose primary series administered, then every 5 years |
| *Persons aged 2 through 55 years with prolonged increased risk for exposure†* | *1 dose* | *Persons aged 2 through 6 years: after 3 years* |
| | | *Persons aged 7 years or older: after 5 years§* |

*Abbreviation: HIV = human immunodeficiency virus.*

* *Such as C5--C9, properidin, or factor D.*

† *Microbiologists routinely working with Neisseria meningitidis and travelers to or residents of countries where meningococcal disease is hyperendemic or epidemic.*

§ *If the person remains at increased risk.*

## Polysaccharide vaccine

The quadrivalent meningococcal polysaccharide vaccine, MPSV4 (Menomune-A/C/Y/W135®, sanofi pasteur) has been available since the 1970s. Meningococcal polysaccharide vaccines have been used extensively in mass vaccination programs, among international travelers, and in the military.[6] Usefulness of the polysaccharide vaccine is limited because it does not confer long-lasting immunity and does not cause a sustainable reduction of nasopharyngeal carriage of *N. meningitidis*, and therefore does not interrupt transmission sufficiently to elicit herd immunity.[6]

## Conjugate vaccine

The characteristics of conjugate vaccines offer a number of improvements over polysaccharide vaccines. Examples of the successful implementation of conjugate vaccines can be seen in the reduction of *Haemophilus influenzae* serotype b disease in children younger than 5 years old in

the United States[4] and in the dramatic reduction in invasive disease caused by *Streptococcus pneumoniae*.[3]

Conjugating polysaccharide to a protein carrier that contains T-cell epitopes creates a T-cell–dependent immune response. This results in a strong anamnestic response at re-exposure, a substantial primary response in infants, and possibly in reduction in the frequency of *N. meningitidis* carriage, protecting unvaccinated persons through herd immunity.[6]

MCV4 was demonstrated to be non-inferior to MPSV4 and was licensed based on safety and immunogenicity data. Studies to evaluate the effectiveness of the vaccine, including its effect on carriage, are currently under way.

## X. Enhancing Surveillance

CDC coordinates active, population- and laboratory-based surveillance for invasive meningococcal disease as part of the Active Bacterial Core surveillance (ABCs) system, through the Emerging Infections Program (EIP). ABCs comprises 10 sites which collect data from all patients from whom *N. meningitidis* was isolated from a normally sterile body site. This surveillance program allows for detection of patterns in causative meningococcal serogroups and accurate estimation of age-specific incidence rates.[6] ABCs data have been used to track meningococcal disease trends, including the emergence of serogroup Y meningococcal disease. ABCs website is at http://www.cdc.gov/abcs/index.html.

In addition, many states have their own enhanced surveillance system for meningococcal disease.

## XI. Case Investigation

All reports of suspected meningococcal disease should be investigated immediately. CDC is available to assist with epidemiologic and laboratory investigations during outbreaks. A critical component of case investigation is ensuring that all close contacts (see definitions) receive appropriate chemoprophylaxis to eradicate nasopharyngeal carriage of meningococci and prevent secondary disease. Approximately 70% of secondary cases occur within 7 days of disease onset in the index patient. Antibiotic administration within 24 hours of identifying a case is ideal; after 14 days it is unlikely that antibiotic chemoprophylaxis is helpful.[6] Rifampin, ciprofloxacin, ceftriaxone, and azithromycin are all effective as chemoprophylaxis against meningococcal disease.[6,18 (Table 1)]

## XII. Outbreaks

More than 98% of meningococcal disease cases in the United States are sporadic, while the other 2% are associated with outbreaks.[28] Historically, the majority of outbreaks have been caused by serogroup C, although in recent years serogroup Y and serogroup B outbreaks have been reported (CDC, unpublished data).

### *Attack rates*

Attack rates are calculated to determine the risk for disease among the general population and to determine whether overall rates have increased. Related cases, defined as secondary and co-primary, should not be included in the calculation of the attack rate. To calculate a primary attack rate all confirmed cases of the same serogroup should be summed, secondary cases should be excluded, and each set of co-primary cases should be counted as one case.

**To calculate an attack rate:**

$$\text{attack rate/100,000} = \frac{\text{number of primary confirmed or probable cases occurring during a 3-month period}}{\text{number of population at risk during the same time period}} \times 100{,}000$$

### Community and organization outbreaks

A community-based outbreak is defined as the occurrence of three or more confirmed or probable primary cases of meningococcal disease in a period of 3 months or less among persons residing in the same area who are not close contacts and who do not share a common affiliation, with a primary attack rate of 10 or more cases per 100,000 population.[6] Examples of a community-based outbreak include a neighborhood, town, or county.

An organization-based outbreak is defined as the occurrence of three or more confirmed or probable cases of meningococcal disease of the same serogroup in period of 3 months or less among persons who have a common affiliation but no close contact with each other, resulting in a primary disease attack rate of 10 or more cases per 100,000 persons.[6] In some instances the attack rate will be greater than 10 cases per 100,000 population with only two or three cases.[6] In these situations, vaccination may be considered after only two primary cases are identified. Examples of an organization-based outbreak include cases in schools, churches, and universities.

### Population at risk

A population at risk comprises persons who are considered to be at increased risk for meningococcal disease compared with historical rates of disease in the same group of the general U.S. population. Population at risk is usually defined on the basis of community of residence or organizational affiliation. The population at risk is used as the denominator in calculations of the disease attack rate. In organization-based outbreaks the population at risk can be defined as the group of persons that best represent the affiliation. In community-based outbreaks, patients do not share any common affiliation besides an area of residence.[6]

### Decision to vaccinate

When deciding to implement a mass vaccination campaign to prevent meningococcal disease, one must consider whether the cases represent an outbreak or an unusual clustering of endemic cases. Mass vaccination programs are expensive, require considerable public health effort, and may create excessive concern among the public. Because the number of cases in outbreaks is usually not substantial, this determination requires evaluation and analysis of the patterns of disease occurrence.[15]

Vaccination of the population at risk should be considered if the attack rate is greater than 10 cases per 100,000 population, but the actual attack rate at which the decision to vaccinate is made will vary. The following factors should be considered when making the decision to vaccinate:

- Completeness of case reporting and number of possible cases of meningococcal disease for which bacteriologic confirmation or serogroup data are not available
- Occurrence of additional cases of meningococcal disease after recognition of a suspected outbreak (e.g., if the outbreak occurred 2 months previously and no additional case have occurred, vaccination might be unlikely to prevent additional cases of meningococcal disease)
- Logistic and financial considerations

Current meningococcal vaccines are not effective against *N. meningitidis* serogroup B; therefore, vaccination should not be considered during a serogroup B outbreak.

### Other control measures

Mass chemoprophylaxis is not recommended for control of large outbreaks of disease for multiple reasons: cost of drug and administration, difficulty of ensuring simultaneous administration of drugs to substantial populations, drug side effects, and emergence of resistant organisms. In most outbreak settings, these disadvantages outweigh the potential benefit. Situations in which mass chemoprophylaxis could be successful include those involving limited or closed populations, such as a single school or residential facility. This is especially important in serogroup B outbreaks, since vaccines cannot be used for control and prevention. If the decision is made to use mass chemoprophylaxis, it should be administered to all persons at the same time.[6]

It is possible that even in a vaccine-preventable, organization-based outbreak, antibiotic distribution may be a more timely intervention, since preventive antibodies take 7–10 days to develop after vaccination.[6] Again, the potential benefit of mass chemoprophylaxis must be weighed against the possible emergence of antibiotic resistance and the logistics of launching a prophylaxis campaign.

Restricting travel to areas with an outbreak, closing schools or universities, or cancelling sporting or social events are not recommended measures for outbreak control in the United States. A crucial part of managing suspected meningococcal disease outbreaks and promoting early case recognition is educating communities, physicians and other healthcare workers about meningococcal disease.[6]

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# Chapter 9: *Mumps*

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## I. Disease Description

Mumps is an acute viral illness caused by a paramyxovirus. The classic symptom of mumps is parotitis (i.e., acute onset of unilateral or bilateral tender, self-limited swelling of the parotid or other salivary gland(s)), lasting at least two days, but may persist longer than ten days.[1] The mumps incubation period ranges from 12–25 days, but parotitis typically develops 16 to 18 days after exposure to mumps virus.[2] Nonspecific prodromal symptoms may precede parotitis by several days, including low-grade fever which may last three to four days, myalgia, anorexia, malaise, and headache. However, mumps infection may present only with nonspecific or primarily respiratory symptoms or may be a subclinical infection.[3]

### *Clinical manifestations*

In the prevaccine era, rates of classical parotitis among all age groups typically ranged from 31% to 65%, but in specific age groups could be as low as 9% or as high as 94% depending on the age and immunity of the group.[4–7] Several articles discuss mumps symptoms as nonspecific or primarily respiratory, however, findings in these articles were based on serologies taken every six months or a year, so it is difficult to prove that the respiratory symptoms were because of mumps or that the symptoms occurred at the same time as the mumps infection.[6, 7] In the prevaccine era, 15% to 27% of infections were asymptomatic.[4–6] In the post-vaccine era, it is difficult to estimate the number of asymptomatic infections, because it is unclear how vaccine modifies clinical presentation. Serious complications can occur in the absence of parotitis.[8, 9]

### *Prevaccine era complications*

In the prevaccine era, mumps gained notoriety as an illness that substantially affected armies during mobilization.[1] The average annual rate of hospitalization resulting from mumps during World War I was 55.8 per 1,000, which was exceeded only by the rates for influenza and gonorrhea.[1] Mumps caused transient deafness in 4.1% of infected adult males in a military population.[10] Permanent unilateral deafness caused by mumps occurred in 1 of 20,000 infected persons;[11] bilateral, severe hearing loss was very rare.[11] Before the introduction of the live attenuated mumps vaccine in 1967, mumps accounted for approximately 10% of cases of aseptic meningitis in the United States with men afflicted three times as often as women.[12] Mumps encephalitis accounted for 35.9% of all reported encephalitis cases in the United States in 1967.[13] The incidence of mumps encephalitis is reported to range from 1 in 6000 mumps cases (0.02%)[14] to 1 in 300 mumps cases (0.3%).[13] Orchitis has been reported in 11.6% to 66% of postpubertal males infected with mumps.[15, 16] In 60% to 83% of males with mumps orchitis, only one testis was affected.[4, 9] Sterility from mumps orchitis, even bilateral orchitis, occurred infrequently.[15] Oophoritis was reported in approximately 5% of postpubertal females affected with mumps[17, 18] Mastitis was reported in a few case reports[19, 20] but was also described in an outbreak in 1956–1957 affecting 31% of postpubertal females.[4] Pancreatitis was reported in 3.5% of persons infected with mumps in one community during a two year period[6] and was described in case reports.[21, 22] Permanent sequelae such as paralysis, seizures, cranial nerve palsies, and hydrocephalus occurred very rarely.[23] Death due to mumps is exceedingly rare, and is primarily caused by mumps-associated encephalitis.[13] In the United States during 1966–1971, there were two deaths per 10,000 reported mumps cases.[13]

### *Post-vaccine era complications*

Results from a recent outbreak showed that complications are lower in vaccinated case-patients compared to unvaccinated case-patients;[24] however, in another recent outbreak, vaccination status was not significantly associated with complications.[25] Among vaccinated persons, severe complications of mumps are uncommon but occur more frequently among adults than children. In recent U.S. outbreaks in 2006 and 2009–2010, rates of orchitis among postpubertal males have ranged from 3.3% to 10%;[25–27] among postpubertal females, mastitis rates have ranged

from <1% to 1%[25–27] and oophoritis rates have ranged from <1% to 1%.[25–27] Among all persons infected with mumps, reported rates of pancreatitis, deafness, meningitis, and encephalitis were all <1%.[25–27] No mumps-related deaths have been reported in recent U.S. outbreaks.

### *Mumps during pregnancy*

An association between maternal mumps infection during the first trimester of pregnancy and an increase in the rate of spontaneous abortion or intrauterine fetal death has been reported in a large prospective controlled cohort study,[28] but this association was not found in another study.[29] One study with methodological flaws showed that congenital malformations may occur from mumps during pregnancy, but because the author did not compare rates with infants born to women not affected with mumps, these findings must be interpreted with caution;[30] other papers have not reported similar findings.[4, 31]

### *Infectious period*

Although mumps virus has been isolated from seven days before, through 11–14 days after parotitis onset,[7, 32, 33] the highest percentage of positive isolations and the highest virus loads occur closest to parotitis onset and decrease rapidly thereafter. Mumps is therefore most infectious in the several days before and after parotitis onset. Most transmission likely occurs before and within five days of parotitis onset.[32] Transmission also likely occurs from persons with asymptomatic infections and from persons with prodromal symptoms.[34] In 2008, the period of isolation for mumps patients was changed from nine days to five days.[32, 33] The recommended period for contact tracing for mumps is two days before through five days after parotitis onset.

### *Other etiologies of parotitis*

Not all cases of parotitis—especially sporadic ones—are due to mumps infection. Parotitis can be caused by parainfluenza virus types 1 and 3, Epstein Barr virus, influenza A virus, Coxsackie A virus, echovirus, lymphocytic choriomeningitis virus, human immunodeficiency virus, and noninfectious causes such as drugs, tumors, immunologic diseases, and obstruction of the salivary duct. However, other causes do not produce parotitis on an epidemic scale.[35, 36]

## II. Background

Mumps vaccine was licensed in the United States in 1967. The Advisory Committee on Immunization Practices (ACIP) made an official recommendation for one dose of mumps vaccine for all children at any age after 12 months in 1977.[37] In 1989, children began receiving two doses of mumps vaccine because of the implementation of a two-dose measles vaccination policy using the combined measles, mumps, and rubella vaccine (MMR) vaccine.[38] In 2006, a two-dose mumps vaccine policy was recommended for school-aged children, students at post high school educational institutions, healthcare personnel, and international travelers.[39]

Following mumps vaccine licensure, reported mumps decreased steadily from more than 152,000 cases reported in 1968 to 2,982 in 1985.[40] During 1986–1987, a resurgence occurred with more than 20,000 reported mumps cases. The primary cause of this resurgence was low vaccination levels among adolescents and young adults.[40] In the late 1980s and early 1990s, outbreaks were reported among primary and secondary school children who had previously received one dose of mumps-containing vaccine.[41, 42] By 2003, only 231 mumps cases were reported, the lowest annual number since reporting began. However, in 2006, another resurgence occurred, with 6,584 reported cases.[25] The incidence was highest among persons aged 18–24 years, many of whom were college students. Approximately 63% of all case-patients with known vaccination status in the main outbreak states had received two doses of MMR vaccine.[25] In 2007 and 2008, the number of annual cases declined to 800 and 454 cases, respectively.

Between June 28, 2009, and June 27, 2010, another large outbreak (3,502 mumps cases) occurred in Orthodox Jewish communities in the Northeast. The source case was an 11-year-old U.S. resident with a history of two doses of MMR vaccine who developed parotitis while

attending a summer camp in New York after traveling to the United Kingdom. The median age of persons with mumps was 15 years (range: 3 months to 90 years), 2,479 (71%) were male, and of the 2,519 (72%) for whom vaccination status was reported, 76% had received two doses, 14% had received one dose, and 10% had received no doses.[26]

From December 9, 2009, through December 31, 2010, the U.S. Territory of Guam also experienced an outbreak, with 505 mumps cases reported; 48% of cases were male, and the median age was 12 years with a range of 2 months to 79 years.[27] Of the 287 school-aged children aged 6–18 years with reported mumps, 270 (94%) had received at least two doses of MMR vaccine, 8 (3%) had received one dose, 2 (1%) were unvaccinated, and 7 (2%) had unknown vaccination status. Two-dose MMR vaccine coverage in the most highly affected schools ranged from 99.3%–100%.[27]

In the Northeast and Guam mumps outbreaks, third doses of MMR vaccine were administered under Institutional Review Board protocols to the most affected populations.[27, 43] In both studies, there were declines in attack rates that were more pronounced in the age groups targeted for the intervention, but due to the late timing of the intervention and other factors, the results are inconclusive as to whether the decrease was due to the intervention. Other locations that were experiencing mumps outbreaks during the same time frame among similar populations also showed a decline in attack rates without the third dose intervention (New York City, unpublished data). There is currently no recommendation for a third dose of mumps-containing vaccine for mumps outbreaks in highly vaccinated populations, but ACIP is considering a permissive recommendation for such situations. Catch-up vaccination efforts to ensure that populations at risk are up to date with the recommended number of vaccine doses, as well as reducing opportunities for close contact, remain the recommended strategies for mumps outbreak control.

Cases of mumps will continue to be imported into the United States as long as mumps continues to be endemic globally. Mumps vaccine is routinely used in 61% of countries in the world.[44]

## III. Disease Reduction Goals

The 338 reported cases of mumps in 2000 met the *Healthy People 2000* reduction goal of fewer than 500 cases. Subsequently, a goal of elimination of indigenous mumps by the year 2010 was made.[45] However, major resurgences in mumps during 2006, 2009, and 2010 highlighted the challenges of obtaining this goal with currently available vaccines and the existing vaccination policy and resulted in re-evaluation of the mumps program goal in the U.S. Mumps is endemic throughout the world, and achieving elimination was considered difficult in the context of ongoing mumps virus importations and the current two-dose vaccination program. Subsequently, the *Healthy People 2020* goal for mumps is a disease reduction goal (i.e., to have fewer than 500 reported cases of mumps annually), rather than an elimination goal.[46]

### *Vaccination*

Live attenuated mumps virus vaccine is incorporated into combined MMR vaccine. Monovalent mumps vaccine is no longer produced in the United States. For prevention of mumps, two doses of MMR vaccine are recommended routinely for children with the first dose at 12–15 months of age and the second dose at 4–6 years of age (school entry).[47]

For prevention of mumps, two doses of MMR vaccine are also recommended for adults at high risk, including international travelers, college and other post high school students, and healthcare personnel born during or after 1957.[39, 47] All other adults born during or after 1957 without other evidence of mumps immunity should be vaccinated with one dose of MMR vaccine[39, 47] Vaccination recommendations for an outbreak setting are discussed in the "Outbreak Control" section later in this chapter.

The mumps vaccine component of the MMR vaccine has a lower effectiveness compared to the measles and rubella components. Mumps vaccine effectiveness has been estimated at a median of 78% (range: 49%−91%) for one dose[1, 42, 48–51] and a median of 88% (range: 66%−95%) for two doses.[34, 50–53]

Mumps vaccine can also be administered as a combined vaccine with measles, rubella, and varicella vaccines (MMRV); however, MMRV vaccine is currently available in limited supply.[54] MMRV vaccine can be used for children aged 12 months through 12 years who need a first dose of MMR and varicella vaccine, or who need a second dose of MMR and either a first or second dose (as indicated) of varicella vaccine.[55]

For the first dose of measles, mumps, rubella, and varicella vaccines at age 12–47 months, either MMR vaccine and varicella vaccine or MMRV vaccine may be used. Providers who are considering administering MMRV vaccine should discuss the benefits and risks of both vaccination options with the parents or caregivers. Compared with use of MMR and varicella vaccines given separately at the same visit, use of MMRV vaccine results in one fewer injection but is associated with a higher risk for fever and febrile seizures 5 through 12 days after the first dose among children aged 12 through 23 months (about one extra febrile seizure for every 2,300–2,600 MMRV vaccine doses). Unless the parent or caregiver expresses a preference for MMRV vaccine, CDC recommends that MMR vaccine and varicella vaccine should be administered for the first dose in this age group.[55] For the first dose of measles, mumps, rubella, and varicella vaccines at ages 48 months and older and for dose two at any age (15 months through 12 years), use of MMRV vaccine generally is preferred over separate injections of its equivalent component vaccines (i.e., MMR and varicella vaccines).

## IV. Presumptive Evidence of Mumps Immunity

According to ACIP recommendations published in 2006,[39] acceptable presumptive evidence of mumps immunity includes at least one of the following:

(a) written documentation of receipt of one or more doses of a mumps-containing vaccine administered on or after the first birthday for preschool-aged children and adults not at high risk, and two doses of mumps-containing vaccine for school-aged children and adults at high risk (i.e., healthcare personnel, international travelers, and students at post high school educational institutions);

(b) laboratory evidence of immunity;

(c) birth before 1957; or

(d) documentation of physician-diagnosed mumps.

Persons who do not meet the above criteria are considered susceptible.[39] Healthcare settings have slightly different criteria for acceptable presumptive evidence of immunity, and these criteria are detailed in the 'Healthcare Personnel: Presumptive Evidence of Immunity' section below.

## V. Case Definition

The following case definition for mumps was updated and approved by the Council of State and Territorial Epidemiologists (CSTE) in 2011.[56]

### *Disease specific data elements:*

Disease-specific data elements to be included in the initial report are listed below.

**Clinical presentation**

- parotitis or swelling of sublingual or submandibular salivary glands for two or more days
- onset date of symptoms
- mumps-associated complications (describe)

**Epidemiological evidence**

- contact (or in a chain of contacts) of a laboratory-confirmed mumps case
- contact of a person with parotitis
- contact of a person with a mumps-associated complication
- member of a risk group defined by public health authorities during an outbreak

- return from international travel within 25 days of symptom onset
  - Travel location
  - Date of return to U.S.

**Immunization history**

- number of doses of mumps-containing vaccine received
- date of all doses of mumps-containing vaccine received

### *Case definition for case classification*

**Suspect:**

- parotitis, acute salivary gland swelling, orchitis, or oophoritis unexplained by another more likely diagnosis,

or

- a positive lab result with no mumps clinical symptoms (with or without epidemiological linkage to a confirmed or probable case).

**Probable:**

- Acute parotitis or other salivary gland swelling lasting at least 2 days, or orchitis or oophoritis unexplained by another more likely diagnosis, in:
  - a person with a positive test for serum anti-mumps IgM antibody, or
  - a person with epidemiologic linkage to another probable or confirmed case or linkage to a group/community defined by public health during an outbreak of mumps.

**Confirmed:**

- A positive mumps laboratory confirmation for mumps virus with RT-PCR or culture in a patient with an acute illness characterized by any of the following:
  - Acute parotitis or other salivary gland swelling, lasting at least 2 days
  - Aseptic meningitis
  - Encephalitis
  - Hearing loss
  - Orchitis
  - Oophoritis
  - Mastitis
  - Pancreatitis

**Case classification for import status**

***Internationally imported case:*** An internationally imported case is defined as a case in which mumps results from exposure to mumps virus outside the United States as evidenced by at least some of the exposure period (12–25 days before onset of parotitis or other mumps-associated complications) occurring outside the United States and the onset of parotitis or other mumps-associated complications within 25 days of entering the United States and no known exposure to mumps in the U.S. during that time. All other cases are considered U.S.-acquired cases.

***U.S.-acquired case:*** A U.S.-acquired case is defined as a case in which the patient had not been outside the United States during the 25 days before onset of parotitis or other mumps-associated complications or was known to have been exposed to mumps within the United States.

U.S.-acquired cases are sub-classified into four mutually exclusive groups:

- **Import-linked case:** Any case in a chain of transmission that is epidemiologically linked to an internationally imported case.
- **Imported-virus case:** A case for which an epidemiologic link to an internationally imported case was not identified but for which viral genetic evidence indicates an imported mumps genotype (i.e., a genotype that is not occurring within the United States in a pattern indicative

of endemic transmission). An endemic genotype is the genotype of any mumps virus that occurs in an endemic chain of transmission (i.e., lasting ≥12 months). Any genotype that is found repeatedly in U.S.-acquired cases should be thoroughly investigated as a potential endemic genotype, especially if the cases are closely related in time or location.

- **Endemic case:** A case for which epidemiological or virological evidence indicates an endemic chain of transmission. Endemic transmission is defined as a chain of mumps virus transmission continuous for ≥12 months within the United States.
- **Unknown source case:** A case for which an epidemiological or virological link to importation or to endemic transmission within the U.S. cannot be established after a thorough investigation. These cases must be carefully assessed epidemiologically to assure that they do not represent a sustained U.S.-acquired chain of transmission or an endemic chain of transmission within the U.S.

***Note:*** *Internationally imported, import-linked, and imported-virus cases are considered collectively to be import-associated cases.*

States may also choose to classify cases as "out-of-state-imported" when imported from another state in the United States. For national reporting, however, cases will be classified as either internationally imported or U.S.-acquired.

## VI. Laboratory Testing

If mumps is suspected, laboratory testing should be performed. Acute mumps infection can be detected by the presence of serum mumps IgM, a significant rise in IgG antibody titer in acute- and convalescent-phase serum specimens, IgG seroconversion, positive mumps virus culture, or detection of virus by real-time reverse transcriptase polymerase chain reaction (rRT-PCR). However, in both unvaccinated and vaccinated persons, false positive results can occur because assays may be affected by other diagnostic entities that cause parotitis. In addition, laboratory-confirming the diagnosis of mumps in highly vaccinated populations may be challenging, and serologic tests should be interpreted with caution because false negative results in vaccinated persons (i.e., a negative serologic test in a person with true mumps) are common. With previous contact with mumps virus either through vaccination (particularly with two doses) or natural infection, serum mumps IgM test results may be negative; IgG test results may be positive at the initial blood draw; and viral detection in RT-PCR or culture may have low yield if the buccal swab is collected more than three days after parotitis onset. Therefore, mumps cases should not be ruled out by negative laboratory results. These challenges are discussed in more detail below.

### *Virus detection (real-time RT-PCR and culture)*

Mumps virus can be detected from fluid collected from the parotid duct, other affected salivary gland ducts, the throat, from urine, and from cerebrospinal fluid (CSF). Parotid duct swabs yield the best viral sample. This is particularly true when the salivary gland area is massaged approximately 30 seconds prior to swabbing the buccal/parotid duct, so that the specimen contains the secretions from the parotid or other salivary duct glands. Efforts should be made to obtain the specimen as soon as possible after onset of parotitis or meningitis. Clinical specimens should ideally be obtained within three days and not more than eight days after parotitis onset.

Successful virus isolation should always be confirmed by immunofluorescence with a mumps-specific monoclonal antibody or by molecular techniques. Molecular techniques such as real-time RT-PCR can also be used to detect mumps RNA directly for mumps confirmation in appropriately collected specimens.

Urine samples are less likely than oral specimens to contain sufficient virus copies or virus-infected cells for culture or detection by molecular methods, and therefore are not preferred.

Molecular typing is recommended because it provides important epidemiologic information. Molecular epidemiologic surveillance, (i.e., virus genotyping) allows the building of a sequence database that will help track transmission pathways of mumps strains circulating in the United

States. In addition, genotyping methods are available to distinguish wild-type mumps virus from vaccine virus.

- **Unvaccinated persons:** Virus may be isolated from the buccal mucosa until 11–14 days after salivary enlargement; however, viral isolation is most likely to be successful just prior to and within the first three days of parotitis onset.
- **Vaccinated persons:** In order to optimize virus yield, emphasis should be placed on obtaining mumps clinical specimens from buccal mucosa within 1 to 3 days after onset of symptoms (usually parotitis).

In the case of specimens for virus culture or PCR assay, immediately place specimens in a cold storage container and transport to the laboratory.

### *Serologic testing*

The serologic tests available for laboratory confirmation of mumps acute infection and confirmation of previous exposure to mumps vary among laboratories. The State health department can provide guidance regarding available laboratory services. At the direction of the State health department, healthcare providers and State and local health departments may send serum specimens from suspected mumps cases to the CDC Measles, Mumps, Rubella, and Herpes Laboratory Branch for IgM detection by EIA. See "Specimen collection and management" section below.

- At the initial visit, a serum specimen should be obtained to test for mumps IgM antibodies.
  - If the acute-phase specimen is positive for IgM, a second specimen is not necessary.
  - A second negative IgM does not rule out mumps unless the IgG result is also negative.
- Paired serum specimens may also be used to demonstrate seroconversion from negative to positive from acute to convalescent, which is considered a positive diagnostic result for mumps. In unvaccinated individuals, a four-fold increase in IgG titers is also considered a positive diagnostic result for mumps, but these are rarely done.

### *Tests for IgM antibody*

**Enzyme immunoassay (EIA):** a highly specific test for diagnosing acute mumps infection. The use of the IgM capture EIA is preferred over the Immunofluorescence assay (IFA).

**Immunofluorescence assay (IFA):** a test that is relatively inexpensive and simple, but the IFA format is particularly susceptible to interference by high levels of mumps-specific IgG. Reading the test requires considerable skill and experience since this nonspecific staining may cause false positive readings if the serum is not treated with an agent to remove human IgG antibody.

***Note:*** *Commercially available EIA kits and IFA antibody assays for detection of mumps IgM are not currently FDA-approved. Therefore, each laboratory must validate these tests independently.*

### *Serum collection and timing of the mumps IgM response*

- **Unvaccinated persons:** IgM antibody is detectable within 5 days after onset of symptoms, reaches a maximum level about a week after onset, and remains elevated for several weeks or months.[57, 58] If an acute-phase serum sample collected ≤3 days after parotitis onset is negative for IgM, testing a second sample collected 5–7 days after symptom onset is recommended since the IgM response may require more time to develop.
- **Vaccinated persons:** Patients that mount a secondary immune response to mumps, as seen in most previously vaccinated persons, may not have an IgM response or it may be transient and not detected depending on the timing of specimen collection.[57] Because of this, a high number of false negative results may occur in previously vaccinated individuals. False positive IgM results may also occur and appear to be more prevalent with certain IgM test formats, such as the IFA. There is some evidence that serum collected ≥10 days after parotitis onset may improve the ability to detect IgM among persons who have received one or two doses of MMR vaccine[59] (CDC, unpublished data). However, persons with a history of mumps vaccination may not have detectable mumps IgM antibody regardless of the timing of specimen collection.

### Tests for IgG antibody

Tests for IgG antibody may be used for mumps diagnosis or for testing mumps immunity. A variety of tests for IgG antibodies to mumps are available and include EIA, IFA, and plaque reduction neutralization. The specific criteria for documenting an increase in titer depend on the test.

#### *Diagnosis of Mumps with IgG*

IgG testing for laboratory confirmation of mumps requires the demonstration of seroconversion from negative to positive by EIA or a four-fold rise in the titer of antibody against mumps as measured in plaque-reduction neutralization assays or similar quantitative assays. The tests for IgG antibody should be conducted on both acute- and convalescent-phase specimens at the same time. The same type of test should be used on both specimens. EIA values are not titers, and increases in EIA values do not directly correspond to titer rises.

- **Unvaccinated persons:** In unvaccinated persons, IgG antibody increases rapidly after onset of symptoms and is long lasting.
- **Vaccinated persons:** In vaccinated persons, the IgG may already be quite elevated in the acute-phase blood sample which frequently prevents detection of a four-fold rise in IgG titer in the convalescent serum specimen.

#### *Testing Mumps Immunity with IgG*

A single serum sample tested for mumps-specific IgG is not useful for diagnosing acute mumps infections. The presence of mumps-specific IgG, as detected using a serologic assay (EIA or IFA), is considered evidence of mumps immunity but does not necessarily predict the presence of neutralizing antibodies or protection from mumps disease.

### Specimen collection and management

Specific instructions for specimen collection and shipping may be obtained from the CDC mumps website at: http://www.cdc.gov/mumps/lab/specimen-collect.html[60] or by contacting the CDC MMR and Herpes Virus Laboratory Branch at 404-639-1156 or 404-639-3512. Specimens for virus isolation and genotyping should be sent to CDC as directed by the State health department.

For additional information on use of laboratory testing for surveillance of vaccine-preventable diseases, see Chapter 22, "Laboratory Support for the Surveillance of Vaccine-Preventable Diseases."

## VII. Reporting

Each state and U.S. territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[61] These regulations and laws list the diseases that are to be reported and describe those persons or groups responsible for reporting, such as healthcare providers, hospitals, schools, laboratories, daycare and childcare facilities, and other institutions. Persons reporting these conditions should contact their State health department for state-specific reporting requirements.

### Reporting to CDC

A provisional report of all probable and confirmed mumps cases should be sent by the State health department to CDC via the National Notifiable Diseases Surveillance System (NNDSS). Electronic reporting of case records should not be delayed because of incomplete information or lack of confirmation. Following completion of case investigations, case records should be updated with any new information and resubmitted to CDC. Final laboratory results may not be available for the initial report but should be submitted via NNDSS when available.

### Information to collect

The following data should be collected in the course of the case investigation. Additional information may be collected at the direction of the State health department.

- Demographic information
  - Name
  - Address
  - Date of birth
  - Age
  - Sex
  - Ethnicity
  - Race
  - Country of birth
  - Length of time in United States
  - Reporting source
  - County
  - Earliest date reported
- Clinical
  - Date of illness onset (note: this may be earlier than parotitis onset due to prodromal symptoms)
  - Parotitis or other salivary gland involvement (pain, tenderness, swelling)
  - Date of parotitis (or other salivary gland swelling) onset
  - Duration of parotitis (or other salivary gland swelling)
  - Other symptoms (e.g., headache, anorexia, fatigue, fever, body aches, stiff neck, difficulty in swallowing, nasal congestion, cough, earache, sore throat, nausea, abdominal pain)
  - Complications
    - Deafness (transient or permanent; unilateral or bilateral)
    - Encephalitis
    - Mastitis
    - Meningitis
    - Oophoritis
    - Orchitis (unilateral or bilateral)
    - Pancreatitis
    - Other
  - Hospitalization, reason/association to mumps, duration of stay
  - Outcome (patient survived or died)
  - Date of death
  - Postmortem examination results
  - Death certificate diagnoses
- Treatment
  - Medications given
  - Duration person was on each medication
- Laboratory
  - Serology (IgM, IgG)
  - Virus detection (PCR, culture)
  - Specimen collection date(s)
- Vaccine information
  - Number of doses of vaccine given
  - Type of vaccine administered (i.e., MMR, MMRV, or single antigen mumps vaccine)
  - Dates of mumps vaccination for each dose
  - Manufacturer of vaccine

- Vaccine lot number
- If not vaccinated, reason

- Epidemiologic
  - Epidemiologic linkages
  - Transmission setting (e.g., college, school, doctor's office)
  - Import status (e.g., internationally imported or U.S.-acquired). See "Case classification for import status" section above.
  - Location of exposure (country, if international import; state, if out-of-state import)
  - Travel history

## VIII. Case Investigation

The Mumps Surveillance Worksheet (Appendix 10) may be used as a guideline to collect case information during a case investigation; the details are discussed below.

### *Case identification*

Identification of suspected or confirmed cases of mumps is important in the initiation of control measures to prevent the spread of the disease among persons who do not have presumptive evidence of immunity. Once a sporadic case has been identified, several factors should be taken into consideration before initiating a public health response, such as epidemiological risk factors, vaccination status, and other etiologies. However, in transmission settings with high risk, such as households, schools, and camps, health departments may want to be a little more aggressive. In these settings, health departments should consider conducting case investigations and assessing immune status of close contacts before laboratory results are known or before additional cases are identified. Nonetheless, control measures are unlikely to be implemented until either the laboratory results are back or until at least two infected persons have a confirmed epidemiological link.

### *Establishing a diagnosis of mumps*

Clinical diagnosis of mumps may be unreliable. Cases of suspected mumps should be laboratory confirmed; however, negative laboratory results among vaccinated persons do not necessarily rule out the diagnosis of mumps, particularly if there is an outbreak of parotitis.

Efforts should be made to obtain clinical specimens (buccal cavity/parotid duct fluids, throat swabs, urine, or CSF) for viral isolation for all sporadic cases and at least some cases in each outbreak at the time of the initial investigation.

### *Obtaining accurate, complete immunization histories*

Mumps case investigations should include complete immunization histories that are verified by documentation of administration of all doses. Verbal history of receipt of mumps vaccine is not considered adequate proof of vaccination. Some case-patients or their caregivers may have personal copies of immunization records available that include dates of administration; these are acceptable for reporting purposes.

### *Identifying the source of infection*

Efforts should be made to identify the source of infection for every confirmed case of mumps (i.e., case-patients should be asked about contact with other known patients). However, this is not always possible, especially with sporadic cases, and this should not occur at the expense of higher public health priorities. If it can be determined when and where transmission likely occurred, investigative efforts should be directed to these locations.

### *Assessing potential transmission and identifying contacts*

The potential for further transmission should be assessed. Contacts of the case-patient during the two days prior through five days after onset of parotitis should be identified, assessed for immunity, offered vaccine as appropriate, and educated about signs and symptoms.

CDC recommends a five-day period after onset of parotitis for: 1) isolation of persons with mumps in the community and for 2) use of droplet precautions, in addition to standard precautions in healthcare settings.[32]

## IX. Enhancing Surveillance

### *Importance of surveillance*

Information obtained through surveillance is used to follow disease trends in the population, to assess progress towards disease reduction goals, and to characterize populations requiring additional disease control measures.

### *Monitoring surveillance indicators*

Regular monitoring of surveillance indicators can help identify specific areas of the surveillance and reporting system that need improvement. The following indicators should be monitored.

- The proportion of confirmed cases reported to NNDSS with complete information (e.g., date of birth, onset date, clinical case definition, hospitalization, laboratory testing, vaccine history, date reported to health department, transmission setting, outbreak-related, and epidemiologic linkage)
- The interval between date of symptom onset and date of public health notification
- The proportion of cases that are laboratory confirmed
- The proportion of cases that have an imported source

The activities listed below can help increase the number of suspected mumps cases that are reported and improve the comprehensiveness and quality of reports that are received. Additional guidelines for enhancing surveillance are given in Chapter 19, "Enhancing Surveillance."

### *Promoting awareness*

In the event of an outbreak, surveillance should be enhanced by promoting awareness in the public affected by the outbreak and healthcare personnel. Healthcare personnel should be aware that mumps outbreaks have occurred in highly vaccinated populations in high transmission settings, including school settings (e.g., elementary school, middle school, high school, and college students). Therefore, mumps should not be ruled out on the assumption that individuals have evidence of mumps immunity because of vaccination.

## X. Outbreak Investigation

A mumps outbreak is defined as three or more cases linked by time and place. In recent years, mumps outbreaks have occurred in highly vaccinated populations in high transmission settings, including elementary, middle, and high schools, colleges, and camps. Especially in these settings, rapid detection and investigation of cases, and implementation of control measures may reduce the magnitude of outbreaks.[50] The following are general guidelines for an outbreak investigation.

### *Collecting tracking information*

During an outbreak, a line listing of cases on a spreadsheet allows for quick identification of known and unknown data and ensures that complete case investigations are done.

### *Identifying the population affected by the outbreak*

During an outbreak, every suspected case should be investigated thoroughly, as described above. In very large outbreaks, it may not be possible to thoroughly investigate each reported case.

Based on the findings of individual case investigations, the population affected by the outbreak should be characterized in terms of:

- person (who is becoming infected with mumps, what is their vaccination status),
- place (where are the cases), and
- time (when did the outbreak start, and is it still going on).

These essential data elements allow public health officials to determine the population at risk of infection (e.g., unvaccinated persons, students who have only received one dose of mumps vaccine, persons who visited the emergency department of Hospital A on a certain day, and highly vaccinated populations in high transmission settings); to determine where transmission is occurring (e.g., schools, colleges, healthcare settings); and to identify individuals who are at potential risk of infection (e.g., other unvaccinated persons, students attending other schools).

### *Obtaining accurate and complete immunization histories*

Vaccination histories may be obtained from schools (generally available for children attending licensed childcare centers or kindergarten through high school, as well as many universities), medical providers, or immunization records provided by the case-patient. Immunization registries, if available, can also readily provide vaccination histories.

### *Investigating contacts*

Identifying contacts (e.g., household, school/college, and other close contacts) and following up with persons without evidence of mumps immunity may reveal previously undiagnosed and unreported cases.

### *Enhancing surveillance for mumps*

Local or State health departments should contact healthcare providers in outbreak areas to inform them of the outbreak and request reporting of any suspected cases. During outbreaks, active surveillance for mumps should be conducted for every confirmed and probable mumps case. Active surveillance should be maintained for at least two incubation periods (50 days) following parotitis onset in the last case. Two incubation periods allow for the identification of transmission from subclinical infections or unrecognized cases. Previously unreported cases may be identified by reviewing laboratory records.

## XI. Outbreak Control

Initial preparation for control activities may need to be started before laboratory results are known, but are unlikely to be implemented until either the laboratory results are back or until at least two infected persons have a confirmed epidemiological link.

The main strategy for controlling a mumps outbreak is to define the population(s) at risk and transmission setting(s), and to rapidly identify and vaccinate persons without presumptive evidence of immunity; or, if a contraindication exists, to exclude persons without presumptive evidence of immunity from the setting to prevent exposure and transmission.

Mumps-containing vaccine should be administered to persons without evidence of immunity and everyone should be brought up to date with age appropriate vaccination (one or two doses). Although mumps-containing vaccination has not been shown to be effective in preventing mumps in persons already infected, it will prevent infection in those persons who are not yet exposed or infected. If persons without evidence of immunity can be vaccinated early in the course of an outbreak, they can be protected prior to exposure. However, because of the long incubation period for mumps, cases are expected to continue to occur for at least 25 days among newly vaccinated persons who may have been infected before vaccination.[62] As with all vaccines, some individuals will not develop protective immunity after receipt of mumps vaccine. Depending on the epidemiology of the outbreak (e.g., the age groups and/or institutions involved), a second dose of mumps-containing vaccine should be considered for children aged 1–4 years and adults who have received one dose previously.[39]

To assist with control of mumps outbreaks in schools and colleges, students with zero doses of MMR vaccine and with no other evidence of mumps immunity should be excluded from schools/colleges affected by a mumps outbreak or other schools that are unaffected but deemed by local public health authorities to be at risk for transmission of disease.[47] Excluded students can be readmitted immediately after they are vaccinated. Students who have a history of one dose of MMR vaccination should receive their second vaccine dose and be allowed to remain in school. Students who have been exempted from mumps vaccination for medical, religious,

or other reasons should be excluded until the 26th day after the onset of parotitis in the last person with mumps in the affected school.[47]

Currently, data are insufficient to recommend for or against the use of a third dose of MMR vaccine for mumps outbreak control. CDC has issued guidance for considerations for use of a third dose in specifically identified target populations along with criteria for public health departments to consider for decision making.

During mumps outbreaks, public health authorities may administer a third dose of MMR vaccine for specifically identified target populations.

Criteria to consider prior to administering a third dose in a target population for mumps outbreak control include:

- high two-dose vaccination coverage (i.e., vaccination coverage >90%);
- intense exposure settings likely to facilitate transmission (e.g., schools, colleges, correctional facilities, congregate living facilities) or healthcare settings;
- high attack rates (i.e., >5 cases per 1,000 population); and evidence of ongoing transmission for at least two weeks in the target population (i.e., population with the high attack rates)

Additional data on the effectiveness and impact of a third dose of MMR vaccine for mumps outbreak control are needed to guide control strategies in future outbreaks. Authorities who decide to administer a third dose as part of mumps outbreak control are encouraged to collect data to evaluate the impact of the intervention. The following data should be collected:

- incidence of mumps in target population (before and after the intervention, by vaccination status),
- incidence of adverse events following vaccination with a third dose, and
- costs associated with the intervention (vaccine, personnel)

Catch-up vaccination efforts to ensure that populations at risk are up to date with the recommended number of vaccine doses, as well as reducing opportunities for close contact, remain the recommended strategies for mumps outbreak control.

## XII. Healthcare Settings

### *Prevention and control strategies in healthcare settings*

Prevention and control strategies should be applied in all healthcare settings, including outpatient and long-term care facilities. These measures include:

1. assessment of presumptive evidence of immunity of healthcare personnel, including documented administration of two doses of live mumps virus vaccine, laboratory evidence of immunity or laboratory confirmation of disease, or birth before 1957 (refer to next section, "Healthcare personnel presumptive evidence of immunity" for footnotes),
2. vaccination of those without evidence of immunity,
3. exclusion of healthcare personnel with active mumps illness, as well as healthcare personnel who do not have presumptive evidence of immunity who are exposed to persons with mumps,
4. isolation of patients in whom mumps is suspected, and
5. implementation of droplet precautions, in addition to standard precautions.

An effective vaccination program is the best approach to prevent healthcare-associated mumps transmission. Healthcare Infection Control Practices Advisory Committee (HICPAC) and CDC have recommended that secure, preferably computerized, systems should be used to manage vaccination records for healthcare personnel so records can be easily retrieved as needed.[63] Facilities are also encouraged to review employee evidence of immunity status for mumps and other vaccine preventable infections. Healthcare facilities should provide MMR vaccine to all personnel without evidence of mumps immunity at no charge.

### Healthcare personnel: presumptive evidence of immunity

The presumptive evidence of immunity criteria for healthcare personnel differs slightly from the criteria for community settings. The following criteria should be followed to assess presumptive evidence of immunity among healthcare personnel.[64]

- Written documentation of vaccination with two doses of live mumps or MMR vaccine administered at least 28 days apart*
- Laboratory evidence of immunity†
- Laboratory confirmation of disease
- Birth before 1957‡§¶#

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* *The first dose of mumps-containing vaccine should be administered on or after the first birthday; the second dose should be administered no earlier than 28 days after the first dose.*

† *Mumps immunoglobulin (IgG) in the serum; equivocal results should be considered negative.*

‡ *Most persons born before 1957 are likely to have been infected naturally between birth and 1977— the year mumps vaccination was recommended for routine use— and may be presumed immune, even if they have not had clinically recognizable mumps disease.*

§ *May vary depending on current state or local requirements.*

¶ *For unvaccinated personnel born before 1957 who lack laboratory evidence of mumps immunity or laboratory confirmation of disease, healthcare facilities should consider vaccinating personnel with two doses of MMR vaccine at the appropriate interval.*

\# *For unvaccinated personnel born before 1957 who lack laboratory evidence of mumps immunity or laboratory confirmation of disease, healthcare facilities should recommend two doses of MMR vaccine during an outbreak of mumps.*

In the event that a nosocomial outbreak occurs, healthcare facilities should have a plan in place for the implementation of the two-dose recommendation for all healthcare personnel, including those who were born before 1957 and lack laboratory evidence of immunity or laboratory confirmation of disease. Healthcare facilities may choose to proceed with appropriate assessment and vaccination of personnel born before 1957 before an outbreak occurs.

Although there are no data that correlate levels of serum antibody with protection from disease, presence of mumps-specific IgG antibodies is considered evidence of mumps immunity. For healthcare personnel who do not have adequate presumptive evidence of mumps immunity, prevaccination antibody screening before MMR vaccination is not necessary.

Results of serum antibody tests in vaccinated persons are difficult to interpret. In vaccinated persons, antibody levels are often lower than following natural infection, and commercially available tests may not detect such low levels of antibody. As a result, postvaccination serologic testing to verify an immune response to MMR or its component vaccines is not recommended. There are no data on the effect of additional (greater than two) doses of mumps vaccine on antibody levels or protection from disease.

### Healthcare personnel exclusion

Healthcare personnel with active mumps illness and those who lack evidence of immunity and have had unprotected exposures to mumps should be excluded from work from the 12th day after the first unprotected exposure to mumps through the 25th day after the last exposure. Unprotected exposures are defined as being within three feet of a patient with a diagnosis of mumps without the use of proper personal protective equipment. Irrespective of their immune status, all exposed healthcare personnel should report any signs or symptoms of illness during the incubation period, from 12 through 25 days after exposure.

### Management of healthcare personnel with illness due to mumps

- A diagnosis of mumps should be considered in exposed healthcare personnel who develop non-specific respiratory infection symptoms during the incubation period after unprotected exposures to mumps, even in the absence of parotitis.
- Healthcare personnel with mumps illness should be excluded for five days after the onset of parotitis.

### *Management of healthcare personnel who are exposed to persons with mumps*

**For healthcare personnel who do not have acceptable presumptive evidence of immunity**

- Healthcare personnel without evidence of immunity should be excluded from the 12th day after the first unprotected exposure to mumps through the 25th day after the last exposure. Previously unvaccinated healthcare personnel who receive a first dose of vaccine after an exposure are considered non-immune and should be excluded from the 12th day after the first exposure to mumps through the 25th day after the last exposure. The mumps vaccine cannot be used to prevent the development of mumps after exposure.

**For healthcare personnel with partial vaccination**

- Healthcare personnel who had been previously vaccinated for mumps, but received only one dose of mumps vaccine may continue working following an unprotected exposure to mumps. Such personnel should receive a second dose as soon as possible, but no sooner than 28 days after the first dose. They should be educated about symptoms of mumps, including non-specific presentations, and should notify occupational health if they develop these symptoms.

**For healthcare personnel who have presumptive evidence of immunity**

- Healthcare personnel with evidence of immunity do not need to be excluded from work following an unprotected exposure. However, two doses of MMR vaccine do not provide 100% protection from mumps. Some vaccinated personnel may remain at risk for mumps. Therefore, healthcare personnel should be educated about symptoms of mumps, including nonspecific presentations, and should notify occupational health if they develop these symptoms.

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# Chapter 10: Pertussis

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## I. Disease Description

Pertussis, a cough illness commonly known as whooping cough, is caused by the bacterium *Bordetella pertussis*. The illness is characterized by a prolonged paroxysmal cough often accompanied by an inspiratory whoop. Disease presentation varies with age and history of previous exposure or vaccination. Young infants can present to a clinic or hospital with apnea and no other disease symptoms. Adults and adolescents with some immunity can exhibit only mild symptoms or have the typical prolonged paroxysmal cough. In all persons, cough can continue for months.

Severe disease is infrequent in healthy, vaccinated persons. Infants, particularly those who have not received the primary vaccination series against pertussis, are at risk for complications and mortality. Pneumonia is the most common complication in all age groups. Seizures and encephalopathy are rare and generally only reported in young infants. Death is rare and most likely to occur in young, unvaccinated infants, although fatalities are occasionally reported among older children and adults with serious underlying health conditions.[1]

In addition to *B. pertussis*, three other *Bordetella* species can cause disease in humans: *B. parapertussis*, *B. holmesii*, and *B. bronchiseptica*. *B. parapertussis* causes a pertussis-like illness that is generally milder than pertussis because the bacteria do not produce pertussis toxin. Co-infection of *B. pertussis* and *B. parapertussis* is not unusual. Disease attributable to *Bordetella* species other than *B. pertussis* is not reportable to CDC.

## II. Background

In the pre-vaccine era, pertussis was a common childhood disease and a major cause of child and infant mortality in the United States. Routine childhood vaccination led to a reduction in disease incidence from an average of 150 reported cases per 100,000 persons between 1922 and 1940, to 0.5 per 100,000 in 1976.[2] The incidence of reported pertussis began increasing in the 1980s. In 2009, the incidence of reported pertussis was 5.54 per 100,000 persons (CDC, unpublished data). While the reasons for this increase are not fully understood, multiple factors have likely contributed to the increase including waning immunity from childhood pertussis vaccines, increased recognition of the disease, and better diagnostic testing and increased reporting. The incidence of pertussis remains highest among young infants.[3,4] In 2009, most (12 of 14) pertussis-related deaths reported to CDC were among infants aged younger than 6 months, who were too young to have received three doses of DTaP vaccine (CDC, unpublished data). As of 2009, the second highest incidence of pertussis is observed among school-aged children and adolescents, and the proportion of cases in this age group appears to be increasing.

## III. Importance of Rapid Case Identification

Early diagnosis and treatment might limit disease spread. When pertussis is strongly suspected, attempts to identify and provide prophylaxis to close contacts should proceed without waiting for laboratory confirmation. When suspicion of pertussis is low, the investigation can be delayed until there is laboratory confirmation of the diagnosis. However, prophylaxis of infants and their household contacts should not be delayed because pertussis can be severe and life-threatening to young infants.

## IV. Importance of Surveillance

Surveillance data collected through case investigations are used to assess burden of disease and monitor changes in epidemiology over time. Surveillance data are also used to guide policy and development of control strategies. CDC uses surveillance data to monitor national

trends in disease and identify populations at risk. Local and state health departments use surveillance data to identify clusters of related cases that might indicate an outbreak.

Surveillance data have also been used to guide vaccination policy development. Data collected through an enhanced surveillance program suggested that infants often acquire pertussis from close contacts and supported recommendations for vaccination of postpartum mothers and adult and adolescent contacts of infants.[5–7]

Laboratory surveillance to monitor changes in the *B. pertussis* organism is also important. See Section VII, "Laboratory Testing" for more details.

## V. Disease Reduction Goals

A disease reduction goal of 2,500 indigenous pertussis cases per year in children younger than 1 year of age was proposed as a part of the Healthy People 2020 project.[8] In 2009, 3,206 cases were reported in this group (CDC, unpublished data).

## VI. Case Definitions

The following case definition for pertussis was approved by the Council of State and Territorial Epidemiologists (CSTE) in June 1997.[9]

### *Clinical case definition*

A cough illness lasting at least 2 weeks with one of the following: paroxysms of coughing, inspiratory "whoop," or posttussive vomiting; and without other apparent cause (as reported by a healthcare professional).

### *Laboratory criteria for diagnosis*

- Isolation of *B. pertussis* from a clinical specimen
- Positive polymerase chain reaction (PCR) assay for *B. pertussis* DNA

### *Case classification*

**Probable:** Meets the clinical case definition, is not laboratory confirmed, and is not epidemiologically linked to a laboratory-confirmed case.

**Confirmed:**

- A case of acute cough illness of any duration with a positive culture for *B. pertussis*; *OR*
- A case that meets the clinical case definition and is confirmed by PCR; *OR*
- A case that meets the clinical definition and is epidemiologically linked directly to a case confirmed by either culture or PCR

**Comment:** The clinical case definition was designed to increase sensitivity for detecting pertussis cases when confirmatory laboratory testing was not done or was negative. Laboratory tests can be negative even when the patient has pertussis. The clinical case definition is appropriate for endemic or sporadic cases. In outbreak settings, including household exposures, a clinical case can be defined as an acute cough illness lasting 2 weeks or longer without other symptoms. A case definition of cough illness lasting 14 days or longer has demonstrated 84% sensitivity and 63% specificity for detecting culture-positive pertussis in outbreak settings.[10] It is important to note that the outbreak case definition should be used for the epidemiologic investigation and not for reporting purposes.

Collection of epidemiologic and clinical data is essential for reporting cases that meet the clinical case definition. Investigators should make every attempt to collect information on paroxysms of cough, whoop, posttussive vomiting, and duration of cough as these variables are required to determine whether an individual meets the clinical case definition for pertussis. When feasible, case investigations initiated shortly after cough onset should include follow-up calls to collect information on cough duration. Follow-up should be done regardless of confirmatory test results so that cases meeting the clinical case definition can be reported. Both probable and confirmed pertussis cases should be reported to the National Notifiable Diseases

Surveillance System (NNDSS) by the state health department via the National Electronic Telecommunications System for Surveillance (NETSS) or National Electronic Disease Surveillance System (NEDSS).

Laboratory confirmation of pertussis is important because other pathogens can cause symptoms similar to pertussis. Culture of *B. pertussis* is the most specific diagnostic test; all patients with cough and a positive *B. pertussis* culture should be reported as confirmed, even those with cough lasting less than 14 days. PCR is less specific than culture; cases confirmed with only a positive PCR must meet the clinical case definition to be reported as confirmed. To confirm a case by epidemiologic linkage, the case must be directly linked (i.e., a first-generation contact) to a laboratory-confirmed case by either culture or PCR.[9]

## VII. Laboratory Testing

Determining who has pertussis and who does not is often difficult. Whenever possible, a nasopharyngeal swab or aspirate should be obtained from all persons with suspected cases. A properly obtained nasopharyngeal swab or aspirate is essential for optimal results. Health department personnel who are asked to obtain these specimens should receive training and supervision from persons experienced in collection of nasopharyngeal specimens. CDC has developed two short training videos for collection of nasopharyngeal aspirate and swab specimens, which can be accessed on the CDC pertussis website: http://www.cdc.gov/pertussis/clinical/diagnostic-testing/specimen-collection.html.

### *Culture*

Isolation of *B. pertussis* by bacterial culture is the standard pertussis diagnostic laboratory test. A positive culture for *B. pertussis* confirms the diagnosis of pertussis. Culture of the organism is also necessary for antimicrobial susceptibility testing and molecular typing.

Although bacterial culture is specific for diagnosis, it is relatively insensitive. Fastidious growth requirements make *B. pertussis* difficult to isolate. Isolation of the organism using direct plating is most successful during the catarrhal stage (i.e., first 1–2 weeks of cough). Success in isolating the organism declines if the patient has received prior antibiotic therapy effective against *B. pertussis*, if specimen collection has been delayed beyond the first 2 weeks of illness, and if the patient has been vaccinated.

All persons with suspected cases of pertussis should have a nasopharyngeal aspirate or swab obtained from the posterior nasopharynx for culture. For *B. pertussis*, nasopharyngeal aspirates will yield similar or higher rates of recovery than nasopharyngeal swabs;[11–14] throat and anterior nasal swabs yield unacceptably low rates of recovery.[15] Therefore, specimens should be obtained from the posterior nasopharynx (Figure 1), not the throat. Specimens should be obtained using polyester, rayon, nylon, or calcium alginate (not cotton) swabs and should be plated directly onto selective culture medium or placed in transport medium. Regan-Lowe agar or freshly prepared Bordet-Gengou medium is generally used for culture; half-strength Regan-Lowe should be used as the transport medium.

### *Polymerase chain reaction for B. pertussis DNA*

Polymerase Chain Reaction (PCR) is an important tool for timely diagnosis of pertussis and is increasingly available to clinicians. PCR is a molecular technique used to detect DNA sequences of the *Bordetella pertussis* bacterium, and unlike culture, does not require viable (live) bacteria present in the specimen.[16, 17]

Despite these advantages, PCR can give results that are falsely-negative or falsely-positive. PCR results can be optimized by avoiding some of the more common pitfalls leading to inaccurate results. Although early signs and symptoms of pertussis are often non-specific, only patients with signs and symptoms consistent with pertussis should be tested. Asymptomatic close contacts of confirmed cases should not be tested and testing of contacts should not be used for post-exposure prophylaxis decisions. Falsely-positive results may also occur as a result of specimen contamination, which can occur during specimen collection and testing. The

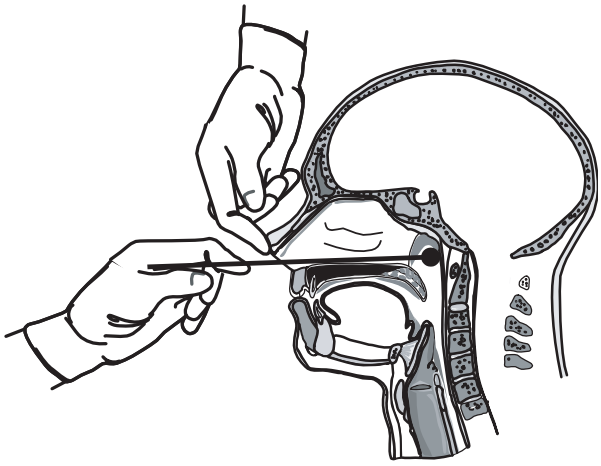
timing of PCR testing for pertussis can significantly affect its ability to accurately diagnose the disease. PCR has optimal sensitivity during the first 3 weeks of cough when bacterial DNA is still present in the nasopharynx. After the fourth week of cough, the amount of bacterial DNA rapidly diminishes which increases the risk of obtaining falsely-negative results.

Since its inclusion in the case definition in 1997, the proportion of cases confirmed by PCR has increased substantially, and many laboratories now use only PCR to confirm pertussis. However, as of March 2011, there are no standardized PCR assays for pertussis, and assay procedures, as well as sensitivity and specificity can vary greatly between laboratories. Thus, interpretation criteria for diagnosis vary. Interpretation of PCR results, especially those with high cycle threshold (Ct) values should be done in conjunction with an evaluation of signs and symptoms and available epidemiological information. For more information about interpretation of PCR Ct values, see Best Practices for Health Care Professionals on the use of Polymerase Chain Reaction (PCR) for Diagnosing Pertussis, which is located on the CDC Pertussis Website (http://www.cdc.gov/pertussis/clinical/diagnostic-testing/diagnosis-pcr-bestpractices.html).[18]

While PCR is increasingly used as the sole diagnostic test for pertussis, CDC recommends that PCR be used alongside culture, rather than as an alternative test. Even when a laboratory has validated its PCR method, culturing for *B. pertussis* should continue; this is especially important when an outbreak is suspected. State laboratories should retain the capability to culture pertussis.

Collection methods for PCR are similar to those for culture, and often the same sample can be used for both tests. **However, calcium alginate swabs cannot be used to collect nasopharyngeal specimens for PCR.**

**Figure 1: Proper technique for obtaining a nasopharyngeal specimen for isolation of *Bordetella pertussis***



## Serologic testing

Serologic testing can be a useful tool for diagnosis of pertussis. However, standardized tests are not available making the results of commercially available tests sometimes difficult to interpret. As of March 2011, positive serology results from a private laboratory are not confirmatory for the purpose of reporting. A single-point serologic assay has been validated at the Massachusetts state public health laboratory for persons aged 11 years or older and is used for clinical diagnosis and reporting in that state only.[19] A serologic test performed at CDC or at the Massachusetts state laboratory might be used to help investigate outbreaks. In states other than Massachusetts, cases meeting the clinical case definition that are serologically positive but not culture or PCR positive should be reported as probable cases.

### Direct fluorescent antibody testing

Direct fluorescent antibody (DFA) testing of nasopharyngeal secretions is sometimes used to screen for pertussis. While DFA testing can provide rapid results to providers treating ill infants, these results are not confirmatory because the tests are of variable specificity.[13] Since it is not a confirmatory test, DFA should be used alongside culture or PCR. Cases meeting the clinical case definition that are DFA positive but not culture or PCR positive should be reported as probable cases.

### Pulsed-field gel electrophoresis

Pulsed-field gel electrophoresis (PFGE), a type of DNA fingerprinting, can be performed on *B. pertussis* isolates to help track transmission (e.g., strains from the same household or small community), but it is not done for routine surveillance.[20,21]

Inquiries regarding PFGE molecular typing, erythromycin susceptibility testing, serologic testing and other *B. pertussis* laboratory questions should be directed to the CDC Epidemic Investigations Laboratory: Dr. M. Lucia Tondella, at 404-639-1239, or Ms. Pam Cassiday at 404-639-1231. When sending *B. pertussis* samples to CDC, please make appropriate arrangements with the laboratory before shipping samples to the address below:

Centers for Disease Control and Prevention
1600 Clifton Road, NE
DASH Unit 12
Atlanta, GA 30333

Additional information on use of the laboratory for support of vaccine-preventable disease surveillance is available in Chapter 22, "Laboratory Support for Surveillance of Vaccine-Preventable Diseases."

## VIII. Reporting

Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[22] These regulations and laws list the diseases to be reported and describe those persons or institutions responsible for reporting, including healthcare providers, hospitals, laboratories, schools, daycare and childcare facilities, and other institutions. Persons reporting should contact the state health department for state-specific reporting requirements.

### Reporting to CDC

State health departments should report all probable and confirmed pertussis cases to NNDSS via the NETSS or NEDSS. When provisional information is reported to NNDSS, NETSS and NEDSS reports can be updated as additional information is collected. NETSS and NEDSS accept information about clinical symptoms, laboratory confirmation and vaccination history; this information is included in the Pertussis Surveillance Worksheet (Appendix 11) available for reference and use in case investigation.

### Information to collect

Case investigation should include collection of the epidemiologic information listed below. State health departments often supplement this list with additional information relevant to cases in their communities.

- Demographic
  - Name
  - State of residence
  - Date of birth
  - Age
  - Sex
  - Ethnicity
  - Race

- Reporting Source
  - County
  - Earliest date reported
- Clinical
  - Hospitalization and duration of stay
  - Cough, date of cough onset and duration
  - Symptoms: paroxysms, whoop, posttussive vomiting, apnea
  - Complications: pneumonia (x-ray results), seizures, encephalopathy
  - Outcome (patient survived or died) and date of death
- Treatment
  - Antibiotics used
  - Date started and duration of therapy
- Laboratory
  - Culture
  - PCR
  - Serology for antibody to pertussis antigens
- Vaccination with pertussis-containing vaccine
  - Dates of vaccination
  - Type (formulation) of vaccines and manufacturers' names
  - Doses of pertussis-containing vaccine prior to illness onset
  - If not vaccinated with at least three doses of DTaP or DTP, reason
- Epidemiologic
  - Date case investigation initiated
  - Epidemiologic linkage to a laboratory-confirmed case
  - Association with an outbreak
  - Transmission setting
  - Setting outside household of further documented spread

### *Comments on reporting*

The limitations of laboratory diagnostics make the clinical case definition essential to pertussis surveillance. It is important to determine duration of cough—specifically whether it lasts 14 days or longer—in order to determine if a person's illness meets the definition of a clinical case. If the first interview is conducted within 14 days of cough onset and cough is still present at the time of interview, it is important to follow up at 14 days or later after onset.

Accurate assessment of pertussis symptoms can be challenging. The following symptom definitions and variable explanations are appropriate for pertussis case investigations.

**Paroxysmal or spasmodic cough.** Sudden uncontrollable "fits" or spells of coughing where one cough follows the next without a break for breath.

**Whoop.** High-pitched noise heard when breathing in after a coughing spasm.

**Apnea.** Transient cessation of respiration which might occur spontaneously or after a coughing spasm. Apnea is generally associated with cyanosis or syncope (passing out) and might be accompanied by slowing of the heartbeat (bradycardia). Apnea is a common pertussis symptom in infants and might be the only presenting sign of pertussis in young infants with no cough; apnea is rarely associated with pertussis in older children and adults.

**Cyanosis.** Paleness or blueness of the skin, most noticeable on the lips and tongue, occurring after coughing paroxysms and apnea.

**Posttussive vomiting.** Vomiting following paroxysms of cough.

**Cold-like symptoms.** Coryza (runny nose) and/or conjunctival infection (redness of the eyes).

**Positive chest x-ray for pneumonia.** Evidence of acute pneumonia on chest x-ray.

**Acute encephalopathy.** Acute illness of the brain manifested by a decreased level of consciousness (excluding transient drowsiness after a seizure) occurring with or without seizures. Patients are almost always hospitalized and most undergo extensive diagnostic evaluations.

## IX. Vaccination

Currently, the pertussis vaccines available in the United States are acellular pertussis antigens in combination with diphtheria and tetanus toxoids (DTaP, DTaP- combination vaccines, and Tdap).

The Advisory Committee on Immunization Practices (ACIP) recommends a four-dose primary series of DTaP, administered at 2, 4, 6 and 15–18 months of age, followed by a fifth booster dose given at 4–6 years.22 In 2005 and 2006, the ACIP recommended the replacement of a single Td booster with a dose of Tdap for adolescents (ages 11–18) and adults (ages 19–64)6, 23 who have not previously received Tdap.

On October 27, 2010, ACIP expanded Tdap recommendations to include both under-vaccinated children and senior adults. The new recommendations state that children aged 7-10 years who are not up-to-date with their childhood pertussis vaccinations should receive a single dose of Tdap. Additionally, Tdap is recommended for adults aged 65 years and older who anticipate close contact with an infant and who have not previously received the vaccine. ACIP further recommended that Tdap be administered regardless of time since last tetanus and diphtheria-containing booster.[24] On February 23, 2011, ACIP recommended that all healthcare personnel who have not yet received a dose of Tdap, regardless of age, should be vaccinated.

**Table 1** lists vaccines likely to appear in case-patients' vaccination histories. Immunization Information Systems , provider records, and parents are the best sources of this information.

**Table 1. Persussis-containing vaccines**

| Pertussis-Containing Vaccines for Children | Brand | Licensed Date and Used For |
|---|---|---|
| DTaP | INFANRIX® DAPTACEL® Tripedia® | First licensed in 1991; used for all childhood doses |
| DTaP+Hib | TriHiBit® | Used for the fourth dose only |
| DTap+IPV+HepB | PEDIARIX® | Used for the first three doses |
| DTap+IPV+Hib | PENTACEL™ | Approved in 2008; used for primary four-dose series |
| DTap+IPV | KINRIX™ | Approved in 2008; used for booster dose at 4–6 years |
| **Pertussis-Containing Vaccines for Adolescents and Adults** | **Brand** | **Licensed Date** |
| Tdap | ADACEL® BOOSTRIX® | First available in 2005 |
| **Other Vaccines** | **Brand** | **Licensed Date** |
| Pertussis Only | | Not available in the U.S. |
| DT/Td | DECAVAC™ TENIVAC™ | Do not contain pertussis; DT used for primary series when pertussis vaccination is contraindicated; Td used in persons aged ≥7 years |

## X. Enhancing Surveillance

A number of surveillance activities can improve detection and reporting of cases as well as the completeness and accuracy of the information reported. In addition to those outlined below, Chapter 19, "Enhancing Surveillance," lists activities that might be applicable to pertussis surveillance.

### *Assuring appropriate diagnostic testing for pertussis is being performed regularly*

Unlike many other vaccine-preventable diseases of childhood, pertussis remains endemic in the United States. Cases are expected to occur in all communities; a period of several years in which no cases are reported from a jurisdiction likely reflects failures to diagnose and/or report disease rather than an absence of disease. The level of diagnostic testing being undertaken can be evaluated by reviewing the number of pertussis diagnostic tests (e.g., cultures or PCR results) submitted by a jurisdiction.

### *Monitoring surveillance indicators*

Regular monitoring of surveillance indicators might identify specific areas of the surveillance and reporting system that need improvement. Some suggested surveillance indicators to monitor include:

- The proportion of probable cases that did not meet the clinical case definition because the cough duration was less than 14 days and the patient was coughing at follow-up. These are cases for which later follow-up calls can improve case status classification.
- The proportion of probable and confirmed cases with complete information on vaccination history (dates, vaccine types and manufacturers). Now that pertussis vaccination is available for adolescents and adults, many states will for the first time be collecting vaccination histories for adolescents and adults. Some electronic reporting systems will require coding changes to allow this information to be entered.
- Median interval between onset of cough and notification of state or local public health authorities in probable and confirmed cases.

## XI. Case Investigation

Case investigations generally include reviews of laboratory, hospital, clinic records, and immunization registries, which are the best sources for information about diagnoses and immunization histories. Investigations also include interviews of case-patients, which are necessary to identify sources of infections and contacts at risk. Investigations can include treatment of case-patients and chemoprophylaxis and or vaccination of contacts.

### *Treatment and chemoprophylaxis*

Antimicrobial treatment does not generally lessen the severity of disease unless it is begun in the catarrhal phase, prior to paroxysmal coughing.[25] Treatment reduces transmission and is essential for disease control. The spread of pertussis can be limited by decreasing the infectivity of the patient and by protecting close contacts.[26] Persons with pertussis are infectious from the beginning of the catarrhal stage through the third week after the onset of paroxysms or until 5 days after the start of effective antimicrobial treatment. The recommended antimicrobial agents and doses are the same for treatment and chemoprophylaxis.[27]

Three macrolides are recommended by CDC for treatment of pertussis. Azithromycin is most popular because it is given in a short, simple regimen of one dose each day for 5 days. It is the preferred antimicrobial for use in infants younger than 1 month of age. Similarly, the regimen of two doses a day for 7 days makes clarithromycin another well-accepted choice. Erythromycin, which is given as four doses each day for 14 days, continues to be used, but adherence to the regimen and completion of the course are generally lower than for the other macrolides, and adverse effects (gastrointestinal distress, pyloric stenosis, etc.) occur more frequently. Resistance of *B. pertussis* to macrolides is rare, and antimicrobial susceptibility testing is not routinely recommended. Testing is appropriate in some circumstances and is recommended when treatment failure is suspected. Refer to Section VII, "Laboratory Testing" for information on how to contact the CDC Pertussis Laboratory to discuss susceptibility testing. If resistance to macrolides is suspected or if their use is contraindicated, CDC recommends treatment with trimethoprim–sulfamethoxazole (TMP-SMZ) in a regimen of two doses a day for 14 days. TMP-SMZ should not be used to treat infants younger than 2 months of age.[27]

CDC recommends administration of chemoprophylaxis to all close contacts and all household members of a pertussis case-patient, regardless of age and vaccination status; this might prevent

or minimize transmission. A close contact is anyone who had face-to-face contact or shared a confined space for a prolonged period of time with an infected person or had direct contact with respiratory secretions from a symptomatic person. Contact with respiratory secretions can occur in many ways, including through an explosive cough or sneeze in the face, sharing food or eating utensils, mouth-to-mouth resuscitation, and conducting a medical exam which includes nose and throat examination.[27]

Limited available data suggests *Bordetella parapertussis* is less susceptible to antibiotics than pertussis; erythromycin, azithryomycin, clarithromycin, TMP-SMZ, and ciprofloxacin may have activity against *B. parapertussis*.[27-35] No clinical studies have evaluated the effectiveness of these antibiotics for treatment or chemoprophylaxis; however, prophylaxis of infant contacts of persons with *B. parapertussis* infection should be considered, and infants with *B. parapertussis* should be treated.

### Vaccination

Close contacts younger than 7 years of age who have not received four doses of a pertussis vaccine should complete the series using the minimum recommended intervals between doses (minimum age for first dose is 6 weeks; minimum intervals from dose 1 to dose 2, and from dose 2 to dose 3 are 4 weeks; minimum interval from dose 3 to dose 4 is 6 months). Vaccination with a fifth dose of DTaP is recommended for close contacts aged 4–6 years who have only received four doses. Close contacts can be vaccinated with Tdap in accordance with ACIP recommendations. Vaccination is not a substitute for chemoprophylaxis and might not prevent illness in a person who has already been infected with *B. pertussis*.[23,24,36]

## XII. Outbreak Control

Pertussis outbreaks can be difficult to identify and manage. Other respiratory pathogens often cause clinical symptoms similar to pertussis, and co-circulation with other pathogens does occur. To respond appropriately (e.g., provide appropriate prophylaxis), it is important to confirm that *B. pertussis* is circulating in the outbreak setting and to determine whether other pathogens are contributing to the outbreak. PCR tests vary in specificity, so obtaining culture confirmation of pertussis for at least one suspected case is recommended any time there is suspicion of a pertussis outbreak.

If cases are occurring among young infants, consideration can be given to vaccinating infants at an accelerated schedule. The first dose of DTaP can be given as early as 6 weeks of age, with a minimum interval of 4 weeks between each of the first three doses. Adults in close contact with infants should be vaccinated with Tdap, particularly during an outbreak. The ACIP recommends vaccination of postpartum mothers who have not previously received Tdap.[6]

Institutional outbreaks of pertussis are common. Outbreaks at elementary, middle and high schools can occur as protection from childhood vaccines wanes.[23] In school outbreaks, prophylaxis is recommended for close classroom and sports team contacts.

Pertussis outbreaks in hospitals and other clinical settings can put infants and other patients at risk. Health-care facilities should maximize efforts to prevent transmission of *B. pertussis*. Respiratory precautions should be taken to prevent unprotected exposure to pertussis. Data on the need for postexposure antimicrobial prophylaxis in Tdap-vaccinated healthcare personnel (HCP) are inconclusive. Some vaccinated HCP are still at risk for *B. pertussis*. Tdap may not preclude the need for postexposure antimicrobial prophylaxis. Postexposure antimicrobial prophylaxis is recommend for all HCP who have unprotected exposure to pertussis and are likely to expose a patient at risk for severe pertussis (e.g., hospitalized neonates and pregnant women). Other HCP should either receive postexposure antimicrobial prophylaxis or be monitored daily for 21 days after pertussis exposure and treated at the onset of signs and symptoms of pertussis.

The efficacy of Tdap vaccination in controlling school or institutional outbreaks has not been evaluated; those who have not previously received Tdap can be vaccinated in accordance with the ACIP guidelines for Tdap use in outbreaks and settings of increased risk.[23,37]

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# Chapter 11: Pneumococcal Disease

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## I. Disease Description

*Streptococcus pneumoniae* (pneumococcus) is a gram-positive bacteria bacterium with more than 90 known serotypes. Pneumococcus is spread by airborne droplets and is a leading cause of serious illness, including bacteremia, meningitis, and pneumonia among children and adults worldwide.[1, 2] Although all serotypes may cause serious disease, a relatively limited number of serotypes cause the majority of invasive pneumococcal disease (IPD).

The Centers for Disease Control and Prevention's (CDC) Active Bacterial Core Surveillance (ABCs) has tracked IPD in selected regions of the United States since 1994. ABCs data indicate that individuals aged <2 years and ≥65 years have the highest rates of invasive disease (Table 1).[2, 3] Approximately 10% of all patients with invasive pneumococcal disease die of their illness, but case-fatality rates are higher for the elderly and patients with certain underlying illnesses.[3, 4]

Each year in the United States, pneumococcal disease accounts for a substantial number of cases of invasive and non-invasive disease including meningitis, bacteremia, pneumonia, and acute otitis media (AOM).[3–8] A recent analysis estimated that pneumococcal disease was responsible for 4 million illness episodes, 445,000 hospitalizations and 22,000 deaths annually.[9] Pneumococcal disease is preceded by asymptomatic colonization of the nasopharynx which tends to be especially common in children.[10] Acute otitis media (AOM) is the most common clinical manifestation of pneumococcal infection among children and the most common outpatient diagnosis resulting in antibiotic prescriptions in that group.[11]

**Table 1: Incidence of pneumococcal infections in the United States**

| Type of bacterial infection | # cases / year |
|---|---|
| Meningitis* | 2,000 |
| Bloodstream infection† | 8,000 |
| Pneumonia (hospitalized)§ | 106,000–175,000 |
| Acute otitis media in children <5 yrs¶ | 3,100,000 |

* S. pneumoniae *isolated from cerebrospinal fluid or clinical diagnosis of meningitis with pneumococcus isolated from another sterile site*[2]

† *Bacteremia without focus*[2]

§ *Estimates before introduction of pneumococcal conjugate vaccine for children in 2000.*[12]

¶ *The number of doctor visits per year for acute otitis media in children younger than 5 years is estimated to be 14,106,159.*[8] *Approximately 30% of these visits probably represent otitis media with effusion and do not require antibiotics.*[9] *Recent data from etiologic studies of otitis media in two different areas of the United States suggest that approximately 31% of acute otitis media episodes are caused by* S. pneumoniae.[10, 11] *[14.1 million x 70% x 31% = 3.1 million]*

## II. Background

### *Pneumococcal vaccines*

Two different types of pneumococcal vaccines, polysaccharide and conjugate vaccines, are employed in the prevention of pneumococcal disease. Polysaccharide vaccines contain capsular pneumococcal polysaccharide antigens, while conjugate vaccines contain an immunogenic nonpneumococcal protein conjugated to individual pneumococcal polysaccharides.

A pneumococcal polysaccharide vaccine (PPV) targeting 23 of the most common serotypes of *S. pneumoniae* has been available since 1983. The Advisory Committee on Immunization Practices (ACIP) recommends that it be administered to persons ≥2 years of age who have any of several underlying medical conditions and to all persons >65 years of age.[5, 12]

In February 2000, a 7-valent pneumococcal conjugate vaccine (PCV7) was licensed by the Food and Drug Administration (FDA) for use among infants and young children. In pre-licensure randomized trials, PCV7 was demonstrated to be safe and highly efficacious

against invasive pneumococcal disease (IPD), moderately efficacious against pneumonia, and somewhat effective in reducing otitis media episodes and related office visits.[13–15] On the basis of the results of these clinical trials, in 2000, ACIP recommended routine use of PCV7 for all children aged 2–23 months and for children aged 24–59 months who are at increased risk for pneumococcal disease (e.g., children with anatomic or functional asplenia, sickle cell disease (SCD), HIV infection or other immunocompromising condition, or chronic illness including chronic heart or lung disease, cerebrospinal fluid leaks, and diabetes mellitus).[11] In 2007, the ACIP revised its recommendation for routine use to include all children aged 2–59 months.[16]

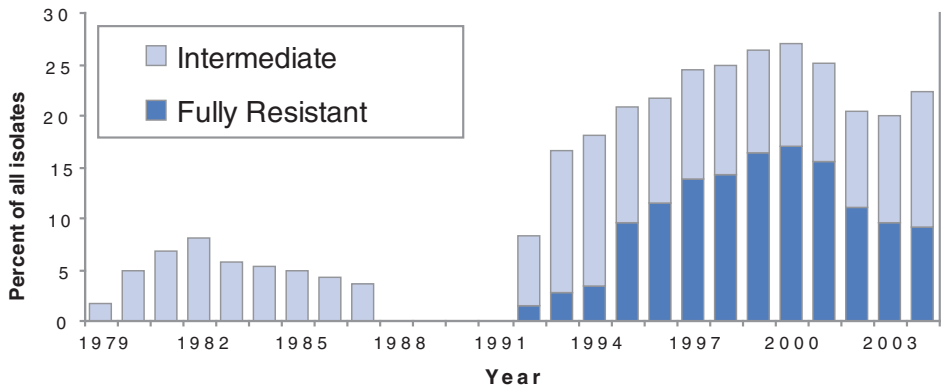
In February, 2010, a new 13-valent pneumococcal conjugate vaccine (PCV13) was approved by the FDA and has now replaced PCV7.[17] PCV13 is formulated and manufactured using the same processes as PCV7 and was licensed by FDA on the basis of studies demonstrating safety and ability comparable to that of PCV7 to elicit antibodies protective against IPD. PCV13 is made by the same manufacturer as PCV7 and contains the seven serotypes included in PCV7 (4, 6B, 9V, 14, 18C, 19F and 23F) as well as six additional serotypes (1, 3, 5, 6A, 7F and 19A). PCV13 is approved for prevention of IPD among infants and young children caused by the 13 serotypes in the vaccine. It is also approved for the prevention of otitis media caused by the seven serotypes covered by PCV7; however, no efficacy data for prevention of otitis media are available for the six additional serotypes.

### *Trends in invasive pneumococcal disease*

Following the introduction of PCV7 in 2000, dramatic declines in invasive pneumococcal disease were reported among children aged <5 years as early as 2001. Before introduction of PCV7, rates of PC7-type invasive pneumococcal disease among children in this age were around 80 cases per 100,000 population. After the introduction of PCV7, rates of disease due to these 7 serotypes dropped dramatically to less than 1 case per 100,000 by 2007 (Figure 1).

The use of PCV7 also reduced the burden of invasive pneumococcal disease among older children and adults through reduced transmission of vaccine serotype pneumococci (herd protection). Declines in the incidence of PCV7-type invasive disease among adults were observed as early as 2001 and have continued since that time, reducing the incidence to 64–77% below the 1998–1999 baselines, depending on age.[18–20] Increases in disease caused by serotypes not included in PCV7 (i.e., replacement disease) are evident in children and certain adult populations with underlying illnesses but are small in magnitude compared with the overall reduction in disease.[21, 22] With the introduction of PCV13, it is anticipated that cases of invasive disease due to the 6 additional serotypes covered by the vaccine will decrease.

**Figure 1. Penicillin resistance in *Streptococcus pneumoniae*, United States, 1979–2004**




*1979–1994: CDC Sentinel Surveillance System*
*1995–2004: CDC Active Bacterial Core Surveillance (ABCs) System, Emerging Infections Program*[28]

### *Antimicrobial resistance trends*

Before 1990, *S. pneumoniae* was almost uniformly susceptible to penicillin, allowing most physicians to treat persons with severe infections with penicillin alone. However, during the 1990's, resistance to penicillin and to multiple classes of antimicrobial agents spread rapidly in the United States with an increasing trend of invasive pneumococci resistant to 3 or more drug classes.[23–26]

Following the introduction of PCV7 into the routine childhood immunization program in 2000, the incidence of antibiotic-resistant invasive disease declined substantially among both young children and older persons.[20, 27–31] Between 1998–99 and 2008, penicillin-nonsusceptible IPD rates declined 64% for children aged <5 years and 45% for adults aged ≥65 years.[31] An increase in penicillin-nonsusceptible disease caused by serotypes not included in PCV7 was also identified during the same time period, although the magnitude of this effect remains small.[27] The prevalence of resistance varied by geographic area both before and after PCV7 introduction, with higher prevalence noted for the southeastern U.S.[23, 27] During 2007–08, serotypes unique to PCV13 (i.e., serotypes contained in PCV13 but not PCV7) caused 78–97% of penicillin-nonsusceptible IPD, depending on age.[31] With the introduction of PCV13 in 2010, further reductions in antibiotic-nonsusceptible IPD rates are anticipated.

In 2008, the Clinical and Laboratory Standards Institute (CLSI) established new, higher minimum inhibitory concentration (MIC) breakpoints for defining pneumococcal susceptibility to parenterally administered penicillin when treating non-meningitic pneumococcal disease.[32] Regardless of whether the old or new parenteral penicillin breakpoints are used, penicillin-nonsusceptible IPD caused by PCV7 serotypes has decreased significantly for all age groups and has almost disappeared except among adults aged ≥65 years. Under the new parenteral breakpoints, rates of penicillin-nonsusceptible IPD remain markedly below the rates that existed before PCV7 introduction for all age groups except adults aged 50–64 years.[31]

The emergence of drug resistant *S. pneumoniae* (DRSP) has made treatment of pneumococcal disease more difficult. Because of a lack of rapid, sensitive, and specific diagnostic tests, therapy for pneumonia and milder illnesses such as otitis media remains empiric. Groups of experts have provided national guidance for treating infections commonly caused by pneumococcus, such as otitis media and pneumonia, because of the increasing prevalence of DRSP.[33–36] Few communities exist in which resistance remains uncommon and even in these communities, resistant infections can occur. For these reasons, clinicians and public health officials should follow national guidelines rather than attempt to create local treatment recommendations based on local resistance data. Due to the limitations of current diagnostic testing, clinicians often prescribe empiric antibacterial therapy that is not indicated or is unnecessarily broad. Inappropriate antimicrobial use contributes to the development of DRSP. Principles have been developed to encourage appropriate use of antimicrobial agents for adults and children with upper respiratory infections.[6, 37–40]

## III. Importance of Surveillance

Surveillance for invasive pneumococcal disease has four main goals:

- Characterization of national and local trends
- Detection of geographic and temporal changes in the prevalence of DRSP
- Monitoring impact of vaccines on disease
- Informing future vaccine development

With the recent introduction of PCV13, surveillance for invasive pneumococcal disease among children aged <5 years is particularly important for identifying populations that may not be receiving vaccination and for monitoring the incidence of disease caused by non-vaccine serotypes (i.e., replacement disease). Surveillance for invasive pneumococcal disease in persons ≥5 years is useful to monitor the impact of PPV vaccination, the indirect effects of PCV13, and replacement disease.

Serotyping of pneumococcal isolates can improve understanding of vaccine effects. However, serotyping is expensive and requires specialized reagents and extensive technical training; therefore, serotyping capacity is not widely available. The use of polymerase chain reaction (PCR) to identify pneumococcal capsular genes specific for individual capsular serotypes may be feasible for some state public health and academic research centers.[41, 42]

Pneumococcal surveillance enables recognition of new or rare resistance patterns. Surveillance information can be used on the national level for research and policy development and at the state or local level to raise awareness of DRSP among clinicians and the general public. Surveillance data also may be useful for tracking the impact of interventions aimed at reducing unnecessary use of antimicrobial agents.

## IV. Disease Reduction Goals

Healthy People 2010 included targeted goals for reduction in invasive pneumococcal disease among children and adults as well as reduction in penicillin-resistant pneumococcal disease among children. Since the introduction of PCV7 into the childhood immunization schedule in 2000, a significant decrease in invasive pneumococcal disease among infants, children and adults has been observed.[20, 43] Among children aged <5 years, the incidence of invasive pneumococcal disease decreased by 74% between 1997 and 2008, from 77 to 22 new cases per 100,000 population, exceeding the 2010 target of 46 cases per 100,000.[44] Among adults aged ≥65 years, the incidence of invasive pneumococcal disease decreased by 34% between 1997 and 2008, from 62 to 41 new cases per 100,000 population, exceeding the 2010 target of 42 per 100,000. The incidence of penicillin-resistant pneumococcal infections among young children aged <5 years declined by 56% between 1997 and 2008, from 16 to 7 new cases per 100,000 moving toward the target of 6 cases per 100,000.[44]

Healthy People 2020 includes additional targets for reducing invasive pneumococcal disease in the coming years.[45] Target reduction goals for children aged <5 years and adults aged ≥65 years are 12 and 31 IPD cases per 100,000 respectively. In addition, Healthy People 2020 includes a target goal to decrease penicillin-resistant pneumococcal infections among children aged <5 years and adults aged ≥65 years to 3 and 2 cases per 100,000 respectively. Continuous surveillance is important to evaluate the impact of PCV13 on the incidence of invasive pneumococcal disease, antibiotic-resistant pneumococcal infections, and to monitor disease caused by pneumococcal serotypes not included in PCV13 (i.e., replacement disease).

Disease reduction goals also focus on minimizing complications of DRSP infections through prevention and control measures. Geographic differences in antibiotic prescribing practices have been described.[46] In sites where antibiotic prescribing is high, the proportion of nonsusceptible IPD is also high, suggesting that local prescribing practices may contribute to local resistance patterns.

In 1995, the CDC launched a national campaign to reduce antimicrobial resistance through promotion of appropriate antibiotic use. Initial efforts targeted the pediatric population and later expanded to adults. CDC surveys have shown that there is a perception among providers that patient expectations may encourage overuse of antibiotics. To overcome this, patient education resources were developed and are now available to aid in physician-patient communication (www.cdc.gov/getsmart). The program also works closely with a small number of state and local health departments to address appropriate antibiotic use in their communities. Formative research is currently underway to explore provider and patient knowledge and attitudes related to factors influencing antibiotic choices made by providers.

## V. Case Definition

Case definitions for drug resistant *S. pneumoniae* (DRSP) and invasive pneumococcal disease were originally approved by the Council of State and Territorial Epidemiologists (CSTE) in 1994 and 2000, respectively.[47, 48] They were modified in 2006 to prevent duplicate reporting of individual cases.[49] The definition was further modified in 2009 to include all invasive

pneumococcal disease, regardless of drug resistance or the case patient's age. Beginning in 2010, the following definitions are in use for national reporting in the U.S.[50]

**Confirmed:** Isolation of *S. pneumoniae* from a normally sterile site (e.g., blood, cerebrospinal fluid, or, less commonly, joint, pleural or pericardial fluid). (Event code 11723)

**Suspected:** The absence of the above criterion and either a medical record containing a diagnosis of invasive *Streptococcus pneumoniae* disease or death certificate listing invasive *S. pneumoniae* disease as the cause or a contributing cause of death.

Confirmed and suspected cases of invasive pneumococcal disease should be reported to public health authorities within one week of diagnosis. CSTE also recommends certain clinical and epidemiological information be collected, including date of illness onset, clinical syndrome (e.g., pneumonia, meningitis), underlying medical conditions, and pneumococcal vaccination history. DRSP is no longer collected in national surveillance as a separate event from invasive pneumococcal disease.[50]

## VI. Laboratory Testing

Definitive diagnosis of pneumococcal infection is confirmed by the recovery of *S. pneumoniae* from a normally sterile body site (e.g., blood, CSF, pleural fluid, or peritoneal fluid). Because pneumococci frequently colonize the upper respiratory tract in the absence of disease, the clinical significance of recovering the organism from nonsterile body sites (e.g., expectorated sputum, conjunctiva) is less certain. Gram stain may be helpful in interpreting cultures of expectorated sputum; finding a predominance of gram-positive diplococci and >25 leukocytes with <10 epithelial cells per high power field on microscopic examination supports the diagnosis of pneumococcal pneumonia, but does not satisfy the case definition for national surveillance for invasive pneumococcal disease. Also, detection of pneumococcal capsular antigen in urine is useful for the diagnosis of pneumococcal pneumonia in adults.

Based on recommendations from the Clinical and Laboratory Standards Institute (CLSI, formerly the National Committee for Clinical Laboratory Standards, or NCCLS), clinical laboratories should test all isolates of *S. pneumoniae* from CSF for resistance to penicillin and cefotaxime, ceftriaxone, or meropenem, and vancomycin.[51] Penicillin susceptibility breakpoints were recently changed for nonmeningitis isolates, resulting in somewhat lower proportions of nonmeningeal isolates characterized as nonsusceptible.[52] For organisms from other sources, laboratories should consider testing for resistance to erythromycin, penicillin, trimethoprim-sulfamethoxazole, clindamycin, cefotaxime, ceftriaxone, meropenem, tetracycline, vancomycin, and a fluoroquinolone such as levofloxacin. Pneumococci resistant to vancomycin or linezolid have never been described. For vancomycin, a strain is considered non-susceptible if it has a minimum inhibitory concentration of >1 µg/ml or zone diameter <17 mm. For linezolid, nonsusceptible strains are those with a minimum inhibitory concentration of >2 µg/ml or zone diameter <21 mm. Strains found to be nonsusceptible to vancomycin or linezolid should be submitted to a reference laboratory for confirmatory testing, and if resistant, reported to the state health department.[51] Because pneumococci are fastidious organisms, some susceptibility testing methods used for other organisms are not appropriate for pneumococci (see the CLSI document for testing recommendations).[51]

Currently licensed vaccines target a limited number of pneumococcal polysaccharide capsule serotypes. Identifying the serotypes of pneumococcal strains can be useful for evaluating outbreaks of pneumococcal disease such as those that occur in institutional settings. Serotyping is currently performed in only a limited number of state public health laboratories, academic centers, or at the Centers for Disease Control and Prevention. CDC's Streptococcal Reference Laboratory will conduct serotyping of pneumococcal isolates from blood, CSF or other sterile sites in outbreak settings. State public health laboratories might consider adopting a PCR-based technique for determining capsular serotypes.[41, 42] CDC's Streptococcal Reference Laboratory provides numerous references and protocols for interested state public health laboratories which can be accessed at: http://www.cdc.gov/ncidod/biotech/strep/PCR.htm.

## VII. Reporting

Each state and territory has regulations and laws governing the reporting of diseases and conditions of public health importance.[53] These regulations and laws list the diseases that are to be reported, and describe those persons or institutions responsible for reporting, such as health-care providers, hospitals, laboratories, schools, daycare and childcare facilities, and other institutions. Detailed information on reportable conditions in each state is available through the Council of State and Territorial Epidemiologists.[54]

### *Reporting to CDC*

Most states currently require invasive pneumococcal disease to be reported to local or state health authorities, regardless of the age of the case or drug resistance. Additional states require reporting in limited populations, such as children <5 years of age. Confirmed and suspected cases of IPD should be reported to state or local health departments by clinicians, laboratories, hospitals, and pharmacies. Cases should be identified through microbiology laboratories, death certificates, hospital discharge or outpatient records, and electronic medical records. The following data are recommended for case investigation and reporting: patient's date of birth or age, the anatomic site of specimen collection, and type of infection. Other epidemiological information that is useful includes patient's gender, race and ethnicity, specimen collection date, whether the patient was hospitalized, clinical syndrome, antibiotic susceptibility, details of pneumococcal vaccination history, underlying medical conditions, daycare attendance, and outcome. Additional information may be collected at the direction of the state health department. The *S. pneumoniae* Surveillance Worksheet is included as Appendix 13. Confirmed cases of IPD should be reported using event code 11723 in the National Electronic Telecommunications System for Surveillance (NETSS).[50]

## VIII. Vaccination

### *13-valent pneumococcal conjugate vaccine (PCV13)*

The Advisory Committee on Immunization Practices (ACIP) recommends that the 13-valent pneumococcal conjugate vaccine (PCV13) be used for all children aged <5 years.[55] For routine immunization of infants, PCV13 is recommended as a 4-dose series at age 2, 4, 6, and 12–15 months.[1] Infants and children who have received ≥1 dose of PCV7 should complete the immunization series with PCV13. A single supplemental dose of PCV13 is recommended for all children aged 14–59 months who have received 4 doses of PCV7 or another age-appropriate, complete PCV7 schedule. For children who have underlying medical conditions, a supplemental PCV13 dose is recommended through age 71 months. Children aged 2–18 years with underlying medical conditions should also receive PPSV23 after completing all recommended doses of PCV13.

In addition, a single dose of PCV13 may be administered to children aged 6–18 years who are at increased risk for IPD because of sickle cell disease, human immunodeficiency virus (HIV) infection or other immunocompromising condition, cochlear implant, or cerebrospinal fluid leaks, regardless of whether they have previously received PCV7 or PPSV23.[55] Routine use of PCV13 is not recommended for healthy children aged ≥5 years.

### *23-valent pneumococcal polysaccharide vaccine (PPV23)*

PPV23 is approximately 56%–75% efficacious for the prevention of invasive pneumococcal infection caused by vaccine serotypes.[56, 57] Children aged ≥2 years with underlying medical conditions should receive PPV at least 8 weeks after completing all recommended doses of PCV131. A dose of PPV should be administered to all persons aged 5–64 years at increased risk of serious pneumococcal infection because of underlying medical conditions and to all persons ≥65 years of age.5

A single revaccination after at least 3–5 years (3 years if <10 years of age, 5 years if 10 or more years of age) should be considered for persons aged ≥2 to 64 years who are at highest risk or likely to have rapid declines in antibody levels. This includes those with functional or anatomic asplenia, HIV infection, leukemia, lymphoma, Hodgkin's disease, multiple myeloma,

generalized malignancy, chronic renal failure, nephrotic syndrome or immunosuppression (e.g., organ transplants or receiving chemotherapy). Previously vaccinated persons should be revaccinated at 65 years of age or older, providing at least 5 years has passed since the first dose. Pneumococcal vaccine may be administered concurrently with influenza vaccine by separate injection in the opposite arm.

## IX. Enhancing Surveillance

Several surveillance activities may improve the detection and reporting of pneumococcal disease and the quality of the reports.

### *Establishing reporting of all invasive pneumococcal disease in young children*

CSTE has recommended reporting of all invasive pneumococcal disease in children aged <5 years to monitor the impact of the pneumococcal conjugate vaccine for this age group; to track progress toward Healthy People 2020 objectives; to monitor drug resistance among pneumococci, and; to assist public health jurisdictions in raising awareness of vaccine recommendations.

### *Enhancing reporting of Antibiotic Susceptibility Results*

Concern over rising resistance to antibiotics has prompted many state health departments to increase their focus on reporting susceptibility results. CDC has worked with state health departments to evaluate different surveillance methods to determine which methods would enhance the reliability of surveillance data, given certain goals and resource limitations.[58] Use of aggregated antibiogram data collected from all hospital laboratories in an area has been shown to give a relatively accurate description of the proportion of isolates that are resistant to penicillin and a limited number of other drugs,[59] but such data typically cannot be analyzed by age group or other factors of interest. Sentinel systems, which may collect individual reports with more details from a limited number of laboratories, can give an accurate view of resistance if designed well.[60]

### *Encouraging provider reporting*

Most states' infectious disease surveillance systems depend upon the receipt of case reports from health-care providers and laboratories. These data are often incomplete and may not be representative of certain populations; completeness of reporting has been estimated to vary from 6% to 90% for many of the common notifiable diseases.[53] Therefore, it is important to educate providers about which events should be reported, and about how accurate reporting is critical to control of communicable diseases. Increasing provider awareness of local rates of IPD and local reporting requirements may enhance surveillance.

### *Improving detection of DRSP in laboratories by promoting optimal techniques and appropriate interpretive standards*

Because pneumococci are fastidious organisms, laboratory methods that are appropriate for some organisms are not appropriate for pneumococci.[61] In addition, many laboratories are not monitoring resistance to some agents that are widely used for suspected pneumococcal infections, such as fluoroquinolone agents.[24] Universal adoption of optimal testing methods and testing for resistance to recommended antibiotics would improve our ability to detect and monitor resistant pathogens.

### *Streamlining reporting using electronic methods*

Many surveillance systems still rely on paper and pencil for data collection; use of electronic data transferred directly from clinical laboratories significantly improves reporting speed and data quality as well as reduces workload. Efforts are underway to implement electronic reporting, including the creation of a CSTE/CDC Joint Electronic Laboratory Reporting Taskforce.[62]

## X. Case Investigations

As with most respiratory pathogens, rapid, sensitive, and specific diagnostic tests are not available; thus, early in the course of illness, diagnosis of *S. pneumoniae* infection is usually presumptive and the choice of antimicrobial therapy is nearly always empiric. However, once *S. pneumoniae* is isolated from a normally sterile body site, antimicrobial susceptibility testing may be necessary for patient management. Case investigations are not usually warranted, except in outbreaks or as determined by the state health department. CDC is available during outbreaks to assist with epidemiologic and laboratory investigations.

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# Chapter 12: Poliomyelitis

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## I. Disease Description

Poliomyelitis is a highly contagious disease caused by three serotypes of poliovirus. Infection with poliovirus results in a spectrum of clinical manifestations from inapparent infection to nonspecific febrile illness, aseptic meningitis, paralytic disease, and death. Two phases of acute poliomyelitis can be distinguished: a nonspecific febrile illness (minor illness) followed, in a small proportion of patients, by aseptic meningitis and/or paralytic disease (major illness). The ratio of cases of inapparent infection to paralytic disease among susceptible individuals ranges from 100:1 to 1000:1 or more.

Following poliovirus exposure, viral replication occurs in the oropharynx and the intestinal tract. Viremia follows, which may result in infection of central nervous system cells. The virus attaches and enters cells via a specific poliovirus receptor. Replication of poliovirus in motor neurons of the anterior horn and brain stem results in cell destruction and causes the typical clinical manifestations of poliomyelitis. Depending on the site of infection and paralysis, poliomyelitis can be classified as spinal, bulbar, or spino-bulbar disease. Progression to maximum paralysis is rapid (2–4 days), usually associated with fever and muscle pain, and rarely progresses after the temperature has returned to normal. Spinal paralysis is typically asymmetric, more severe proximally than distally, and deep tendon reflexes are absent or diminished. Bulbar paralysis may compromise respiration and swallowing. Between 2%–10% of cases of paralytic poliomyelitis are fatal. Infection with poliovirus results in lifelong, type-specific immunity.

Following the acute episode, many patients recover muscle functions at least partially, and prognosis for recovery can usually be established within six months after onset of paralytic manifestations.

## II. Background

Poliomyelitis became an epidemic disease in the United States (U.S.) at the turn of the 20th century. Epidemics of ever-increasing magnitude occurred, with more than 20,000 cases of poliomyelitis with permanent paralysis reported in 1952. Following the introduction of effective vaccines, first inactivated poliovirus vaccine (IPV) in 1955, and oral poliovirus vaccine (OPV) starting in 1961, the reported incidence of poliomyelitis in the U.S. declined dramatically to <100 cases in 1965 and to <10 cases in 1973. With the introduction and widespread use of OPV (containing live attenuated poliovirus strains), vaccine-associated paralytic poliomyelitis (VAPP) was recognized. By 1973, for the first time in the U.S., more cases of vaccine-associated disease were reported than paralytic disease caused by wild poliovirus.[1] This trend continued, and in 1997 the Advisory Committee on Immunization Practices (ACIP) recommended changing to a sequential polio immunization schedule that included two doses of IPV, followed by two doses of OPV.[2] VAPP occurred less frequently under this schedule, and in 2000, this recommendation was updated to a schedule of all IPV.[3,4,5] OPV is no longer manufactured or available in the United States.

The last U.S. cases of indigenously transmitted wild poliovirus disease were reported in 1979. Since 1986, with the exception of one imported wild-type poliomyelitis case in 1993, all reported cases of paralytic poliomyelitis in the United States have been vaccine-associated (see **Figure 1**).[6, 7] VAPP was a very rare disease, with an average of eight reported cases annually during 1980–1999, or one case reported for every 2.4 million doses of OPV distributed.[6, 7] The risk of VAPP is highest following the first dose of OPV and among immunodeficient persons. Since changing to an all-IPV immunization schedule in 2000, there have been only two cases of VAPP reported in the U.S., one in an imported case and one in a genetically immunocompromised person who was most likely exposed to OPV before it use was discontinued.

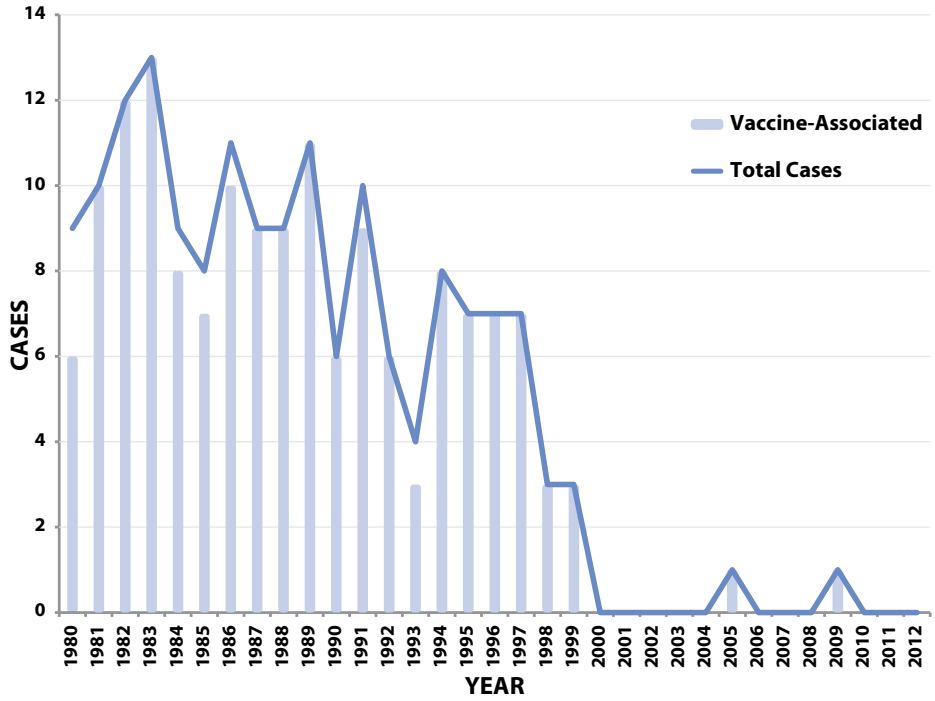


**Figure 1: Total number of reported paralytic poliomyelitis cases (including imported cases) and number of reported vaccine-associated cases— United States, 1980–2012**

Following the successful implementation of the polio eradication initiative in the Americas beginning in 1985, the last case of wild poliovirus-associated disease was detected in Peru in 1991. The hemisphere was certified as free of indigenous wild poliovirus in 1994.[8] In 1988, the World Health Assembly adopted the goal of worldwide eradication of poliomyelitis by the year 2000.[9] By 2001, substantial progress toward eradication had been reported: a more than 99% decrease in the number of reported cases of poliomyelitis was achieved. Wild poliovirus remains endemic in just three countries: Afghanistan and Pakistan in Asia, and Nigeria in Africa.[10,11,12] Due to the successful implementation of the global poliomyelitis eradication initiative, the risk of importation of wild poliovirus into the U.S. decreased substantially over the last decade. Nevertheless, the potential for importation of wild poliovirus into the United States remains until worldwide poliomyelitis eradication is achieved. More information on the status of poliomyelitis eradication can be found at: http://www.polioeradication.org/.

Because inapparent infection with OPV or wild virus strains no longer contributes to establishing or maintaining poliovirus immunity in the U.S., universal vaccination of infants and children is the only means of establishing and maintaining population immunity against poliovirus to prevent poliomyelitis cases and epidemics caused by importation of wild virus into the U.S. Population-based surveys have confirmed that the prevalence of poliovirus antibodies among school-age children, adolescents, and young adults in the United States is high (> 90% to poliovirus types 1 and 2, and > 85% to type 3).[13,14] In addition, seroprevalence surveys conducted in two inner-city areas of the United States (areas in which routine coverage was low) during 1990–1991 found that > 80% of all children 12–47 months of age had antibodies to all three poliovirus serotypes.[15] Data from 1997–1998 also demonstrate a high seroprevalence of antibody to all poliovirus serotypes among children aged 19–35 months who lived in the inner-city areas of four cities in the U.S., with 96.8%, 99.8%, and 94.5% seropositive to poliovirus types 1, 2, and 3, respectively.[16] However, members of certain religious groups objecting to vaccination have remained susceptible to poliomyelitis. These groups appear to be at highest risk for epidemic poliomyelitis. The last two outbreaks of poliomyelitis in the U.S. were reported among religious groups— in 1972 among Christian Scientists[17] and in 1979 among the Amish.[1] Clustering of other subpopulations that object to vaccination can also occur, which could increase the susceptibility to vaccine-preventable diseases, including polio.[18]

The emergence of circulating vaccine-derived polioviruses (cVDPVs) causing an outbreak of poliomyelitis was first reported in Hispaniola in 2000.[19] One or more cVDPV outbreaks have been reported each year since.[20] These outbreaks have occurred in regions where OPV is being used and overall routine polio vaccination rates are low. The vaccine polioviruses are able to replicate in the intestinal tract of inadequately immunized persons, and may be transmitted to others with inadequate immunity. During these multiple infections, the viruses may regain some of the properties of wild polioviruses, such as transmissibility and neurovirulence. Clinical disease caused by these VDPVs is indistinguishable from that caused by wild polioviruses. Outbreak control measures in these outbreaks have relied upon vaccination with OPV. A circulating VDPV has also been identified in an undervaccinated Amish community in the U.S. in 2005.[21]

## III. Importance of rapid identification

Rapid investigation of suspected poliomyelitis cases is critical to identifying possible wild poliovirus transmission. Rapid detection of wild or virus-related cases permits the timely implementation of controls to limit the spread of imported wild poliovirus or cVDPVs and maintain the eradication of wild poliovirus in the U.S. Moreover, rapid investigation of suspected cases will allow collection of specimens for poliovirus isolation, which is critical for confirming whether a case of paralytic poliomyelitis is the result of wild or vaccine-related virus infection.

## IV. Importance of Surveillance

The poliomyelitis surveillance system serves to 1) detect importation of wild poliovirus into the U.S. and 2) detect the presence of vaccine-derived poliovirus in the U.S.

## V. Disease Reduction Goals

No cases of paralytic polio due to indigenously acquired wild poliovirus have been reported in the U.S. since 1979. There have been two reported cases of VAPP in the U.S. since 2000 when the use of OPV was discontinued. High coverage with poliovirus vaccine is required to maintain elimination of poliomyelitis in the United States until global eradication is achieved.

## VI. Case Definition

### *Poliomyelitis, paralytic*

The following case definition for paralytic poliomyelitis has been approved by the Council of State and Territorial Epidemiologists (CSTE), and was published in 2010.[22]

#### *Case classification*

**Probable:** Acute onset of a flaccid paralysis of one or more limbs with decreased or absent tendon reflexes in the affected limbs, without other apparent cause, and without sensory or cognitive loss.

**Confirmed:** Acute onset of a flaccid paralysis of one or more limbs with decreased or absent tendon reflexes in the affected limbs, without other apparent cause, and without sensory or cognitive loss; AND in which the patient

- has a neurologic deficit 60 days after onset of initial symptoms, or
- has died, or
- has unknown follow-up status.

**Comment:** All suspected cases of paralytic poliomyelitis are reviewed by a panel of expert consultants before final classification occurs. Confirmed cases are then further classified based on epidemiologic and laboratory criteria.[23] Only confirmed cases are included in **Table 1** in the *Morbidity and Mortality Weekly Report (MMWR).* Suspected cases under investigation are enumerated in a footnote to the *MMWR* table.

### *Poliovirus infection, non-paralytic*

The following case definition for non-paralytic poliovirus infection has been approved by CSTE, and was published in 2010.[24]

### *Case classification*

**Confirmed:** Any person without symptoms of paralytic poliomyelitis in whom a poliovirus isolate was identified in an appropriate clinical specimen, with confirmatory typing and sequencing performed by the CDC Poliovirus laboratory, as needed.

## VII. Laboratory Testing

Laboratory studies, especially attempted poliovirus isolation, are critical for confirming whether a case of paralytic poliomyelitis is the result of wild or vaccine-related virus infection. For additional information on laboratory testing, see Chapter 22, "Laboratory Support for Surveillance of Vaccine-Preventable Diseases."

### *Virus isolation*

The likelihood of poliovirus isolation is highest from stool specimens, intermediate from pharyngeal swabs, and low from blood or spinal fluid. The isolation of poliovirus from stool specimens contributes to the diagnostic evaluation but does not constitute proof of a causal association of such viruses with paralytic poliomyelitis.1 Isolation of virus from the cerebrospinal fluid (CSF) is diagnostic but is rarely accomplished. Because virus shedding can be intermittent, and to increase the probability of poliovirus isolation, at least two stool specimens and two throat swabs should be obtained 24 hours apart from patients with suspected poliomyelitis as early in the course of the disease as possible (i.e., immediately after poliomyelitis is considered as a possible differential diagnosis), and ideally within the first 14 days after onset of paralytic disease. Specimens should be sent to the state or other reference laboratories for primary isolation on appropriate cell lines. Laboratories should forward virus isolates to CDC for intratypic differentiation and possible sequencing to determine whether the poliovirus isolate is wild or vaccine-related.

**To increase the probability of poliovirus isolation, at least two stool specimens should be obtained 24 hours apart from patients with suspected poliomyelitis as early in the course of disease as possible (ideally within 14 days after onset).**

**Isolation of wild poliovirus constitutes a public health emergency** and appropriate control efforts must be initiated immediately (in consultation among healthcare providers, the state and local health departments, and CDC).

### *Serologic testing*

Serology may be helpful in supporting the diagnosis of paralytic poliomyelitis. An acute serum specimen should be obtained as early in the course of disease as possible, and a convalescent specimen should be obtained at least three weeks later. A four-fold neutralizing antibody titer rise between the acute and convalescent specimens suggests poliovirus infection. Nondetectable antibody titers in both specimens may help support the rule out of poliomyelitis but may also be falsely negative in immunocompromised persons, who are also at highest risk for paralytic poliomyelitis. In addition, neutralizing antibodies appear early and may be at high levels by the time the patient is hospitalized; thus, a four-fold rise may not be demonstrated. Vaccinated individuals would also be expected to have measurable titers; therefore vaccination history is important for serology interpretation. Polio serology is subject to several limitations, including the inability to to differentiate between antibody induced by immunization from antibody induced by infection and to distinguish between antibody induced by vaccine-related poliovirus and antibody induced by wild virus. Serologic assays to detect antipoliovirus antibodies are available in some commercial and state public health laboratories, and CDC.

### *Cerebrospinal fluid (CSF) analysis*

The cerebrospinal fluid usually contains an increased number of leukocytes—from 10 to 200 cells/mm3 (primarily lymphocytes) and a mildly elevated protein, from 40 to 50 mg/100 ml. These findings are nonspecific and may result from a variety of infectious and noninfectious conditions. Detection of poliovirus in CSF is very uncommon.

## VIII. Reporting

Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[25] These regulations and laws list the diseases to be reported and describe those persons or groups responsible for reporting, such as health-care providers, hospitals, laboratories, schools, daycare and childcare facilities, and other institutions. Contact your state health department for reporting requirements in your state.

### *Reporting to CDC*

Because poliomyelitis has been eliminated from the Americas, each reported case of suspected poliomyelitis should be followed up by local and state health departments in close collaboration with CDC. Paralytic polio has been classified as "Immediately notifiable, Extremely Urgent" which requires that local and state health departments contact CDC within 4 hours. Reports of nonparalytic polio are designated as "Immediately notifiable, Urgent" which requires notification of the CDC within 24 hours. CDC (Emergency Operations Center, 770-488-7100) will provide consultation regarding the collection of appropriate clinical specimens for virus isolation and serology, the initiation of appropriate consultations and procedures to rule out or confirm poliomyelitis, the compilation of medical records, and most importantly, the evaluation of the likelihood that the disease may be caused by wild poliovirus.

### *Information to collect*

Demographic, clinical, and epidemiologic information are collected to:

- Determine whether the suspected case meets the case definition for paralytic poliomyelitis
- Determine whether the disease may be caused by wild poliovirus

The following data elements are epidemiologically important and should be collected in the course of a case investigation. See Appendix 14 for details on each data category. Additional information may be collected at the direction of the state health department or CDC.

- Demographic information
  - Name
  - Address
  - Date of birth
  - Age
  - Sex
  - Ethnicity
  - Race
  - Country of birth
  - Length of time resident in U.S.
- Reporting source
  - County
  - Earliest date reported
- Clinical
  - Hospitalizations: dates and duration of stay
  - Date of onset of symptoms
  - Complications
  - Immunologic status of case-patient

    - Outcome (case survived or died)
        - Date of death
        - Postmortem examination results
        - Death certificate diagnoses
- Laboratory and clinical testing
    - Serologic test
    - Stool test
    - Throat swab test
    - EMG
    - MRI
- Vaccine information
    - Dates and types of polio vaccination
    - Number of doses of polio vaccine received
    - Manufacturer of vaccine
    - Vaccine lot number
    - If not vaccinated, reason
- Epidemiological
    - Recent travel to polio-endemic areas or OPV-using countries
    - Contact with persons recently returning form polio-endemic areas or OPV-using countries
    - Contact with recent OPV recipient
    - Setting (Is case-patient a member of a group objecting to vaccination?)

### *Travel history*

Because the last cases of paralytic poliomyelitis due to indigenously acquired wild poliovirus infection in the U.S. were reported in 1979, it is likely that wild poliovirus in a suspected case-patient is imported, either by the suspected patient directly or by a contact of the case-patient. Results of virus isolation and differentiation may not be available at the time of the case investigation. Therefore, to rule out the possibility of imported wild poliovirus, a detailed travel history of suspected cases and of other household and nonhousehold contacts should be obtained. Any history of contacts with visitors, especially those from polio-endemic areas, might be particularly revealing.

### *Setting*

Because the last two outbreaks of poliomyelitis in the United States were reported among Christian Scientists in 1972[17] and the Amish in 1979,[1] a suspected case of poliomyelitis reported from a group objecting to vaccination should be assigned the highest priority for follow-up and collection of specimens. VDPVs also pose a risk of poliomyelitis in communities with low vaccination coverage. In addition, isolation of wild poliovirus from residents of Canada in 1993[26] and 1996[27] demonstrates the potential for wild poliovirus importation into this continent. The strain isolated in Canada in 1993 was linked epidemiologically and by genomic sequencing to the 1992 poliomyelitis outbreak in the Netherlands, and the 1996 isolate was from a child who had recently visited India.

## IX. Vaccination

All children should receive four doses of IPV given at 2 months, 4 months, 6–18 months, and 4–6 years of age. In addition, because of potential confusion in using different vaccine products for routine and catch-up immunization, recommendations for poliovirus vaccination were updated in 2009.[28] ACIP recommends the following:

- The 4-dose IPV series should continue to be administered at ages 2 months, 4 months, 6–18 months, and 4–6 years.
- The final dose in the IPV series should be administered at age ≥4 years regardless of the number of previous doses.

- The minimum interval from dose 3 to dose 4 is extended from 4 weeks to 6 months.
- The minimum interval from dose 1 to dose 2, and from dose 2 to dose 3, remains 4 weeks.
- The minimum age for dose 1 remains age 6 weeks.

ACIP also updated its recommendation concerning the use of minimum age and minimum intervals for children in the first six months of life. Use of the minimum age and minimum intervals for vaccine administration in the first six months of life are recommended only if the vaccine recipient is at risk for imminent exposure to circulating poliovirus (e.g., during an outbreak or because of travel to a polio-endemic region). ACIP made this precaution because shorter intervals and earlier start dates lead to lower seroconversion rates.

In addition, ACIP is clarifying the poliovirus vaccination schedule to be used for specific combination vaccines. When DTaP-IPV/Hib (Pentacel) is used to provide four doses at ages 2, 4, 6, and 15–18 months, an additional booster dose of age-appropriate IPV-containing vaccine (IPV [Ipol] or DTaP-IPV [Kinrix]) should be administered at age 4–6 years. This will result in a 5-dose IPV vaccine series, which is considered acceptable by ACIP. DTaP-IPV/Hib is not indicated for the booster dose at age 4–6 years. ACIP recommends that the minimum interval from dose 4 to dose 5 should be at least 6 months to provide an optimum booster response. In accordance with existing recommendations, if a child misses an IPV dose at age 4–6 years, the child should receive a booster dose as soon as feasible.

## X. Enhancing surveillance

A number of activities can improve the detection and reporting of cases and improve the comprehensiveness and quality of reporting. Additional surveillance activities are listed in Chapter 19, "Enhancing Surveillance."

### *Promoting awareness*

Because of the severity of poliomyelitis disease, clinicians are often the first to suspect the diagnosis of poliomyelitis and they are the key to timely reporting of suspected cases. However, disease reporting by clinicians is often delayed because it is only after other differential diagnoses are ruled out that the diagnosis of poliomyelitis is considered. Efforts should be made to promote physicians' awareness of the importance of prompt reporting of suspected cases to the state and local health department and the CDC and the need to obtain stool and throat specimens early in the disease course.

### *Ensuring laboratory capabilities*

Make sure that the state laboratory or other easily accessible laboratory facility is capable of performing, at a minimum, primary virus isolation on appropriate cell lines. The CDC polio laboratory is always available for consultation and/or testing.

### *Obtaining laboratory confirmation*

Appropriate stool and throat specimens (two specimens taken at least 24 hours apart during the first 14 days after onset of paralytic disease) should be collected.

### *Active surveillance*

Active surveillance should be conducted for every confirmed case of poliomyelitis to assure timely reporting. The diagnosis of a case of poliomyelitis, particularly in a member of a group that refuses vaccination (such as the Amish or Christian Scientists), should prompt immediate control measures as well as active surveillance activities. These activities should include active contact tracing among at risk populations.

## XI. Case investigation

Guidelines and a worksheet for the investigation of suspected cases of poliomyelitis are included as **Appendix 14**. Suspected cases of poliomyelitis should be reported immediately to the state health department. CDC Emergency Operations Center should be contacted at 770-488-7100.

Timely collection of stool specimens is important in establishing the diagnosis and determining appropriate control measures, in the event of wild poliovirus isolation (see "Virus isolation" in Section VII, "Laboratory testing").

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# Chapter 13: Rotavirus

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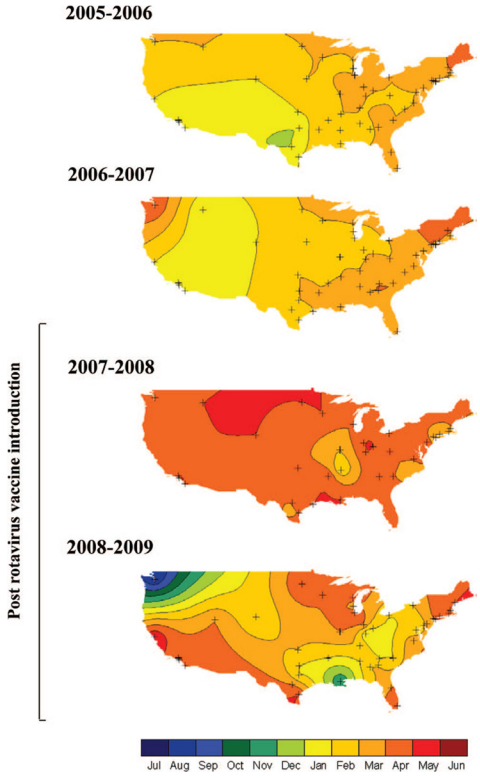
## I. Disease Description

Rotavirus is the most common cause of severe gastroenteritis in infants and young children worldwide. Nearly every US child who is not vaccinated against rotavirus as an infant is expected to be infected with rotavirus within the first years of life, and the majority will have symptomatic gastroenteritis. The clinical spectrum of rotavirus illness ranges from mild, watery diarrhea of limited duration to severe diarrhea with vomiting and fever that can result in dehydration with shock, electrolyte imbalance, and death. Following an incubation period of 1–3 days, the illness often begins abruptly, and vomiting often precedes the onset of diarrhea. Gastrointestinal symptoms generally resolve in 3–7 days. Up to one-third of patients have a temperature of >102°F (>39°C). Severe, dehydrating rotavirus infection occurs primarily among unvaccinated children aged 3–35 months.[1,2,3,4,5,6]

Rotaviruses are shed in high concentrations in the stools of infected children and are transmitted primarily by the fecal-oral route, both through close person-to-person contact and through fomites.[7] Rotaviruses also are probably transmitted by other modes, such as fecally contaminated food and water and respiratory droplets.[8] Rotavirus is highly communicable, with a small infectious dose of < 100 virus particles.[9]

During the pre-rotavirus vaccine era, rotavirus caused marked winter seasonal peaks of gastroenteritis in the US, usually beginning in the Southwest during November–December and spreading to the Northeast by April–May. However, since the widespread use of rotavirus vaccines, this seasonality has shifted and this trend in rotavirus peak activity is no longer consistently observed.[10, 11, 12, 13] (Figure 1)

**Figure 1. The peak month of rotavirus activity in the United States by surveillance year during July 2005 through June 2009. [Curns et al. *Pediatr Infect Dis J* 2011; 30:S54-5.]**




*Crosses indicate the location of reporting laboratories whose data were included for analysis each season.*

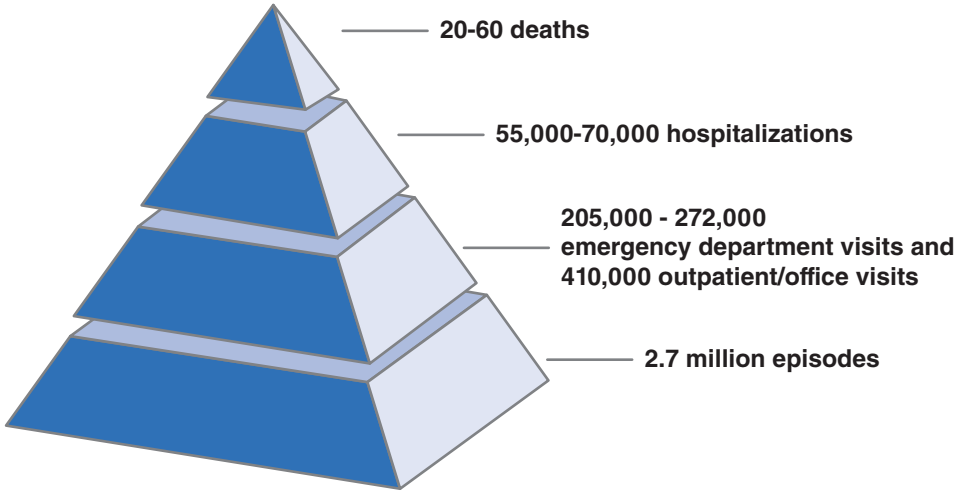
Repeated infections occur from birth to old age, but natural immunity renders the majority of infections asymptomatic after the first years of life.[14] Additionally, no indication of waning vaccine-induced immunity has yet been observed during the rotavirus vaccine post-licensure period.[15, 16] Children who are immunocompromised sometimes experience severe, prolonged, and even fatal rotavirus gastroenteritis.[17, 8, 19, 20] Rotavirus also is an important cause of nosocomial gastroenteritis.[3, 21, 22, 23, 24, 25, 26] Among US adults, rotavirus infection can cause gastroenteritis primarily in travelers returning from developing countries, persons caring for children with rotavirus gastroenteritis, immunocompromised persons and older adults.[27]

## II. Background

### *Burden of disease*

During the pre-rotavirus vaccine era, four of five children in the US had symptomatic rotavirus gastroenteritis,[4 28, 29] one in seven required a clinic or emergency department (ED) visit, one in 70 was hospitalized, and one in 200,000 would die from this disease, within the first 5 years of life.[5, 30] The direct and indirect costs of these 410,000 physician visits, 205-272,000 ED visits, and 55-70,000 hospitalizations was estimated to be approximately $1 billion (Figure 2). Relatively few childhood deaths have been attributed to rotavirus in the US (approximately 20–60 deaths per year among children aged <5 years).[31] However, in developing countries, rotavirus gastroenteritis continues to be a major cause of severe childhood morbidity; responsible for approximately half a million deaths per year among children aged <5 years.[32]

**Figure 2. Estimated number of annual deaths, hospitalizations, emergency department visits, and episodes of rotavirus gastroenteritis among United States children aged <5 years during the pre-rotavirus vaccine era [Parashar UD, et al. *Emerg Inf Dis J* 2003; 9:565-71. /and/ Parashar UD, et al. *J Infect Dis* 1997;177:13–7.]**

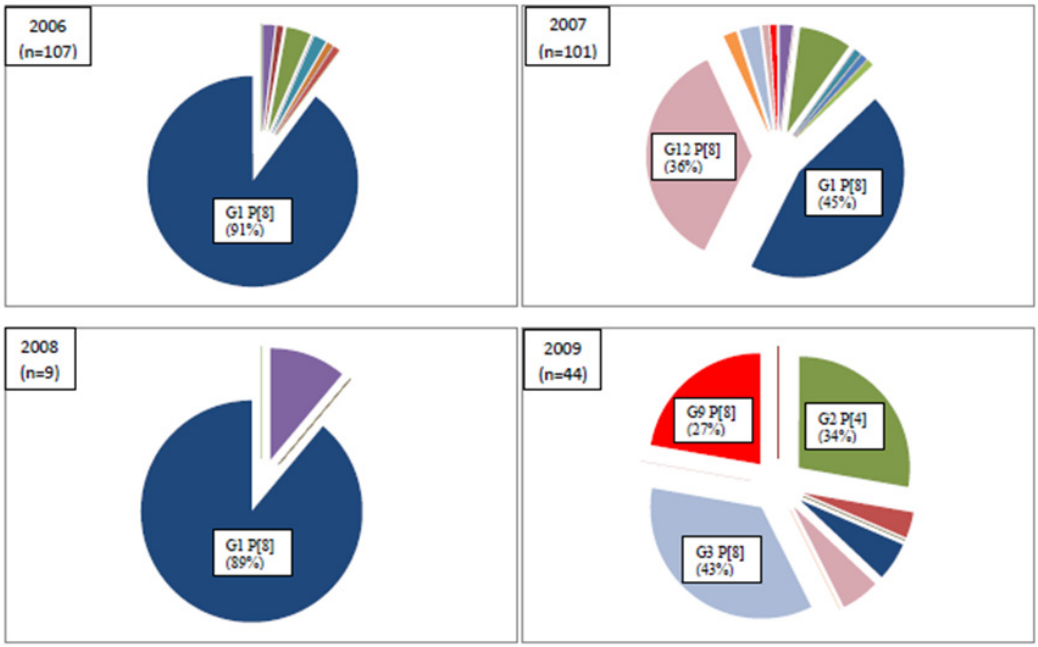



### *Virology*

Rotaviruses are nonenveloped RNA viruses belonging to the Reoviridae family. The viral nucleocapsid is composed of three concentric shells that enclose 11 segments of double-stranded RNA. The outermost layer contains two structural viral proteins (VP): VP4, the protease-cleaved protein (P protein) and VP7, the glycoprotein (G protein). These two proteins define the serotype of the virus and are considered critical to vaccine development because they are targets for neutralizing antibodies that might be important for protection. Because the two gene segments that encode these proteins can segregate independently, a typing system consisting of both P and G types has been developed. Several animal species (e.g., primates, cows, horses, pigs, sheep) are susceptible to rotavirus infection and suffer from rotavirus diarrhea, but common animal rotavirus serotypes differ from prevalent human strains. Although human rotavirus strains that possess a high degree of genetic homology with animal strains have been identified, animal-to-human transmission of whole virions appears to be uncommon. Most human rotaviruses having some genetic similarity to animal rotaviruses appear formed by reassortment of one or more animal rotavirus genes into a human rotavirus during a mixed infection in vivo.

In the US, viruses containing six distinct P and G combinations are most prevalent: P[8]G1, P[4] G2, P[8] G3, P[8] G4, P[8] G9, and P[6] G9, although more than 40 rare or regional strains have been identified in the US and globally.[33] In recent years P[8],G3 has become the predominant strain among severe rotavirus gastroenteritis cases in the US, although secular variation by geographic region may still exist.[34, 35, 36] (Figure 3)

**Figure 3. Predominant rotavirus serotypes among hospitalized children, New Vaccine Surveillance Network, <3 years old, January-June 2006-2009 [Payne et al, *Clin Inf Dis* 2011.]**




## III. Vaccination

*Descriptions and clinical trial results from high and middle income countries:*

In 2006, a live, oral, human-bovine reassortant rotavirus vaccine (RotaTeq®, produced by Merck and Company, Whitehouse Station, New Jersey) was recommended by the Advisory Committee on Immunization Practices (ACIP) for routine vaccination of US infants. Three doses of this vaccine are recommended to be administered at ages 2, 4, and 6 months, concurrently with other vaccines given at this age.[1] RotaTeq® contains five reassortant rotaviruses developed from human and bovine parent rotavirus strains that express human outer capsid proteins of five common circulating strains (G1, G2, G3, G4, and P[8] (subgroup P1A)).

RotaTeq® has been tested in two phase III trials,[37, 38] including a large scale clinical trial of more than 70,000 infants enrolled primarily in the US and Finland. The efficacy of 3 doses of RotaTeq® against G1-G4 rotavirus gastroenteritis of any severity was 74% (95% confidence interval [CI] = 67%, 80%) and against severe G1-G4 rotavirus gastroenteritis was 98% (CI = 88%, 100%). RotaTeq® was observed to be effective against each targeted serotype and reduced the incidence of medical office visits by 86% (CI = 74%, 93%), ED visits by 94% (CI = 89%, 97%), and rotavirus gastroenteritis hospitalizations by 96% (CI = 91%, 98%). Efficacy against all gastroenteritis hospitalizations of any etiology was 59% (CI = 52%, 65%) for the period beginning after dose.[1]

Rotarix® (produced by GlaxoSmithKline Biologicals, Rixensart, Belgium), was recommended for routine vaccination of US infants by the ACIP in 2008. This live vaccine contains the attenuated monovalent G1, P[8] human rotavirus strain and is recommended by the manufacturer to be orally administered in 2 doses to infants at ages 2 and 4 months.

Rotarix® efficacy was evaluated in a large clinical trial of more than 63,000 infants from 11 Latin American countries, and was found to be safe and highly immunogenic. During the first year after vaccination, the efficacy of 2 doses of Rotarix® against hospitalization due to severe rotavirus was 85% and 100% against more severe rotavirus gastroenteritis, as defined by the Vesikari 20-point scoring system.[39] After two years of follow-up the vaccine demonstrated 83% (CI=73%, 90%) efficacy in preventing rotavirus-related hospitalizations. Rotarix® was

protective against hospitalizations due to all causes of gastroenteritis (42% protection for the first year, CI=27%, 54%). Rotarix® provided protection against a broad range of rotavirus serotypes during the study's 2-year period, including against the less common G9, P[8] strain.

In a randomized, double-blind, placebo-controlled study conducted in 6 European countries, Rotarix® was observed to be highly immunogenic. Efficacy of Rotarix® against any grade of severity of rotavirus gastroenteritis through one rotavirus season was 87% (CI= 80%, 92%) and against severe rotavirus gastroenteritis, as defined by a score ≥11 on the Vesikari scale, through one rotavirus season was 96% (CI=90%, 99%). Rotarix® reduced hospitalizations for all cause gastroenteritis regardless of presumed etiology by 75% (CI= 46%, 89%). The efficacy of Rotarix® against severe rotavirus gastroenteritis through two rotavirus seasons was 90% (CI= 85%, 94%), and the efficacy of Rotarix® in reducing hospitalizations through two rotavirus seasons was 96% (CI= 84%, 100%).[40, 41]

No clinical trial has yet compared the efficacy of Rotarix® against that of RotaTeq®, and ACIP offers no vaccine preference. For harmonization of vaccination administration scheduling, the ACIP now recommends that, for both vaccines, the maximum age for dose 1 is 14 weeks and 6 days (previous recommendation: 12 weeks), and the maximum age for the last dose of rotavirus vaccine is 8 months and 0 days (previous recommendation: 32 weeks).[1]

### *Post-licensure vaccine effectiveness and impact:*

Since the introduction of RotaTeq® in 2006, several field studies have been conducted to determine vaccine effectiveness (VE) in the United States. A case-control study in Texas of 3-dose RotaTeq® VE in children age-eligible to receive vaccination during the 2007-08 and 2008-09 rotavirus seasons showed a combined VE of 84% (CI=70%, 92%). VE was highest during the 2007-2008 season (90%, CI=72%, 96%), and, while slightly decreased, remained significant during the 2008-2009 season (78%, CI=47%, 91%).[35] In a further case-control study of children aged 15 days-23 months enrolled at this Texas clinical setting during February-June 2008, even partial immunization with RotaTeq® provided protection against rotavirus disease, with a VE of 69% (CI=13%, 89%) for a single dose, 81% (CI=13%, 96%) for two doses, and 88% (CI=68%, 96%) for a full course of three doses.[15]

RotaTeq® vaccine effectiveness was evaluated in a multi-site study during the first three years following licensure by the New Vaccine Surveillance Network (NVSN), finding 3-dose efficacy against G1-G4 rotavirus hospitalizations and ED to be 94.5% (CI=91%, 97%), with estimated effectiveness of 91% (CI=73%, 97%) using controls with non-rotavirus acute gastroenteritis and 86% (CI=70%, 94%) using acute respiratory infection controls. Vaccine effectiveness estimates were comparable between the first and second years of life, and these estimates were similar across observed rotavirus strains.[42]

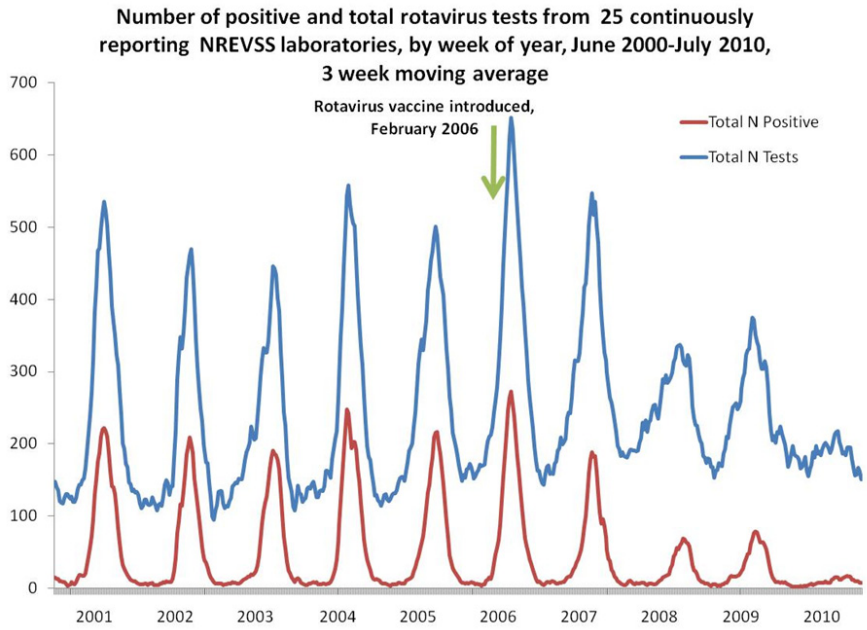
Similar estimates of VE have been observed using different methodologies and in other geographic areas of the country. A case-control study of children aged 8 weeks to 3 years was conducted in Connecticut during January 2006-August 2009. The adjusted VE for a complete 3-dose course of RotaTeq® was 96% (CI=29%, 100%) when calculated using hospitalized controls and 99% (CI=78%, 100%) using community controls. Incomplete vaccination was also found to be highly effective at preventing hospitalization due to rotavirus gastroenteritis, with a VE of 93% (CI=41%, 99%) when calculated using hospitalized controls and 94% (CI=23%, 100%) when using community controls.[43]

Multiple studies have shown that the US rotavirus season has shortened and become less pronounced since the introduction of RotaTeq®. The National Respiratory and Enteric Viruses Surveillance System (NREVSS) is a national, passive laboratory surveillance network to which participating laboratories submit weekly reports of the number of rotavirus antigen detection tests performed and the number positive. The median onset of rotavirus season, defined as the first of two consecutive weeks during which the percentage of positive rotavirus tests exceeds 10%, during the pre-vaccine years of 2000-06 occurred in mid-December. During the 2007-08, the onset of rotavirus season did not occur until early March, approximately 11 weeks later than the median for 2000-06. Onset during the 2008-09 season was again delayed and occurred in

January, approximately 6 weeks later. Median season duration during 2000-06 was 26 weeks (range 25-28). However, this was reduced to 14 weeks during 2007-08 and 17 weeks during 2008-09. During all three time periods, the total number of tests performed each year remained similar at approximately 14,000 tests.[44, 45] (Figure 4)

In another analysis of hospital discharge data from 18 states (accounting for 49% of the US population), acute, all-cause gastroenteritis hospitalization rates for children aged <5 years were calculated from 2000 to 2008. Compared with the median rate for the 2000–2006 rotavirus seasons the rates for 2007 and 2008 were 16% and 45% lower, respectively, reinforcing the finding that RotaTeq® vaccine introduction was associated with a dramatic reduction in hospitalizations for acute gastroenteritis among US children during the 2008 rotavirus season.[46]

**Figure 4: Rotavirus incidence trends from 2001–2010 using passively reported laboratory rotavirus test data from the National Respiratory and Enteric Virus Surveillance System (NREVSS) [Tate JE, *Pediatrics* 2009; 124:465-71. /and/ Cortese MM. Presented to the US Advisory Committee on Immunization Practices (ACIP), October 2010, Atlanta, Georgia.]**




Indirect protective benefits of rotavirus vaccination to unvaccinated individuals were not studied during the clinical trials of either currently licensed rotavirus vaccine. However, NVSN surveillance from 2006 through 2009 empirically indicated that reductions among older, largely unvaccinated children in 2008 likely resulted from indirect protection conferred by younger, vaccinated children within the household and community. Compared with 2006, a significant reduction in rotavirus hospitalization rates ($P<0.001$) was observed in 2008 among all age groups (87% reduction in 6 to <12 month olds [vaccine coverage=77%], 96% reduction in 12 to <24 months olds [vaccine coverage=46%], and a 92% reduction in 24 to <36 month olds [vaccine coverage=1%], which far exceeded reductions that would be expected based on vaccine coverage and effectiveness estimates. While rotavirus hospitalization rates among age groups eligible for vaccination remained low in 2009, indirect protective benefits from vaccine disappeared and the median age for rotavirus hospitalizations increased.[36]

Indirect protective benefits from rotavirus vaccination were likely caused by disrupted rotavirus transmission among household and community contacts following the large increase in vaccination coverage in 2008. Although indirect benefits were not observed in 2009, these effects may re-emerge in future years even within specific communities. Several studies have also suggested that the median and mean ages of hospitalized, rotavirus positive children have increased during the post-licensure period.[34, 35, 36]

### *Mathematical modeling of rotavirus trends:*

Several recent mathematical modeling analyses have been conducted to better understand the effects of rotavirus vaccination upon disease trends. Using a deterministic, age-structured model in a developed country setting, Atchinson, et al.,[47] computed that short-term age-specific fluctuations in rotavirus incidence and age distributions were consequences of a rotavirus vaccination program in a developed country and were unrelated to waning immunity or falling vaccine coverage. Pitzer et al.,[48] calculated that the mean age of severe rotavirus cases would increase with higher vaccine coverage due to delays in primary rotavirus infection, that the spatiotemporal characteristics of rotavirus epidemics are largely related to accumulations of fully susceptible individuals by geographic location, and that the reduction in rotavirus prevalence would be greater than that predicted by the direct effect of vaccination alone. These modeling predictions have matched published empirical observations.[36]

### *Vaccine safety:*

A modestly elevated risk of intussusception (~1-2 cases per 100,000 vaccine recipients) among rotavirus vaccine recipients has been noted in some international settings, a level that would be 5-10 fold lower than the risk observed in 1999 with the Rotashield vaccine (no longer on the market). It is not known whether any association is also present in the United States. US studies so far have found no increase in risk of intussusception after vaccination. However, while the US studies have been powerful enough to exclude a risk of the size observed in 1999 with the earlier generation Rotashield vaccine, they do not yet have the power to exclude the lower risk observed overseas.

## IV. Importance of Surveillance

With the introduction of a new rotavirus vaccine into the US childhood immunization program, it is important to conduct surveillance to: 1) monitor the impact of vaccination in reducing the morbidity and mortality from rotavirus disease; 2) evaluate vaccine effectiveness in field use and identify and determine the causes of possible vaccine failure; 3) monitor the possible emergence of rotavirus strains that might escape vaccination; 4) identify population groups that might not be adequately covered by vaccination; and 5) continue to monitor the safety of rotavirus vaccines. Since nearly every child suffers from rotavirus gastroenteritis by age 5 and confirming a diagnosis of rotavirus requires laboratory testing of fecal specimens, identification of every case of rotavirus is not practical or necessary at this stage of the vaccination program. Instead, surveillance efforts should focus on monitoring trends of severe rotavirus disease, such as rotavirus hospitalizations or emergency room visits, at the national level and through more intensive efforts at some sentinel sites. In addition to severe and medically-attended disease surveillance, viral strain surveillance is also important to evaluate whether strain variability is a secular phenomenon or whether it is the result of a potential selection of rotavirus serotypes through vaccine pressures.

## V. Disease Reduction Goals

*Healthy People 2020* does not state a goal for overall rotavirus disease reduction or target for vaccination coverage at this time.

## VI. Case Definitions

Definitive diagnosis of rotavirus gastroenteritis requires laboratory confirmation of infection. Currently, no case definition for rotavirus gastroenteritis is approved by the Council of State and Territorial Epidemiologists (CSTE).[49] Active surveillance being conducted at sentinel sites by CDC defines a confirmed case of rotavirus gastroenteritis as a child with diarrhea (≥3 loose stools in 24 hrs) OR vomiting (≥1 episodes in 24 hrs) and with detection of rotavirus in a fecal specimen by a standard assay (e.g., commercially available enzyme immunoassays).

## VII. Laboratory Testing

It is not possible to diagnose rotavirus infection by clinical presentation because the clinical features of rotavirus gastroenteritis do not differ from those of gastroenteritis caused by other pathogens. Confirmation of rotavirus infection by laboratory testing is necessary for reliable rotavirus surveillance and can be useful in clinical settings to avoid inappropriate use of antimicrobial therapy.

Rotavirus is shed in high concentration in the stool of children with gastroenteritis and a fecal specimen is the preferred specimen for diagnosis. The most widely available method for detection of rotavirus antigen in stool is an enzyme immunoassay (EIA) directed at an antigen common to all group A rotaviruses. Several commercial EIA kits are available that are inexpensive, easy to use, rapid, and highly sensitive (approximately 90-100%), making them suitable for rotavirus surveillance and clinical diagnosis.[50] Polyacrylamide gel electrophoresis and silver staining is about as sensitive as EIA but is very labor intensive.[51] Latex agglutination is less sensitive and specific than EIA but is still used in some settings.[33] Other techniques, including electron microscopy, reverse transcription-polymerase chain reaction, nucleic acid hybridization, sequence analysis, and culture are used primarily in research settings.

Rotavirus serotypes can be determined directly from rotavirus positive stool specimens using both EIA and reverse transcriptase polymerase chain reaction (RT-PCR) methods. Monoclonal antibody-based EIA techniques have been invaluable in defining four globally common serotypes (G1-G4) that represent >90% of the circulating strains and make up 4/5 serotypes in the RotaTeq® vaccine.[52, 53] More recently, molecular methods, predominantly multiplexed, semi-nested RT-PCR genotyping and nucleotide sequencing have been developed as a surrogate for serotypes and have become widely used to identify the most common and several uncommon rotavirus G and P genotypes.[54, 55, 56, 57] Nucleotide sequencing has been extensively used to identify uncommon strains and genetic variants that cannot be identified by RT-PCR genotyping and to confirm the results of genotyping methods.

## VIII. Reporting

Rotavirus gastroenteritis is not a nationally reportable disease and notification is not required by CDC. Contact the state health department for reporting requirements in your state.

Current national rotavirus surveillance includes the following:

1. **New Vaccine Surveillance Network (NVSN):** Active rotavirus surveillance activities through NVSN commenced in the 2005-2006 rotavirus season with 3 original sites and have continued prospectively with 7 sites in 2011. These participating medical centers are in Tennessee, New York, Ohio, Texas, Kansas, Washington, and California that conduct active, population-based surveillance for rotavirus-associated hospitalizations and emergency room visits among children <5 years of age. Acute gastroenteritis cases are identified and additional epidemiological and clinical information is collected from parental interviews and medical chart reviews. Stool specimens are tested for rotavirus antigen at each study site, and CDC laboratories type all positive specimens. Analyses are conducted to estimate disease burden and to assess rotavirus vaccine effectiveness in field use.
2. **National Respiratory and Enteric Virus Surveillance System (NREVSS) and the National Rotavirus Strain Surveillance System (NRSSS):** NREVSS is a laboratory-based sentinel surveillance system that monitors temporal and geographic patterns associated with the detection of several viruses, including rotavirus. Approximately 90 laboratories located in state and local health departments, universities, and hospitals have participated in the NREVSS since 2001. Participating laboratories report on a weekly basis to the CDC the total number of fecal specimens submitted for rotavirus testing and the number that tested positive for rotavirus. A subset of 10-12 NREVSS laboratories participate in NRSSS. These NRSSS laboratories submit a representative sample of rotavirus-positive fecal specimens to CDC for strain characterization by molecular methods.

3. **Secondary Analysis of National Health Utilization Datasets:** National estimates of the burden of rotavirus disease have been derived primarily through review of passive surveillance data on diarrhea mortality, hospitalizations, and ambulatory visits collected by the National Center for Health Statistics (e.g, National Hospital Discharge Survey, National Ambulatory Care Survey). In this approach, a set of International Classification of Diseases, 9th Volume, Clinical Module (ICD–9–CM) codes have been first used to identify events attributable to acute gastroenteritis. Then, the unique epidemiologic characteristics of rotavirus gastroenteritis (i.e., predilection for children 4-35 months of age, marked winter seasonality) have been used to estimate the proportion of diarrhea events attributable to rotavirus. A rotavirus-specific ICD-9-CM code was introduced in 1992. One validation study found that this code had a high positive predictive value (i.e., coded events were highly likely to be true cases) but had a sensitivity of <50%. Nonetheless, applying a variety of ICD-9-CM codes related to acute gastroenteritis to these large databases and accounting for the seasonal and age-specific distributions of rotavirus incidence, it is possible to deduce large-scale rotavirus disease patterns and impacts using these methods.

## IX. Case Investigation

Case investigations are usually not warranted, except perhaps during outbreaks or in the case of deaths or other serious manifestations of rotavirus infections. Because diarrheal outbreaks can be caused by many pathogens, a laboratory investigation for the causative agent that includes viral, bacterial and parasitic agents should be considered for gastroenteritis cases seeking medical attention.

## X. Control

Routine immunization of infants is anticipated to be the most effective public health intervention for population-wide rotavirus infection control. Post-exposure vaccine prophylaxis is not a recommended strategy in response to an outbreak of rotavirus gastroenteritis.

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# Chapter 14: Rubella

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## I. Disease Description

Rubella is a viral illness caused by a togavirus of the genus *Rubivirus* and is characterized by a mild, maculopapular rash. The rubella rash occurs in 50%–80% of rubella-infected persons and is sometimes misdiagnosed as measles or scarlet fever. Children usually develop few or no constitutional symptoms, but adults may experience a 1–5-day prodrome of low-grade fever, headache, malaise, mild coryza, and conjunctivitis. Postauricular, occipital and posterior cervical lymphadenopathy is characteristic and precedes the rash by 5–10 days. Arthralgia or arthritis may occur in up to 70% of adult women with rubella. Rare complications include thrombocytopenic purpura and encephalitis.[1–3] Rubella is transmitted through direct or droplet contact from nasopharyngeal secretions and has an average incubation period of 17 days (range: 12–23 days). Persons with rubella are most infectious when rash is erupting, but they can shed virus from 7 days before to 7 days after rash onset.

When rubella infection occurs during pregnancy, especially during the first trimester, serious consequences can result. These include miscarriages, fetal deaths/stillbirths, and a constellation of severe birth defects known as congenital rubella syndrome (CRS). The most common congenital defects are cataracts, heart defects and hearing impairment. See Chapter 15, "Congenital Rubella Syndrome," for more details.

## II. Background

Before the availability of rubella vaccines in the United States, rubella was a common disease that occurred primarily among young children. Incidence was highest during the spring with epidemics every 6 to 9 years.[4] The last major epidemic in the United States occurred during 1964–1965, when there was an estimated 12.5 million rubella cases in the United States, resulting in 2,000 cases of encephalitis, 11,250 therapeutic or spontaneous abortions, 2,100 neonatal deaths, and 20,000 infants born with CRS.[5]

In 1969, live attenuated rubella vaccines were licensed in the United States. The goal of the rubella vaccination program was and continues to be to prevent congenital infections, including CRS.[6] Following vaccine licensure, the number of reported cases of rubella in the United States has declined dramatically to a median of 11 cases annually in 2005–2011 (CDC, unpublished data). During the 1990s, the incidence of rubella among children younger than 15 years decreased (from 0.63 per 100,000 population in 1990 to 0.06 1999), whereas the incidence among adults aged 15 to 44 years increased (from 0.13 per 100,000 in 1990 to 0.24 in 1999).[7] However, since 2001, the incidence both among persons younger than age 15 years and those aged 15 to 44 years has been less than 1/10,000,000 population.[8, 9]

During the 1990s and in 2000, rubella outbreaks occurred among members of religious communities that traditionally refuse vaccination and among adults from countries without a history of routine rubella vaccination programs.[7, 8] Since 2001, only three rubella outbreaks have been reported, each with five or fewer cases.

In 2004, an independent panel of internationally recognized experts in public health, infectious diseases, and immunizations reviewed available data and unanimously agreed that rubella elimination (i.e., the absence of endemic transmission) was achieved in the United States.[6]

Although rubella has been eliminated in the United States, it continues to be endemic in many parts of the world. It is estimated more than 100,000 infants are born with CRS annually worldwide.[10] According to a survey of the member countries in the World Health Organization (WHO), the number of countries that have incorporated rubella-containing vaccines into their routine national immunization programs increased from 83 (13% of the birth cohort) in 1996 to 130 countries (40% of the birth cohort) in 2010. As of October 2010, the WHO Region of the Americas and European Region have established rubella elimination goals for the year 2010 and

2015, respectively; the Western Pacific Region has established targets for accelerated rubella control and CRS prevention goal (<1 case per 100,000) by 2015; and the Eastern Mediterranean Region has established a goal of CRS prevention without a target date for countries that have introduced national rubella vaccination programs.[11] In addition, in 2011, WHO recommended for all countries that are providing two doses of measles vaccine and have not introduced rubella vaccine, to consider including rubella-containing vaccine in their immunization program.[12] In 2010, the Pan American Health Organization (PAHO) announced that the Region of the Americas had achieved the rubella and CRS elimination goals set in 2003 based on surveillance data. Although regional documentation of elimination is ongoing, an expert panel unanimously agreed in December 2011 that rubella elimination has been maintained in the United States.[11, 13]

## III. Maintenance of Elimination

The United States has established and achieved the goal of eliminating endemic rubella transmission and CRS. Elimination of endemic rubella was documented and verified in the United States in 2004.[6] However, because of international travel and countries without routine rubella vaccination, imported cases of rubella are likely. To maintain elimination, the United States should continue to maintain high vaccination rates among children; ensure that women of childbearing age, particularly women born outside of the United States, are vaccinated; and maintain sensitive surveillance to detect both rubella and CRS.

## IV. Vaccination

Two combination vaccines are licensed and available in the United States to prevent rubella: MMR vaccine (measles, mumps, and rubella; M-M-R II®, Merck & Co., Inc.) and tetravalent MMRV vaccine (measles, mumps, rubella, and varicella; ProQuad®, Merck & Co., Inc.). Monovalent rubella vaccine is no longer available in the United States.

### *Recommendations for use of rubella-containing vaccines[14]*

For prevention of rubella, measles, mumps, rubella (MMR) vaccine is recommended for persons aged ≥12 months.

Two doses of MMR vaccine are recommended routinely for children with the first dose at age 12 through 15 months and the second dose at age 4 through 6 years. Because two doses of combined measles-mumps-rubella (MMR) vaccine are recommended in the current schedule for measles and mumps vaccination, most children and adolescents now receive two doses of rubella-containing vaccine.

MMRV vaccine can be used in place of MMR vaccine to implement the two-dose recommendation for children aged 12 months to 12 years.[15]

Adults born during or after 1957, including those who may be at increased risk for rubella exposure or transmission, should receive at least one dose of rubella-containing vaccine. These persons include students attending colleges or other post high school educational institutions, healthcare personnel, international travelers, and nonpregnant women of childbearing age. Healthcare providers should routinely assess women of childbearing age for presumptive evidence of rubella immunity (see below) and vaccinate those who lack acceptable evidence of immunity and who are not pregnant. Pregnant women who do not have acceptable evidence of rubella immunity should be vaccinated immediately postpartum.

For unvaccinated healthcare personnel born before 1957 who lack laboratory evidence of rubella immunity or laboratory confirmation of disease, healthcare facilities should consider vaccinating personnel with one dose of MMR vaccine.

## V. Presumptive Evidence of Rubella Immunity

Persons who have written documentation of adequate vaccination with at least one dose of live rubella virus-containing vaccine on or after age 12 months, laboratory evidence of rubella immunity, laboratory confirmation of disease, or were born before 1957 (except for women who could become pregnant) have acceptable presumptive evidence of rubella immunity. Birth

before 1957 is not acceptable evidence of rubella immunity for women who could become pregnant. Persons who do not have acceptable presumptive evidence of rubella immunity should receive one dose of MMR vaccine.

## VI. Case Definition

### *Case definition for case classification*

The following case definition for rubella has been approved by the Council of State and Territorial Epidemiologists (CSTE) in 2012.[16]

**Suspected:** Any generalized rash illness of acute onset that does not meet the criteria for probable or confirmed rubella or any other illness.

**Probable:** In the absence of a more likely diagnosis, an illness characterized by all of the following:

- acute onset of generalized maculopapular rash; and
- temperature greater than 99.0° F or 37.2° C, if measured; and
- arthralgia, arthritis, lymphadenopathy, or conjunctivitis; and
- lack of epidemiologic linkage to a laboratory-confirmed case of rubella; and
- noncontributory or no serologic or virologic testing.

**Confirmed:** A case with or without symptoms who has laboratory evidence of rubella infection confirmed by one or more of the following:

- isolation of rubella virus; or
- detection of rubella-virus specific nucleic acid by polymerase chain reaction; or
- significant rise between acute-and convalescent-phase titers in serum rubella immunoglobulin G antibody level by any standard serologic assay; or
- positive serologic test for rubella immunoglobulin M (IgM) antibody*,†

OR

An illness characterized by all of the following:

- acute onset of generalized maculopapular rash; and
- temperature greater than 99.0° F or 37.2° C; and
- arthralgia, arthritis, lymphadenopathy, or conjunctivitis; and
- epidemiologic linkage to a laboratory-confirmed case of rubella.

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** Not explained by MMR vaccination during the previous 6–45 days.*

*† Not otherwise ruled out by more specific testing in a public health laboratory.*

### *Epidemiologic classification of internationally-imported and U.S.-acquired*

**Internationally imported case:** An internationally imported case is defined as a case in which rubella results from exposure to rubella virus outside the United States as evidenced by at least some of the exposure period (12–23 days before rash onset) occurring outside the United States and the onset of rash within 23 days of entering the United States and no known exposure to rubella in the United States during that time. All other cases are considered U.S.-acquired cases.

**U.S.-acquired case:** A U.S.-acquired case is defined as a case in which the patient had not been outside the United States during the 23 days before rash onset or was known to have been exposed to rubella within the United States. U.S.-acquired cases are subclassified into four mutually exclusive groups:

**Import-linked case:** Any case in a chain of transmission that is epidemiologically linked to an internationally imported case.

**Imported-virus case:** A case for which an epidemiologic link to an internationally imported case was not identified but for which viral genetic evidence indicates an imported rubella genotype, i.e., a genotype that is not occurring within the United States in a pattern indicative of endemic transmission. An endemic genotype is the genotype of any rubella virus that occurs in an endemic chain of transmission (i.e., ≥12 months). Any genotype that is found repeatedly in U.S.-acquired cases should be thoroughly investigated as a potential endemic genotype, especially if the cases are closely related in time or location.

**Endemic case:** A case for which epidemiological or virological evidence indicates an endemic chain of transmission. Endemic transmission is defined as a chain of rubella virus transmission continuous for ≥12 months within the United States.

**Unknown source case:** A case for which an epidemiological or virological link to importation or to endemic transmission within the United States cannot be established after a thorough investigation. These cases must be carefully assessed epidemiologically to assure that they do not represent a sustained U.S.-acquired chain of transmission or an endemic chain of transmission within the United States.

***Note:*** *Internationally imported, import-linked, and imported-virus cases are considered collectively to be import-associated cases.*

States may also choose to classify cases as "out-of-state-imported" when imported from another state in the United States. For national reporting, however, cases will be classified as either internationally imported or U.S.-acquired.

## VII. Laboratory Testing

Clinical diagnosis of rubella is unreliable, therefore, cases must be laboratory confirmed. Virus detection and serologic testing can be used to confirm acute or recent rubella infection. Serologic tests can also be used to screen for rubella immunity. For additional information on laboratory testing for the surveillance of vaccine-preventable diseases, see Chapter 22, "Laboratory Support for Surveillance of Vaccine-Preventable Diseases."

### *Virus detection (real-time RT-PCR, RT-PCR)*

Rubella virus can be detected from nasal, throat, urine, blood, and cerebrospinal fluid specimens from persons with rubella (see Appendix 15). The best results come from throat swabs. Cerebrospinal fluid specimens should be reserved for persons with suspected rubella encephalitis. Efforts should be made to obtain clinical specimens for virus detection from all case-patients at the time of the initial investigation. Virus may be detected from 1 week before to 2 weeks after rash onset. However, maximum viral shedding occurs up to day 4 after rash onset.

Real-time RT-PCR and RT-PCR can be used to detect rubella virus and has been extensively evaluated for its usefulness in detecting rubella virus in clinical specimens.[17, 18] Clinical specimens obtained for virus detection and sent to CDC are routinely screened by these techniques.

Molecular typing is recommended because it provides important epidemiologic information to track the epidemiology of rubella in the United States now that rubella virus no longer continuously circulates in this country. By comparing virus sequences obtained from new case-patients with other virus sequences, the origin of particular virus types in this country can be tracked.[19] Furthermore, this information may help in documenting the maintenance of the elimination of endemic transmission. In addition, genotyping methods are available to distinguish wild-type rubella virus from vaccine virus.

### *Serologic testing*

The serologic tests available for laboratory confirmation of rubella infections and immunity vary among laboratories. The State health department can provide guidance on available laboratory services and preferred tests. Enzyme immunoassays (EIA) are the most commonly

used and widely available diagnostic test for rubella IgG and IgM antibodies and are sensitive and relatively easy to perform. EIA is the preferred testing method for IgM, using the capture technique, although indirect assays are also acceptable.

Latex agglutination (LA) tests appear to be sensitive and specific for screening when performed by experienced laboratory personnel. Other tests in limited use to detect rubella-specific IgM include hemagglutination inhibition (HI) and immunofluorescent antibody (IFA) assay.

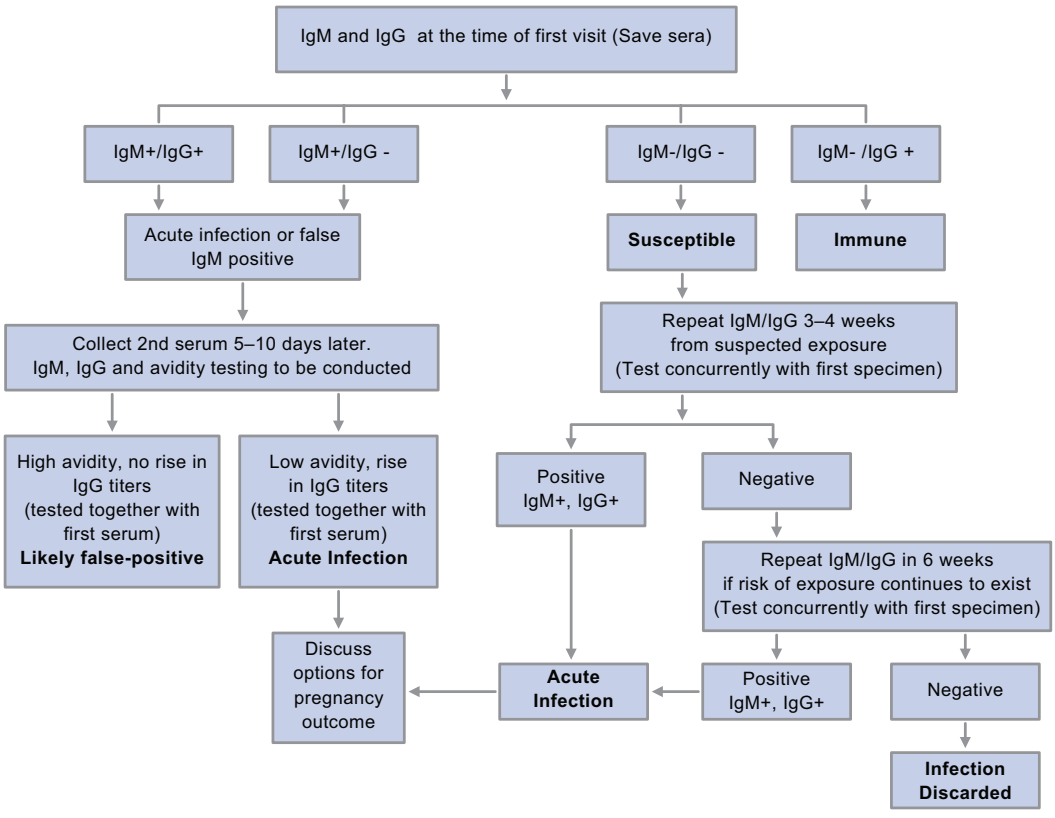
### *Detection of IgM antibody*

Rubella-specific IgM can usually be detected 4–30 days after onset of illness, and often for longer. Sera should be collected as early as possible after onset of illness. However, IgM antibodies may not be detectable before day 5 after rash onset. In case of a rubella IgM-negative result in specimens taken before day 5, serologic testing should be repeated on a specimen collected after day 5.

Because rubella incidence is low, a high proportion of IgM-positive tests will likely be false positive. False-positive serum rubella IgM tests may occur due to the presence of rheumatoid factors (indicating rheumatologic disease) or cross-reacting IgM, or infection with other viruses.[20,21] Avidity testing (see below) and detection of wild-type rubella virus can be used to resolve uncertainties in the serologic evaluation of suspected cases.

Particular care should be taken when rubella IgM is detected in a pregnant woman with no history of illness or contact with a rubella-like illness. Although this is not recommended, many pregnant women with no known exposure to rubella are tested for rubella IgM as part of their prenatal care. If rubella test results are IgM-positive for persons who have no or low risk of exposure to rubella, additional laboratory evaluation should be conducted. Laboratory evaluation is similar to that described in the IgM-positive section of Figure 1.

**Figure 1. Algorithm for serologic evaluation of pregnant women exposed to rubella**



### *Detection of IgG antibody (significant rise or avidity) for diagnostic testing*

To detect a significant rise in rubella-specific IgG concentration, the first serum should be obtained as soon as possible after onset of illness and the second serum sample should be collected about 7–21 days after the first specimen. In most rubella cases, rubella IgG is detectable by 8 days after rash onset.[22] Tests for IgG antibody should be conducted on both acute-and convalescent-phase specimens at the same time with the same test.

Assays for IgG avidity are useful to distinguish the difference between recent and past rubella infections. Low avidity is associated with recent primary rubella infection, whereas high avidity is associated with past infection or reinfection. Avidity tests are not routine tests and should be performed in reference laboratories. A number of avidity assays have been described.[23, 24]

### *Detection of IgG antibody to screen for rubella immunity*

A single serologic IgG test may be used to determine the rubella immune status of persons whose history of rubella disease or vaccination is unknown. The presence of serum IgG rubella-specific antibodies indicates immunity to rubella.

## VIII. Importance of Rubella Surveillance

Surveillance data are needed to identify and control rubella virus introductions to prevent congenital rubella infections and consequent CRS as well as monitor maintenance of disease elimination.

### *Promote awareness of rubella and CRS in the United States*

Although only 62 cases of rubella and 4 cases of CRS were reported between 2005 and 2011, it is likely that not all cases were identified. Efforts should continue to promote physicians' awareness of the possibility of rubella and CRS. When evaluating patients with suspected measles who have negative serologic tests for acute measles infection (i.e., negative serum measles IgM), officials may request additional testing for rubella.

### *Promote awareness of groups at high risk for rubella infection and CRS birth*

Rubella-containing vaccines are not administered routinely in many countries, and in others, rubella-containing vaccine was only recently added to the childhood immunization schedule. Thus, many persons born outside the United States or who received childhood immunizations in other countries may have never received rubella vaccine. Healthcare providers should have a heightened index of suspicion for rubella and CRS births in persons from countries without a history of routine rubella vaccination programs or with recently implemented programs.

## IX. Reporting

Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[25] These regulations and laws list the diseases to be reported and describe those persons or groups who are responsible for reporting, such as healthcare providers, hospitals, laboratories, schools, daycare and childcare facilities, and other institutions. Persons reporting should contact the State health department for state-specific reporting requirements.

Prompt identification and reporting of suspected, probable, or confirmed cases of rubella is important to avoid exposure of susceptible pregnant women. Rapid case identification and investigations are also important so that control measures can be initiated to prevent spread of the disease.

Reports of rubella are designated by CSTE as "immediately notifable, urgent" which requires notification of the CDC within 24 hours. All cases of rubella should be reported by the State health department to CDC/NCIRD/DVD/Epidemiology Branch (404-639-8253) and to the National Notifiable Diseases Surveillance System (NNDSS). Reporting should not be delayed because of incomplete information or laboratory confirmation; following completion of case investigations, data previously submitted to NNDSS should be updated with the available new information.

The following data elements are epidemiologically important and should be collected in the course of a case investigation. Additional information may be collected at the direction of the state or local health department.

- Demographic information
  - Name
  - Address
  - Age
  - Sex
  - Ethnicity
  - Race
  - Country of birth
  - Length of time in United States
- Reporting Source
  - County
  - Earliest date reported
- Clinical
  - Date of illness onset
  - Date of rash onset
  - Duration of rash
  - Symptoms
    - Fever
    - Arthralgia or arthritis
    - Lymphadenopathy
    - Conjunctivitis
  - Complications
    - Encephalitis
    - Thrombocytopenia
    - Other
  - Hospitalizations and duration of stay
  - Outcome (patient survived or died)
    - Date of death
  - If female, pregnancy history
    - If pregnant, pregnancy status
      - Number of weeks gestation at onset of illness
      - Prior evidence, date of serologic immunity, or both
      - Prior diagnosis and date of rubella
      - Number and dates of previous pregnancies and location (e.g., state or country) of these pregnancies
      - Pregnancy outcome, when available (e.g., normal infant, termination, CRS)
- Laboratory
  - Serology
  - Virus isolation
  - Genotype
  - PCR results
- Vaccine Information
  - Number of doses of rubella-containing vaccine received
  - Dates of vaccination
  - Types of vaccine (rubella, MMR, MMRV)
  - If not vaccinated, reason

- Epidemiologic
  - Transmission setting (infection acquired at home, healthcare setting, in daycare, school, or workplace)
  - Relationship to outbreak (Is case part of an outbreak or is it sporadic?)
  - Source of exposure
  - Travel history (countries, dates)

## X. Case Investigation, Contact Investigations, and Outbreak Control

### *Consider a single case of rubella as a potential outbreak*

Because rubella has been eliminated in the United States, health agencies should consider one case a potential outbreak. Rubella is an infectious disease for which up to 50% of cases are asymptomatic, and investigation of an apparently isolated case could reveal additional cases.

### *Confirm a diagnosis of rubella*

Clinical diagnosis of rubella is unreliable, therefore, cases must be laboratory confirmed, especially if the reported cases are not epidemiologically linked to a laboratory-confirmed case. Laboratory testing should be conducted for all suspected cases of rubella.

Laboratory confirmation of rubella infection may be difficult in pregnant women with unknown immune status who experience a rash illness or who are exposed to rubella. A serum specimen should be obtained as soon as possible.

### *Conduct case investigations and vaccinate contacts without evidence of immunity*

Aggressive response to rubella cases may interrupt disease transmission and will increase vaccination coverage among persons who might otherwise not be protected. The main strategies are to define populations at risk, to ensure that persons without evidence of immunity are rapidly vaccinated (or excluded from exposure if a contraindication to vaccination exists) and to maintain active surveillance to permit modification of control measures if the situation changes.

The goal of rubella case investigation is to identify rubella infections, particularly infection in pregnant women, and to prevent exposure of susceptible pregnant women, and thereby prevent cases of CRS. It is essential that exposed pregnant women be identified, evaluated, and counseled (see section on laboratory evaluation of exposed pregnant women). The Rubella Surveillance Worksheet (see Appendix 16) may be used as a guideline in conducting a case investigation. Case investigation and identification of contacts should be conducted for all suspected cases of rubella.

Cases of rubella occurring within 10 days of rubella vaccination should be investigated, and specimens should be obtained for virus isolation to determine if the rash is attributable to vaccine virus or wild virus. Cases in persons vaccinated within 7 days of a rubella-like illness who are IgM-positive should be classified as confirmed cases of wild-type rubella if they are epidemiologically linked to a laboratory-confirmed case.

Any direct contact with a patient with rubella during the infectious period (7 days before to 7 days after rash onset) is defined as an exposure. Every effort should be made to identify all pregnant women who might have been exposed to a patient and evaluate them serologically for rubella-specific IgM and IgG antibodies. All women of childbearing age who are contacts of a person with a suspected or confirmed case should have their pregnancy status determined. If a pregnant woman is infected with rubella, immediate medical consultation is necessary. If a pregnant woman lacks laboratory evidence of rubella immunity, precautions should be taken to prevent any type of exposure to persons infected with rubella; these precautions may include ensuring rubella immunity of household contacts and isolating women from settings where rubella virus has been identified.

### *Identify the source of infection*

Efforts should be made to identify the source of infection for every confirmed case of rubella. Case-patients or their caregivers should be asked about contact with other known cases. Since many rubella cases are asymptomatic, identification of a source will not always be possible. When no history of contact with a known case can be elicited, opportunities for exposure to unidentified cases in populations at high risk (e.g., foreign-born persons) should be sought. Investigating sources of exposure should be directed to the place and time period in which transmission would have occurred.

### *Obtain specimens for virus detection*

Efforts should be made to obtain clinical specimens (throat swabs and urine) for virus detection from all case-patients (or from at least some patients in each outbreak) at the time of the initial investigation.

See Appendix 15 for the procedure to follow in collection of specimens.

### *Conduct laboratory evaluation of exposed pregnant women*

Exposed pregnant women should be tested for the presence of rubella IgG and IgM antibodies as outlined in Figure 1 regardless of symptom history. A blood specimen should be taken as soon as possible and tested for rubella IgG and IgM antibody and stored for possible retesting.

- If the IgM is positive regardless of the IgG response, this may indicate recent or acute infection or a false-positive IgM. The next step is testing with a serum collected in 5–10 days. Testing will include IgM, IgG, and avidity (if IgG is present). If the repeat IgM is positive with low avidity or a significant rise in IgG titers, acute infection is likely. If the IgM and IgG are positive and the avidity is high, this may indicate either a false-positive result or a reinfection. Reinfection with rubella occurs more frequently with vaccine-induced immunity than with natural disease; however, the risk of fetal infection is extremely low.
- If the IgM is negative and the IgG is positive at the time of exposure (the first specimen), this most likely indicates immunity.
- If the IgM and IgG are negative in the first specimen, a second specimen should be taken 3–4 weeks after exposure and tested concurrently with the first specimen for IgM, IgG, and avidity (if IgG is present). A negative IgG response with the first specimen and a positive IgG response with the second specimen indicate that infection has occurred. If the IgG and IgM remain negative and there are no additional exposures, an IgG-negative result at 4 weeks indicates that infection has not occurred. As long as the exposure to rubella continues, it is important to continue testing for IgG and IgM responses.

### *Report the pregnancy outcome for women diagnosed with rubella during pregnancy*

All pregnant women infected with rubella during pregnancy should be followed to document the pregnancy outcome (e.g., normal infant, termination, CRS). Outcomes that are documented should be reported to CDC.

### *Conduct enhanced surveillance*

Active surveillance for rubella should be maintained for at least two incubation periods (46 days) following rash onset of the last case. Two incubation periods allow for the identification of transmission from a subclinical case. In addition, surveillance for CRS should be implemented when confirmed or probable rubella cases are documented in a setting where pregnant women might have been exposed. Women who contract rubella infection while pregnant should be monitored for birth outcome, and appropriate testing should be performed on the infant after birth.

### *Implement control measures*

Control measures should be implemented as soon as at least one case of rubella is confirmed in a community. In settings where pregnant women may be exposed, control measures should begin as soon as rubella is suspected and should not be postponed until laboratory

confirmation. Patients with rubella should be isolated for 7 days after rash onset. All persons at risk who cannot readily provide acceptable evidence of rubella immunity should be considered susceptible and should be vaccinated.

In schools and other educational institutions, exclusion of persons without acceptable evidence of rubella immunity may limit disease transmission and may help to rapidly raise the vaccination level in the target population. All persons who have been exempted from rubella vaccination for medical, religious, or other reasons also should be excluded from attendance. Exclusion should continue until 23 days after the onset of rash of the last reported case-patient in the outbreak setting. Unvaccinated persons who receive MMR vaccine as part of the outbreak control may be immediately readmitted to school provided all persons without documentation of immunity have been excluded.

In healthcare settings, exposed healthcare personnel without adequate presumptive evidence of immunity should be excluded from duty beginning 7 days after exposure to rubella and continuing through either 23 days after last exposure or 7 days after rash appears. Exposed healthcare personnel who are vaccinated as part of control measures should be excluded from direct patient care for 23 days after the last exposure to rubella because effectiveness of postexposure vaccination in preventing rubella infection has not been shown. In addition, because birth before 1957 does not guarantee rubella immunity, during outbreaks in healthcare settings, healthcare facilities should recommend one dose of MMR vaccine for unvaccinated personnel born before 1957 who lack laboratory evidence of rubella immunity or laboratory confirmation of infection or disease.[26]

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# Chapter 15: Congenital Rubella Syndrome

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## I. Disease Description

Congenital rubella syndrome (CRS) is an illness resulting from rubella virus infection during pregnancy. When rubella infection occurs during early pregnancy, serious consequences—such as miscarriages, stillbirths, and a constellation of severe birth defects in infants can result. The risk of congenital infection and defects is highest during the first 12 weeks of gestation and decreases after the 12th week of gestation with defects rare after the 20th week of gestation.[1–3] Common congenital defects of CRS include cataracts, congenital heart disease, hearing impairment, and developmental delay. Infants with CRS usually present with more than one sign or symptom consistent with congenital rubella infection. However, infants may present with a single defect. Hearing impairment is the most common single defect. See Chapter 14, "Rubella," for more information on rubella infection.

## II. Background

The link between congenital cataracts and maternal rubella infection was first made in 1941 by Australian ophthalmologist, Norman Gregg, who had noticed an unusual number of infants with cataracts following a rubella epidemic in 1940. In the absence of vaccination, rubella is an endemic disease with epidemics every 6 to 9 years. If rubella infections occurred among non-immune pregnant women, CRS cases can occur. During the 1962–1965 global rubella pandemic, an estimated 12.5 million rubella cases occurred in the United States, resulting in 2,000 cases of encephalitis, 11,250 therapeutic or spontaneous abortions, 2,100 neonatal deaths, and 20,000 infants born with CRS.[4]

In 1969, live attenuated rubella vaccines were licensed in the United States. The goal of the rubella vaccination program was and continues to be to prevent congenital rubella infections, including CRS.[5] Following vaccine licensure, the number of reported cases of CRS in the United States declined dramatically to <1 case per year or 4 cases total during 2005–2011 (CDC, unpublished data). In 28 (85%) of the 33 cases occurring during 1998–2011, the mother was born outside the United States. Of the 33 CRS cases occurring during this time, 16 (48%) were known importations (CDC, unpublished data). In 2004, an independent panel of internationally recognized experts in public health, infectious diseases, and immunizations reviewed the available data on rubella epidemiology and unanimously agreed that rubella elimination (i.e., the absence of year round endemic transmission) was achieved in the United States.[5]

Although rubella has been eliminated in the United States, it continues to be endemic in many parts of the world. It is estimated that more than 100,000 infants are born with CRS annually worldwide.[6] According to a survey of the member countries in the World Health Organization (WHO), the number of countries that have incorporated rubella-containing vaccines into their routine national immunization programs increased from 83 (13% of the birth cohort) in 1996 to 130 countries (40% of the birth cohort) in 2010. As of October 2010, the WHO Region of the Americas and European Region have established rubella elimination goals for the year 2010 and 2015, respectively; the Western Pacific Region has established targets for accelerated rubella control and CRS prevention goal (<1 case per 100,000) by 2015; and the Eastern Mediterranean Region has established a goal of CRS prevention without a target date for countries that have introduced national rubella vaccination programs.[7] In addition, in 2011, WHO recommended for all countries that are providing two doses of measles vaccine and have not introduced rubella vaccine, to consider including rubella-containing vaccine in their immunization program.[8] In 2010, the Pan American Health Organization (PAHO) announced that the Region of the Americas had achieved the rubella and CRS elimination goals set in 2003 based on surveillance data. Although regional documentation of elimination is ongoing, an expert panel unanimously agreed in December 2011 that CRS elimination has been maintained in the United States.[7, 9]

## III. Maintenance of Elimination

The United States has established and achieved the goal of eliminating indigenous rubella transmission and CRS. Elimination of endemic rubella was documented and verified in the United States in 2004.[5] However, because of international travel and countries without routine rubella vaccination, imported cases of rubella and CRS cases are likely. To maintain elimination, the United States should continue to maintain high vaccination rates among children, ensure that women of childbearing age, particularly women born outside of the United States, are vaccinated, and maintain good surveillance for both rubella and CRS.

## IV. Vaccination

See Chapter 14, "Rubella," for information on vaccination with rubella-containing vaccines.

## V. Case Definition

### *Case definition for case classification*

The following case definition for congenital rubella syndrome was approved by the Council of State and Territorial Epidemiologists (CSTE) and published in 2009.[10]

**Suspected:** An infant who does not meet the criteria for a probable or confirmed case but who has one or more of the following findings:

- cataracts,
- congenital glaucoma,
- congenital heart disease (most commonly patent ductus arterious or peripheral pulmonary artery stenosis),
- hearing impairment,
- pigmentary retinopathy,
- purpura,
- hepatosplenomegaly,
- jaundice,
- microcephaly,
- developmental delay,
- meningoencephalitis, or
- radiolucent bone disease.

**Probable:** An infant who does not have laboratory confirmation of rubella infection but has at least two of the following, without a more plausible etiology:

- cataracts or congenital glaucoma,
- congenital heart disease (most commonly patent ductus arterious or peripheral pulmonary artery stenosis),
- hearing impairment, or
- pigmentary retinopathy;

OR

An infant who does not have laboratory confirmation of rubella infection but has at least one or more of the following, without a more plausible etiology:

- cataracts or congenital glaucoma,
- congenital heart disease (most commonly patent ductus arterious or peripheral pulmonary artery stenosis),
- hearing impairment, or
- pigmentary retinopathy;

AND one or more of the following:

- purpura,
- hepatosplenomegaly,
- jaundice,
- microcephaly,
- developmental delay,
- meningoencephalitis, or
- radiolucent bone disease.

**Confirmed:** An infant with at least one of the symptoms clinically consistent with congenital rubella syndrome listed above; and laboratory evidence of congenital rubella infection demonstrated by:

- isolation of rubella virus, or
- detection of rubella-specific immunoglogulin M (IgM) antibody, or
- infant rubella antibody level that persists at a higher level and for a longer period of time than expected from passive transfer of maternal antibody (i.e., rubella titer that does not drop at the expected rate of a two-fold decline per month), or
- a specimen that is PCR-positive for rubella virus.

**Infection only:** An infant without any clinical symptoms or signs of rubella but with laboratory evidence of infection demonstrated by:

- isolation of rubella virus, or
- detection of rubella-specific immunoglogulin M (IgM) antibody, or
- infant rubella antibody level that persists at a higher level and for a longer period of time than expected from passive transfer of maternal antibody (i.e., rubella titer that does not drop at the expected rate of a two-fold decline per month), or
- a specimen that is PCR-positive for rubella virus.

**Comment:** In probable cases, either or both of the eye-related findings (cataracts and congenital glaucoma) count as a single complication. In cases classified as infection only, if any compatible signs or symptoms (e.g., hearing impairment) are identified later, the case is reclassified as confirmed.

### *Epidemiologic classification of internationally-imported and U.S.-acquired*

Congenital rubella syndrome cases will be classified epidemiologically as internationally imported or U.S.-acquired, according to the source of infection in the mother, using the definitions below, which parallel the classifications for rubella cases.

**Internationally imported case:** To be classified as an internationally imported CRS case, the mother must have acquired rubella infection outside the United States or in the absence of documented rubella infection, the mother was outside the United States during at least some of the period when she may have had exposure to rubella that affected her pregnancy (from 21 days before conception and through the first 24 weeks of pregnancy).

**U.S.-acquired case:** A U.S.-acquired case is one in which the mother acquired rubella from an exposure in the United States. U.S.-acquired cases are subclassified into four groups as described in the rubella case classification section in Chapter 14, "Rubella."

***Note:*** *Internationally imported, import-linked, and imported-virus cases are considered collectively to be import-associated cases.*

States may also choose to classify cases as "out-of-state-imported" when imported from another state in the United States. For national reporting, however, cases will be classified as either internationally imported or U.S.-acquired.

## VI. Laboratory Testing

Diagnostic tests used to confirm CRS include serologic assays and detection of rubella virus.

For additional information on laboratory testing for rubella virus, see Chapter 14, "Rubella." For additional information on use of laboratory testing in surveillance of vaccine-preventable diseases, see Chapter 22, "Laboratory Support for the Surveillance of Vaccine-Preventable Diseases."

### *Virus detection (real-time RT-PCR, RT-PCR)*

Rubella virus can be detected from nasal, throat, urine, and blood specimens from infants with CRS. Efforts should be made to obtain clinical specimens for virus isolation from infants at the time of the initial investigation (see Appendix 15). However, because infants with CRS may shed virus from the throat and urine for a prolonged period (a year or longer), specimens obtained later may also yield rubella virus.

As with rubella infection, molecular typing is recommended because it provides important epidemiologic information to track the epidemiology of rubella in the United States now that rubella virus no longer continuously circulates in this country. By comparing virus sequences from new case-patients with virus sequences from other cases, the origin of particular virus types in this country can be tracked.[11] Furthermore, this information may help in documenting the maintenance of the elimination of endemic rubella virus transmission. Specimens for molecular typing should be obtained from patients with CRS as soon as possible after diagnosis. Appropriate specimens include throat swabs, urine, and cataracts from surgery. Specimens for virus detection and molecular typing should be sent to CDC as directed by the state health department.

### *Serologic testing*

The serologic tests available for laboratory confirmation of CRS infections vary among laboratories. Enzyme immunoassays (EIA) are the most commonly used and widely available diagnostic test for rubella IgG and IgM antibodies. EIAs are sensitive and relatively easy to perform. EIA is the preferred testing method for IgM, using the capture technique, although indirect assays are also acceptable. In infants with CRS, IgM antibody can be detected in the infant's cord blood or serum and persists for about 6–12 months.

## VII. Reporting

Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[12] These regulations and laws list the diseases to be reported and describe those persons or groups responsible for reporting, such as healthcare providers, hospitals, laboratories, schools, daycare and childcare facilities, and other institutions. Persons reporting should contact the state health department for state-specific reporting requirements.

Provisional reports of CRS cases should be sent by the state health department to CDC/NCIRD/DVD/Epidemiology Branch (404-639-8253) and to the National Notifiable Diseases Surveillance System (NNDSS). Reporting should not be delayed because of incomplete information or lack of confirmation; following completion of case investigations, data previously submitted to NNDSS should be updated with the available new information.

The *Congenital Rubella Syndrome Case Report* form (Appendix 17) is used to collect clinical and laboratory information on cases of CRS that are reported by state and local health departments. CRS cases are classified by year of patient's birth.

The following data are epidemiologically important and should be collected in the course of case investigation. Additional information may also be collected at the direction of the state health department.

- Demographic information
  - Name
  - Address
  - Age
  - Sex
  - Ethnicity
  - Race
  - Country of birth (mother)
  - Length of time in United States (mother)
- Reporting source
  - County
  - Earliest date reported
- Clinical
  - Symptoms or syndromes
    - Cataracts
    - Hearing impairment
    - Developmental delay
    - Type of congenital heart defect
    - Pigmentary retinopathy
    - Purpura
    - Radiolucent bone disease
    - Hepatosplenomegaly
    - Meningoencephalitis
    - Microcephaly
    - Other
- Outcome (infant survived or died)
  - Date of death
  - Postmortem examination results
  - Death certificate diagnoses
- Laboratory (performed on both mother and infant)
  - Virus isolation
  - Genotype
  - PCR results
- Maternal history
  - Dates of rubella vaccinations
  - Number of doses of vaccine given
  - If not vaccinated, reason
  - History of documentation of rubella infection or disease during pregnancy
  - Rubella laboratory results
  - History of pregnancies within and outside the United States (including country and years of pregnancies)
- Travel outside the U.S. during pregnancy (countries visited with dates)
- Contact with foreign travelers during pregnancy
- Epidemiologic
  - Transmission setting
  - Source of transmission (e.g., age, vaccination status, relationship to decedent)
  - Source of exposure
  - Travel history

## VIII. Case Investigation

Cases of U.S.-acquired CRS are sentinel events indicating the presence of rubella infections in a community that may have been previously unrecognized. The diagnosis of a single case of U.S.-acquired CRS in a community should result in intensified rubella and CRS surveillance and an investigation to determine where the mother was exposed to rubella. If the mother was exposed in a different state, state health officials should contact the other state to alert public health officials to possible rubella circulation.

Infants with CRS may present with various manifestations of the syndrome, depending on timing of the infection in pregnancy. Infants born to women infected with rubella during pregnancy should be evaluated for infection and CRS; however, depending on the gestational age of the infant at the time of the mother's infection, symptoms may not be apparent. After 20 weeks' gestation, the only defect may be hearing impairment. Furthermore, some children are infected in utero but have no congenital defects.

Laboratory confirmation should be sought in all suspected CRS cases, regardless of signs or symptoms.

### *Conducting active surveillance*

Surveillance for CRS should be implemented when confirmed or probable rubella cases are documented in a setting where pregnant women might have been exposed.[13] Women who contract rubella while pregnant should be monitored for birth outcome, and appropriate testing should be performed on the infant after birth. Healthcare providers should be advised to evaluate infants born with conditions consistent with CRS and to collect specimens for virus detection and to perform a rubella-specific IgM antibody test on infants suspected of having CRS.

## IX. Prevent Transmission from Infants with CRS

Cases of U.S.-acquired rubella have occurred among susceptible persons providing care for infants with CRS.[14] Because infants can shed the virus for prolonged periods, (up to 1 year of age or longer) infants with CRS should be considered infectious until they are at least 1 year old or until two cultures of clinical specimens obtained one month apart after the infant is older than three months of age are negative for rubella virus. Infants with CRS should be placed in contact isolation during any hospital admission before age one year or until the infant is no longer considered infectious. In addition, health officials should consider excluding infants with CRS from child care facilities until he or she is no longer considered infectious. Persons having contact with infants with CRS should have documented evidence of immunity to rubella (see Chapter 14, "Rubella") and caregivers of infants with CRS should be aware of the potential hazard of the infants to susceptible pregnant contacts.

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# Chapter 16: Tetanus

*Tejpratap S. P. Tiwari MD*

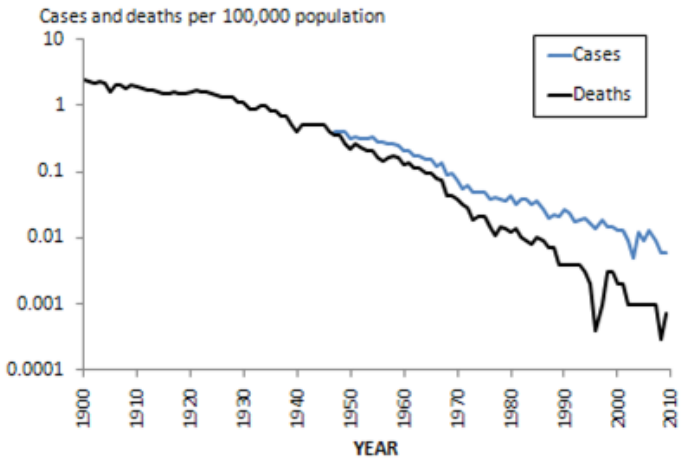
## I. Disease Description

Tetanus is an acute, potentially fatal disease that is characterized by generalized increased rigidity and convulsive spasms of skeletal muscles. Tetanus is caused by the spore-forming bacterium *Clostridium tetani*. *C. tetani* spores (the dormant form of the organism) are found in soil and in animal and human feces. The spores enter the body through breaks in the skin, and germinate under low-oxygen conditions. Puncture wounds and wounds with a significant amount of tissue injury are more likely to promote germination. The organisms produce a potent toxin tetanospasmin which is absorbed into the bloodstream. The toxin then reaches the nervous system, causing painful and often violent muscular contractions. The muscle stiffness usually first involves the jaw (lockjaw) and neck, and later becomes generalized. Tetanus is a noncommunicable disease—it is not transmitted from one person to another.

## II. Background

In the United States, the reported mortality due to tetanus has declined at a constant rate since the early 1900s, and documented tetanus incidence has declined since the mid- to late 1940s, when national reporting of tetanus cases began (Figure 1). In 2009, a total of 19 tetanus cases and 2 deaths were reported to the national tetanus surveillance system. Several factors have contributed to the decline in tetanus morbidity and mortality, including the widespread use of tetanus toxoid–containing vaccines since the late 1940s. Other factors include improved wound care management and the use of tetanus immune globulin (TIG) for postexposure prophylaxis in wound treatment and for the treatment of tetanus. In addition, increased rural-to-urban migration with consequent decreased exposure to tetanus spores may also have contributed to the decline in tetanus mortality noted during the first half of the 20th century.[1]

**Figure 1. Mortality and incidence rates of tetanus reported in the United States, 1900 to 2009**

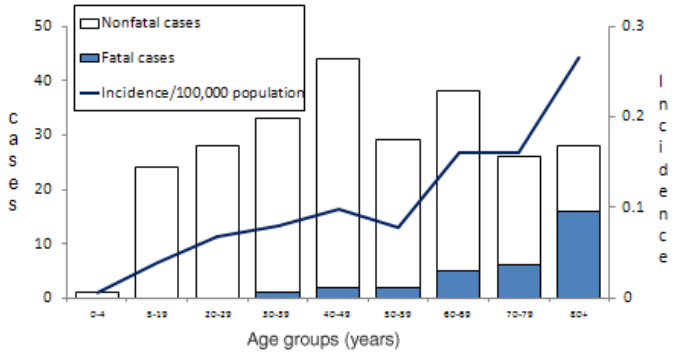



Tetanus is almost entirely preventable through immunization. Vaccination status was known for 1018 (50%) of 2,044 tetanus cases reported from 1972 to 2009.[2, 3] In only 163 (16%) was receipt of three or more doses of tetanus toxoid reported. The remaining patients were either unvaccinated or had received fewer than three doses of tetanus toxoid. Wherever immunization programs are in place, the incidence of tetanus declines and the age distribution of case-patients shifts to reflect underimmunization.[1]

During the period 2001–2008, a total of 233 cases and 26 deaths from tetanus were reported in the United States. Seventy one (30%) were in persons aged 65 years or older, 139 (60%) were in persons aged 20–64 years, and 23 (10%) were in persons younger than 20 years, including one case of neonatal tetanus (Figure 2). The risk of dying from tetanus was five times greater in patients >65 years.[3] During each of these years, coverage among infants and children with at least three doses of DTP/DTaP/diphtheria and tetanus toxoids (DT) was 94% or higher.[4, 5] A review of tetanus in U.S. children under age 15 years from 1992 through 2000 found that 11

of the 13 non-neonatal cases occurred in children who were unvaccinated because of religious or philosophic objections.[6]

**Figure 2. Number of reported cases of tetanus, survival status of patients, and average annual incidence rates by age group—United States, 2001–2009.**




Rates of coverage with booster doses of tetanus toxoid–containing vaccine decrease with increasing age. In a 2008 survey, 64% of adults aged 18–49 years reported receiving a dose of tetanus toxoid–containing vaccine within the preceding 10 years, compared with 52% of adults 65 years of age or older.[7] Serologic studies of the U.S. population correlate well with vaccination coverage and demonstrate lower immunity levels at older ages. A national population-based seroprevalence survey conducted from 1988 to 1994 found that whereas 20% of adolescents 12–19 years of age lacked protective levels of tetanus antibodies (>0.15 IU/ml), 69% of adults 70 years of age or older lacked protective levels.[8]

Diabetes and intravenous drug use may be risk factors for tetanus. From 1987 to 2008, persons with diabetes accounted for 13% of all reported tetanus cases and 29% of all tetanus deaths.[2, 3] The incidence of tetanus among diabetics was more than three times that among non-diabetics.[2] Intravenous drug users accounted for 15% of cases from 2001 to 2008[3] and a cluster of cases was noted in California earlier in the 1990s.[9]

Despite the availability of highly effective tetanus toxoid–containing vaccines, tetanus continues to have a substantial health impact in the world. In 2002, the World Health Organization estimated that 180,000 deaths worldwide were attributable to neonatal tetanus.[10] Neonatal tetanus elimination was defined in 1993 as less than one case of neonatal tetanus for every 1,000 live births per year in each administrative district of a given country.[11] The World Health Organization and its partners (the United Nations Children's Fund and the United Nations Population Fund) are committed to eliminating maternal and neonatal tetanus.

## III. Importance of Rapid Case Identification

Prompt recognition of tetanus is important clinically because hospitalization and treatment are usually required. Prompt administration of tetanus toxoid and TIG may decrease the severity of the disease. Because tetanus is an uncommon disease, consultation on clinical management may be useful. Diabetes may be a risk factor for tetanus, and outbreaks of tetanus among injection-drug users have occurred.[9]

## IV. Importance of Surveillance

Because tetanus is preventable, the possibility of failure to vaccinate should be investigated in every case. Each case should be used as a case study to determine which factors contributed to the failure, and which measures could be taken to improve the vaccine delivery system and prevent such cases in the future.

Information obtained through surveillance is used to assess progress toward the disease elimination goals. The information is also used to raise awareness of the importance of immunization and to characterize persons or geographic areas in which additional efforts are required to raise vaccination levels and reduce disease incidence.

## V. Disease Reduction and Vaccine Coverage Goals

Since herd immunity does not play a role in protecting individuals against tetanus, virtually all persons must be vaccinated in order to achieve this goal. Although the *Healthy People 2010* goal for tetanus was to eliminate all tetanus cases among persons under age 35 years in the United States,[12] 56 non-neonatal cases under age 35 years were reported in the U.S. from 2001-2008.

## VI. Case Definition

The following case definition for tetanus was approved by the Council of State and Territorial Epidemiologists (CSTE) and published in 2009.[13]

### *Tetanus clinical case definition*

In the absence of a more likely diagnosis, an acute illness with muscle spasms or hypertonia and diagnosis of tetanus by a health care provider; or death, with tetanus listed on the death certificate as the cause of death or a significant condition contributing to death.

### *Case classification*

**Probable:** A clinically compatible case, as reported by a healthcare professional.

There is no definition for confirmed tetanus.

## VII. Laboratory Testing

There is no diagnostic laboratory test for tetanus; the diagnosis is entirely clinical. *C. tetani* is recovered from wounds in only about 30% of cases, and the organism is sometimes isolated from patients who do not have tetanus. Serologic results obtained before TIG is administered can support susceptibility if they demonstrate very low or undetectable anti-tetanus antibody levels. However, tetanus can occur in the presence of "protective" levels of antitoxin (>0.1 IU by standard ELISA); therefore, serology cannot exclude the diagnosis of tetanus.

## VIII. Reporting

Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[14] These regulations and laws list the diseases to be reported, and describe those persons or groups responsible for reporting, such as healthcare providers, hospitals, laboratories, schools, daycare and childcare facilities, and other institutions. Persons reporting these conditions should contact their state health department for state-specific reporting requirements. Tetanus is a reportable disease in all states and territories of the United States.

A provisional report should be sent by the state health department to CDC via the National Electronic Telecommunications System for Surveillance (NETSS) or National Electronic Disease Surveillance System (NEDSS), when available, within 14 days of the initial report to the state or local health department. Supplementary information may be sent via NETSS or extended screens, NEDSS investigation screens or on paper forms to CDC (see Appendix 18). Reporting should not be delayed because of incomplete information.

### *Information to collect*

The following data are epidemiologically important and should be collected in the course of case investigation. Additional information may be collected at the direction of the state health department.

- Demographic information
  - Name
  - Address
  - State of residence
  - Date of birth
  - Age
  - Ethnicity
  - Race
  - Occupation
- Reporting source
  - County
  - Earliest date reported

- Clinical
  - Hospitalization and duration of stay
  - Date of onset of symptoms
  - Type of tetanus disease
  - Wound location and management, including receipt of a tetanus toxoid-containing vaccine or TIG
  - Complication and intensive care treatment
  - Pre-existing conditions (e.g., diabetes, chronic otitis media)
  - Outcome (patient survived or died)
  - Date of death
- Treatment
  - Prophylaxis with tetanus toxoid-containing vaccine and TIG
  - Date started
- Vaccine Information
  - Dates of vaccination (prior tetanus toxoid-containing vaccine history)
  - Time since last dose of tetanus toxoid-containing vaccine
  - Maternal vaccination (for neonatal cases)
- Epidemiologic
  - Risk factors for disease (e.g., history of a wound or injury, recent injection drug use, tattooing, or body piercing)
  - For neonatal cases, maternal country or origin and number of years of residence in the United States

## IX. Vaccination

Numerous formulations of tetanus toxoid–containing vaccines are available in the United States. Tetanus and diphtheria toxoids and acellular pertussis (DTaP) and diphtheria and tetanus toxoids (DT) are licensed for infants and children younger than 7 years of age; and tetanus and diphtheria toxoids (Td) and tetanus toxoid (TT) are licensed for children 7 years of age and older and adults. Two tetanus and diphtheria toxoids and acellular pertussis formulation for adolescents and adults (Tdap) were licensed in 2005. Tetanus and diphtheria toxoids and whole-cell pertussis (DTP) vaccine is no longer available for use in the United States. Other pediatric combination vaccines containing tetanus and diphtheria toxoids and acellular pertussis along with other antigens are also available.

Primary tetanus vaccination with DTaP is recommended for all infants and children aged 6 weeks through 6 years who do not have contraindications.[15] DTaP is the preferred vaccine for all doses in the vaccination series (including completion of the series for children who have received one or more doses of whole-cell DTP). Primary vaccination with the DTaP series consists of a three-dose series, administered at ages 2, 4, and 6 months, with a minimum interval of 4 weeks between each of the first three doses. The fourth (first booster) dose is recommended at 15–18 months of age to maintain adequate immunity during preschool years. The fourth dose should be administered 6 months or more after the third dose. If the interval between the third and fourth doses is at least 6 months and the child is unlikely to return for a visit at the recommended age, the fourth dose of DTaP may be administered as early as age 12 months. The fifth (second booster) dose is recommended for children aged 4–6 years to confer continued protection against disease during the early years of schooling. A fifth dose is not necessary if the fourth dose in the series is administered on or after the fourth birthday. Adolescents and adults with a history of incomplete or unknown tetanus vaccination should receive a series of three vaccinations. The preferred schedule is a dose of Tdap, followed by a dose of Td at least 4 weeks after Tdap, and another dose of Td 6–12 months later.[16, 17]

Routine tetanus booster vaccination is recommended for adolescents and adults every 10 years. A single dose of Tdap is recommended for adolescents at age 11–18 years if they have not previously received Tdap.[16] A single dose of Tdap is also recommended for adults age 19 years and older who have not previously received Tdap, to replace the next Td. Adults should receive Td at least every 10 years thereafter.[19] The appropriate use of tetanus toxoid and TIG in wound management (Table 1) is also important for the prevention of tetanus.[16–18]

**Table 1. Guide to tetanus prophylaxis in routine wound management**

| History of adsorbed tetanus toxoid (doses) | Clean minor wounds | | All other wounds* | |
|---|---|---|---|---|
| | Tdap or Td† | TIG§ | Tdap or Td† | TIG§ |
| <3 or unknown | Yes | No | Yes | Yes |
| ≥ 3 doses¶ | No** | No | No†† | No |

* *Such as (but not limited to) wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite.*

† *For children younger than 7 years of age, DTaP is recommended; if pertussis vaccine is contraindicated, DT is given. For persons 7–9 years of age, Td is recommended. For persons >10 years, Tdap is preferred to Td if the patient has never received Tdap and has no contraindication to pertussis vaccine. For persons 7 years of age or older, if Tdap is not available or not indicated because of age, Td is preferred to TT.*

§ *TIG is human tetanus immune globulin. Equine tetanus antitoxin should be used when TIG is not available.*

¶ *If only three doses of fluid toxoid have been received, a fourth dose of toxoid, preferably an adsorbed toxoid, should be given. Although licensed, fluid tetanus toxoid is rarely used.*

** *Yes, if it has been 10 years or longer since the last dose.*

†† *Yes, if it has been 5 years or longer since the last dose. More frequent boosters are not needed and can accentuate side effects.*

## X. Enhancing Surveillance

A number of specific activities can improve the detection and reporting of tetanus cases and the comprehensiveness and quality of reporting. Additional activities are listed in Chapter 19, "Enhancing Surveillance."

### *Promoting awareness*

Efforts should be made to promote awareness among physicians and infection control practitioners of the need to report suspected cases of tetanus promptly. The completeness of reporting of tetanus mortality to CDC has been estimated at 40%, and completeness of reporting for tetanus morbidity may be even lower.[19] Lack of direct benefits, administrative burdens, and a lack of knowledge of reporting requirements are all thought to contribute to incomplete reporting of infectious diseases by physicians and other healthcare providers.

### *Providing feedback*

National and statewide surveillance data concerning tetanus should be regularly shared with infection control nurses, hospital epidemiologists, neurologists, and other clinicians; all should be regularly updated concerning reporting requirements. Feedback should also be provided to the persons who reported the cases. Representatives from state and local health departments should attend meetings of infection control nurses and other scientific gatherings to share surveillance data and to discuss the quality and usefulness of surveillance.

### *Review of mortality data*

Mortality data are available through the vital records systems in all states, and they may be available soon after deaths occur in states using electronic death certificates. Although the number of tetanus cases in the United States is small, each is important and warrants a full investigation. Mortality data should be reviewed each year to identify deaths that may be due to tetanus. Any previously unreported cases identified through this review should be reported. Nationally, the completeness of reporting of tetanus deaths to the vital records system is estimated at 60%.[19]

## XI. Case Investigation

The Tetanus Surveillance Worksheet (Appendix 18) may be used as a guideline for the investigation, with assistance from the state health department. At the direction of the state health department, additional assistance may be obtained from the Meningitis and Vaccine-Preventable Diseases Branch, National Center for Immunization and Respiratory Diseases, CDC (404-639-3158).

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# Chapter 17: Varicella

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## I. Disease Description

Varicella (chickenpox) is a febrile rash illness resulting from primary infection with the varicella-zoster virus (VZV). Humans are the only source of infection for this virus. Varicella is highly infectious, with secondary infection occurring in 61%–100% of susceptible household contacts.[1–5] Transmission occurs from person to person by direct contact with persons with either varicella or herpes zoster (shingles) lesions or by airborne spread from respiratory secretions or lesions of persons with chickenpox. The incubation period for varicella is 10–21 days, most commonly 14–16 days. Varicella is characterized by a pruritic, maculopapular vesicular rash that evolves into noninfectious dried crusts over a 5- to 6-day period.[6]

Varicella severity and complications are increased among immunocompromised persons, children younger than 1 year of age, and adults.7–10 However, healthy children and adults may also develop serious complications and even die from varicella.[8–15] Severe complications include secondary bacterial infections (most notably those caused by group A beta-hemolytic *Streptococcus*, e.g., cellulitis, necrotizing fasciitis, septicemia, and toxic shock syndrome), pneumonia, encephalitis, cerebellar ataxia, Reye syndrome, and death.[7]

Congenital varicella syndrome, characterized by hypoplasia of an extremity, skin abnormalities, encephalitis, microcephaly, ocular abnormalities, mental retardation, and low birth weight, may occur among 0.4%–2.0% of infants born to women infected with varicella during the first or second trimester of pregnancy.[16–18] Infants born to women who develop varicella within the period of 5 days before delivery to 2 days after delivery are at risk of neonatal varicella, which may be severe.

Immunity following varicella infection is considered to be long-lasting and second cases of varicella are thought to be rare. However, second cases may occur more commonly among immunocompetent persons than previously considered.[19, 20]

VZV remains in a latent state in human nerve tissue and reactivates in approximately one in three infected persons during their lifetime, resulting in herpes zoster.[21, 22, 23] Herpes zoster usually presents as a vesicular rash with pain and itching in a dermatomal distribution. Herpes zoster incidence increases with increasing age, especially after age 50, is more common among immunocompromised persons, and among children with a history of intrauterine varicella or varicella occurring within the first year of life; the latter have an increased risk of developing herpes zoster at an earlier age.[24–26] A decline or a relative absence of cell-mediated immunity is considered to be an important factor in development of herpes zoster in these groups. A zoster vaccine (Zostavax™, Merck & Co., Inc.) is licensed and recommended for adults 60 years of age and older in the United States.[23]

## II. Background

Before the availability of varicella vaccine in the United States, almost everyone had varicella. Thus, the number of cases approximated the birth cohort over time, and in the early 1990s (the prevaccine era) this resulted in an average of 4 million cases of varicella, 10,500–13,000 hospitalizations (range, 8,000–18,000), and 100–150 deaths each year.[10, 27-30] Varicella affected mainly children, with approximately 90% of cases occurring before the age of 15 years. In the 1970s and 1980s, the highest rates of disease were among children 5–9 years of age, followed closely by children 1–4 years of age.[8] In the 1990s, the highest rate of disease was reported in the preschool age group. This might have been due to increasing attendance at child care and preschool.[31-32]

Varicella vaccine was licensed in 1995. Two doses are now recommended for routine use, with the first dose given to infants 12–15 months of age and the second dose to children 4–6 years of age. Persons 13 years of age and older without evidence of immunity to varicella should also routinely receive two doses of varicella vaccine 4–8 weeks apart.[33] One-dose varicella

vaccination coverage among children 19–35 months of age was 89.6% nationally in 2009, with state and city estimates ranging from 76% to 95%.[34] In active surveillance areas, varicella vaccination coverage among children age 19–35 months has risen to 92%, and varicella disease incidence declined approximately 90% from 1995 to 2005.[35] Among the states that in the prevaccine era consistently reported a high proportion of varicella cases to the National Notifiable Disease Surveillance System (NNDSS) relative to their birth cohort (West Virginia, Illinois, Texas, and Michigan), a 41% to 81% decline in cases has been reported as of 2009. In reports of varicella as the underlying cause of death, national varicella mortality rates among children younger than 10 years of age declined by 90% comparing the period of 1990-1994 to 1999-2001.[36] During 2000-2006, national varicella-related hospitalization rates declined by 71% compared with rates during the period 1988–1995.[37]

Although increased vaccination of children has lowered the overall burden of disease, a higher proportion of reported cases now occur among older children, adolescents, and adults who may have escaped varicella disease or vaccination. As vaccination rates have increased, the majority of varicella cases now occur among vaccinated persons. Cases of varicella in vaccinated persons (i.e., breakthrough cases) are generally much milder, often with fewer than 50 lesions and fewer vesicles compared with 300 or more lesions and many vesicles typically seen in unvaccinated persons. Persons with breakthrough cases are also less likely to have fever and more likely to have fewer days of illness.[38] Given its modified clinical presentation, breakthrough varicella illness can be challenging for practitioners and parents to recognize clinically.

## III. Importance of Rapid Case Identification

Reporting of varicella cases in child care centers, schools, institutions, military barracks and other group settings will facilitate public health action and outbreak control. In addition, in certain high-risk settings (e.g., hospitals and other healthcare settings, schools that may have students who are immunocompromised), rapid case identification and public health action are important to prevent infection of susceptible persons at high risk for serious complications of varicella, such as immunocompromised persons and pregnant women, and susceptible individuals for whom varicella vaccine is contraindicated.[33]

## IV. Importance of Surveillance

Surveillance data are needed to

1. document and monitor the impact of a vaccination program on disease incidence, morbidity, and mortality;
2. evaluate the effectiveness of prevention strategies; and
3. evaluate vaccine effectiveness under conditions of routine use.

With vaccine coverage increasing and the disease burden declining, varicella disease surveillance is especially important to monitor changes in varicella epidemiology. All states should establish or enhance varicella case-based surveillance to monitor these changes. Surveillance data will be used to assess progress towards the year 2020 disease reduction goals, and determine whether any improvements to the vaccination policy are needed. *Healthy People 2020* goals for varicella include a greater than 80% reduction in the estimated number of varicella cases among children < 18 years of age compared to 2008, greater than 90% vaccine coverage among children 19–35 months, greater than 95% vaccination coverage with 2 doses of varicella vaccine among children in kindergarten, and greater than 90% 2-dose vaccine coverage among adolescents.[39]

## V. Case Definition

The following case definitions were approved by the Council of State and Territorial Epidemiologists (CSTE) for varicella cases in June 1999 with an update in June 2009 [40-41] and varicella deaths in 1998.[42]

### Varicella clinical case definition

An illness with acute onset of diffuse (generalized) maculopapulovesicular rash without other apparent cause. In vaccinated persons who develop varicella more than 42 days after vaccination (breakthrough disease), the disease is usually mild with fewer than 50 skin lesions and shorter duration of illness. The rash may also be atypical in appearance (maculopapular with few or no vesicles).

### Laboratory criteria for diagnosis

- Isolation of varicella-zoster virus (VZV) or demonstration of VZV DNA by direct fluorescent antibody (DFA) or by polymerase chain reaction (PCR) tests from a clinical specimen, ideally scabs, vesicular fluid, or cells from the base of a lesion [See the following website for more details: http://www.cdc.gov/shingles/lab-testing/index.html.] These tests are also useful for diagnosing breakthrough disease (Table 1).
- Positive serologic test for varicella-zoster IgM antibody using a capture assay
- Fourfold or greater rise in serum varicella IgG antibody titer by any standard serologic assay

For both unvaccinated and vaccinated persons, DNA detection methods (PCR, DFA) and culture are the methods of choice for laboratory confirmation. Of these, **PCR is the most reliable and sensitive method for confirming infection.**

In unvaccinated persons, experience is limited with IgM antibody tests and with timing of the IgM response. In vaccinated persons, even less experience with serologic methods for laboratory confirmation is available. Therefore, DNA detection methods are the laboratory methods of choice for diagnosis. A negative IgM result should not be used to rule out the diagnosis. A positive IgM in the absence of rash should not be used to confirm a diagnosis. A fourfold rise in IgG antibody may not occur in vaccinated persons.

### Varicella case classification

**Probable:** A case that meets the clinical case definition, is not laboratory confirmed, and is not epidemiologically linked to another probable or confirmed case.

**Confirmed:** A case that meets the clinical case definition and is laboratory confirmed or is epidemiologically linked to a confirmed or a probable case.

***Note:*** *Two probable cases that are epidemiologically linked are considered confirmed, even in the absence of laboratory confirmation.*

### Varicella deaths case classification

**Probable:** A probable case of varicella that contributes directly or indirectly to acute medical complications that result in death.

**Confirmed:** A confirmed case of varicella that contributes directly or indirectly to acute medical complications that result in death.

### Other definitions

**Varicella-like (vaccine) rash:** A varicella-like rash in a recently vaccinated person that may be caused by either wild- or vaccine-type virus. Approximately 4% of children receiving varicella vaccine (compared with 2% of placebo recipients) develop a generalized rash with a median of five lesions 5–26 days postvaccination, and 4% develop a localized rash with a median of two lesions 8–19 days postvaccination.[43] The rash may be atypical in appearance (maculopapular with no vesicles). Approximately 2% of children who received a placebo in the clinical trials also developed generalized rashes, some of which were varicella-like, indicating that not all rashes following vaccination are attributable to the vaccine.[43] Rash occurring within 2 weeks of or more than 42 days after vaccination are more likely to be wild-type virus, and rash occurring 15–42 days postvaccination are more likely to be vaccine-type virus.[44] Attribution of disease to vaccine strain VZV can only be confirmed by strain differential real-time PCR or by PCR combined with restriction fragment length polymorphism (RFLP) analysis.

**Breakthrough disease:** A case of wild-type varicella infection occurring more than 42 days after vaccination. Such disease is usually mild with a shorter duration of illness, fewer constitutional symptoms, and fewer than 50 skin lesions. Breakthrough cases with fewer than 50 lesions have been found to be one third as contagious as varicella in unvaccinated persons with 50 or more lesions, but breakthrough cases with 50 or more lesions can be just as contagious as cases in unvaccinated persons.[45]

**Secondary transmission of vaccine virus:** A varicella-like rash occurring 10–21 days after exposure to a person recently vaccinated. It is extremely rare. Since 1995, only eight secondary cases of transmission of vaccine virus from seven vaccinees have been documented with the varicella (Oka/Merck) vaccine, five of which occurred in e immunocompetent people. Most secondary transmissions occur from vaccine recipients who develop at least a limited rash illness. One case of secondary transmission was reported from a woman vaccinated post-partum who developed no vaccine rash to her infant. All laboratory-confirmed cases of Oka vaccine secondary transmission have resolved without complications. Transmission of vaccine strain VZV can only be confirmed by strain differential real-time PCR or by PCR combined with restriction fragment length polymorphism analysis. In addition to these episodes, there have been two reports of transmitted vaccine virus from herpes zoster that occurred 5 months after varicella vaccination.

### *Evidence of immunity to varicella*

Evidence of immunity to varicella includes any of the following:[34]

1. Documentation of age-appropriate vaccination
   - Preschool-aged children 12 months of age or older: 1 dose
   - School-aged children, adolescents, and adults: 2 doses
   - For children younger than 13 years of age, the minimum interval between the two doses is 3 months. However, if the child received the first dose before age 13 years and the interval between the two doses was at least 28 days, the second dose is considered valid.
2. Laboratory evidence of immunity or laboratory confirmation of disease
   - Commercial assays can be used to assess disease-induced immunity, but they lack sensitivity to always detect vaccine-induced immunity (i.e., they may yield false-negative results).
3. Born in the United States before 1980
   - For healthcare workers, immunocompromised persons, and pregnant women, birth before 1980 should not be considered evidence of immunity.
4. A healthcare provider diagnosis of varicella or verification of history of varicella disease
   - Verification of history or diagnosis of typical disease can be done by any healthcare provider (e.g., school or occupational clinic nurse, nurse practitioner, physician assistant, physician). For persons reporting a history of or presenting with atypical and/or mild cases, assessment by a physician or designee is recommended and either one of the following should be sought: a) an epidemiologic link to a typical varicella case or laboratory-confirmed case, or b) evidence of laboratory confirmation, if testing was performed at the time of acute disease. When such documentation is lacking, persons should not be considered as having a valid history of disease, because other diseases may mimic mild, atypical varicella.
5. History of herpes zoster based on healthcare provider diagnosis.

## VI. Laboratory Testing

As varicella disease has declined with introduction of vaccine, the need for laboratory confirmation has grown because fewer physicians have direct experience with breakthrough infections, which are often atypical in appearance, result in fewer lesions, and may lack characteristic vesicles. Varicella hospitalizations and deaths, as well as other severe or unusual disease, should routinely be laboratory confirmed. Postvaccination situations for which specimens should be tested include 1) rash with more than 50 lesions occurring 7 to 42 days

after vaccination; 2) suspected secondary transmission of the vaccine virus; 3) herpes zoster in a vaccinated person; or 4) any serious adverse event. In an outbreak, it is recommended that three to five cases be confirmed, regardless of vaccination status. The preferred diagnostic tests to confirm varicella infection include DNA detection methods for virus identification. For additional information on laboratory support for vaccine-preventable disease surveillance, see Chapter 22, "Laboratory Support for Surveillance of Vaccine-Preventable Diseases."

### Specimen collection

Skin lesions are the preferred specimen for laboratory confirmation of varicella disease. Blood specimens are preferred to test for varicella immunity. Specimens from skin lesions are best collected by unroofing a vesicle, preferably a fresh fluid-filled vesicle, and then rubbing the base of a skin lesion with a polyester swab. Scabs from skin lesions are also optimal specimen types for PCR detection of VZV DNA. Other specimen sources such as nasopharyngeal secretions, saliva, blood, urine, bronchial washings, and cerebrospinal fluid are considered less desirable sources than vesicular fluid and skin lesions since they are less likely to give positive results. Collecting skin lesion specimens from breakthrough cases can be especially challenging because the rash is often maculopapular with few or no vesicles. A video demonstrating the techniques for collecting various specimens for varicella confirmation, including specimens from breakthrough cases, can be found at http://www.cdc.gov/shingles/lab-testing/collecting-specimens.html#video. Additional information about collecting and submitting specimens for testing can be found on the CDC shingles web site or by calling the National VZV laboratory at 404-639-0066 or 404-639-2192 or emailing dds1@cdc.gov or kjr7@cdc.gov.

### Virus isolation and identification

Table 1 provides a summary of the laboratory tests used for varicella, the types of specimens appropriate for each test, and comments about the tests. Further details about the most commonly used laboratory tests for varicella are provided below.

**Rapid varicella zoster virus identification:**

- **PCR.** PCR is the method of choice for rapid clinical diagnosis. This test is sensitive, specific, and widely available. Results are available within several hours. PCR is a powerful technique that permits the rapid amplification of specific sequences of viral DNA that would otherwise be present in clinical specimens at concentrations well below detectable limits.
- **DFA.** If PCR is not available, the DFA test can be used, although it is less sensitive than PCR and requires more meticulous specimen collection and handling. A vesicle should be unroofed and scrubbed with sufficient vigor to ensure that cellular matter is collected at the base. Care must also be taken to avoid bleeding from the lesion as serum antibodies can interfere with the test and generate false-negative results. Crusts from lesions are not suitable for use with DFA.

Because viral DNA persists after cessation of viral replication or after viral death, DFA or PCR may be positive when viral cultures are negative.

**Virus strain identification:** Methods are available in specialized laboratories to identify VZV strains and distinguish wild-type VZV from the vaccine (Oka/Merck) strain. Such testing is used in situations when it is important to distinguish wild-type from vaccine-type virus, e.g., in suspected vaccine adverse events. The National VZV Laboratory at CDC has the capacity to distinguish wild-type VZV from Oka strain using both strain differential real-time PCR or PCR combined with restriction fragment length polymorphism analysis.

**Virus culture:** The diagnosis of VZV infection may be confirmed by culture (isolation) of VZV. Newer, more sensitive and rapid culture techniques can provide results within 2–3 days, although they are less sensitive than PCR. Infectious VZV is usually recoverable from fluid from varicella lesions for 2–3 days and from zoster lesions for 7 days or longer. VZV may be cultured from other sites such as blood and cerebrospinal fluid, especially in immunocompromised patients. Viable VZV cannot be recovered from crusted lesions.

**Serologic testing:** Serologic tests are available for confirmation of disease. They include capture IgM or fourfold rise from acute- and convalescent-phase IgG antibodies to VZV. Testing using commercial kits for IgM antibody is not recommended because available methods lack sensitivity and specificity; false-positive IgM results are common in the presence of high IgG levels. The National VZV Laboratory at CDC has developed a reliable IgM capture assay. Paired IgG acute- and convalescent-phase antibody tests are used in situations of mild or atypical presentation of disease when immediate therapy is not indicated and when, for clinical reasons, a confirmed diagnosis of the acute illness is important, e.g., a suspected second infection due to varicella. In addition, the laboratory at CDC has developed an IgG avidity assay, which can be used to identify recent primary VZV infection using a single VZV IgG-seropositive serum specimen.

Single serologic IgG tests may be used to determine the immune status of persons whose history of varicella is negative or uncertain and who may be candidates for varicella zoster immune globulin (VZIG) or vaccination. Commercial ELISAs are recommended for the purpose of screening.[46] Routine testing for varicella immunity following vaccination is not recommended. Commercially available serologic IgG tests are not sufficiently sensitive to detect low levels of antibody following vaccination. There is evidence to suggest that the latex agglutination method, another method to test for serologic IgG, may result in false-positive results that could mistakenly categorize a susceptible person as immune.[47]

**Table 1. Laboratory tests available for varicella confirmation**

| Test | Specimen | Comments |
|---|---|---|
| Tissue culture | Vesicular fluid; biopsy specimens from sterile sites (e.g., CSF, joint fluid) | Used to detect VZV. Can be expensive. Limited availability. Requires up to a week for result. |
| PCR | Vesicular swabs or scrapings; scrapings from maculopapular lesions; scabs from crusted lesions; biopsy tissue | Very sensitive and specific for detecting VZV. Real-time methods (not widely available and require special equipment) have been designed that distinguish vaccine strain from wild-type. Results rapidly available (within 3 hours). |
| DFA | Vesicle scraping; swab of lesion base (must include cells) | Identify VZV. More rapid and sensitive than culture. Less sensitive than PCR. |
| Tzanck smear | Vesicle scraping; swab of lesion base (must include cells) | Detects multinucleated giant cells with inclusions. Diagnostic of alpha herpes viruses (VZV, herpes simplex viruses). Less sensitive than DFA. |
| Capture IgM | Acute or convalescent serum specimens for VZV IgM | Specific. IgM inconsistently detected. Not reliable method for routine confirmation, especially in vaccinated persons, but positive result indicates current/recent VZV immune response. However, positive results in the absence of clinical disease would not be considered confirmation of active varicella disease. Requires special equipment. |
| EIA | Acute and convalescent serum specimens for VZV IgG | Requires special equipment. Specific but may not be sensitive enough to identify vaccine-induced immunity. |
| LA | Acute and convalescent serum specimens for VZV IgG | Rapid (15 min). No special equipment needed. More sensitive but less specific than EIA. Can produce false-positive results. |
| IFA | Acute and convalescent serum specimens for VZV IgG | Requires special equipment. Good sensitivity, specificity. |
| gpELISA | Acute and convalescent serum specimens for VZV IgG | Highly specific and sensitive but not widely or commercially available. Suitable for evaluation of vaccine seroconversion. |
| FAMA | Acute and convalescent serum specimens for VZV IgG | Highly specific and sensitive but not widely or commercially available. Suitable for evaluation of vaccine seroconversion. |

**Abbreviations:** *CSF, cerebrospinal fluid; VZV, varicella-zoster virus; PCR, polymerase chain reaction; DFA, direct fluorescent antibody; EIA, enzyme immunoassay; LA, latex agglutination; IFA, indirect fluorescent antibody; gpELISA, glycoprotein-based enzyme-linked immunosorbent assay; FAMA, fluorescent antibody to membrane antigen.*

## VII. Reporting

Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[48] These regulations and laws list the diseases to be reported and describe those persons or institutions responsible for reporting, including healthcare providers, hospitals, laboratories, schools, child care facilities, and other institutions. Persons reporting should contact the state health department for state-specific reporting requirements.

### *Varicella deaths*

In 1998, the Council of State and Territorial Epidemiologists recommended that varicella-related deaths be placed under national surveillance,[42] and varicella-related deaths became nationally notifiable on January 1, 1999.

Varicella deaths can be identified through death certificates, which may be available through state vital records systems and may be more readily available soon after death in states using electronic death certificates. State public health departments may also request that local health departments, healthcare practitioners, and hospitals report varicella deaths that occur in their community.

Because varicella is preventable with vaccine, all deaths due to varicella should be investigated. Investigation may provide insight into risk factors for varicella mortality and may help identify missed opportunities for, and barriers to, vaccination. A worksheet is provided to guide varicella death investigations (see Appendix 19). Deaths should be reported to CDC/NCIRD/DVD/Epidemiology Branch (404-639-8230) and to NNDSS via the National Electronic Telecommunications Surveillance System (NETSS) or the National Electronic Disease Surveillance System (NEDSS), when available.

The following data are epidemiologically important and should be collected in the course of a death investigation. Additional information may be collected at the direction of the state health department.

- Demographic information
  - Name
  - Address
  - Date of birth
  - Age
  - Sex
  - Ethnicity
  - Race
  - Country of birth
  - Date of death
- Medical history
  - Pre-existing medical conditions
  - History of varicella (to distinguish varicella from herpes zoster)
  - Medications
- Vaccination status
  - Number of doses of varicella or herpes zoster vaccine
  - Date(s) of vaccination
  - Type and manufacturer of vaccine
  - If not vaccinated, reason

- Clinical data
  - Date of rash onset
  - Hospitalization, date of hospital admission
  - Postmortem examination results
  - Death certificate diagnoses
- Complications
  - Pneumonia
  - Infections (e.g., invasive group A beta-hemolytic streptococcal [GAS], cellulitis, sepsis, necrotizing fasciitis, other)
  - Encephalitis
  - Neurologic condition (specify)
  - Hemorrhagic condition (specify)
  - Reye syndrome
- Treatment
  - Medications given (e.g., antiviral drugs, VZIG, aspirin, nonsteroidal anti-inflammatory drugs)
  - Duration of therapy
- Laboratory information
  - Virus isolation test dates and results
  - PCR test dates and results
  - DFA test dates and results
  - Serology test dates and results
- Epidemiologic information
  - Transmission setting
  - Source of transmission (e.g., age, vaccination status, relationship to decedent)

### *Varicella case reporting*

In 2002, CSTE recommended that varicella be included in NNDSS. All states were encouraged to conduct ongoing varicella surveillance to monitor vaccine impact on morbidity.[49] States are encouraged to report varicella cases to NNDSS via NETSS or NEDSS. As of 2010, 36 states were conducting case-based varicella surveillance. Persons reporting should contact the state health department for state-specific reporting requirements.

**Individual case reporting:** States not conducting case-based surveillance are encouraged to progressively implement individual case reporting. This can be done by establishing statewide or sentinel surveillance. Statewide surveillance involves adding varicella to the list of notifiable diseases that are reported to the state health department. Sentinel site surveillance involves identifying sites such as schools, child care centers, physicians' practices, hospitals, colleges, and other institutions to perform surveillance for varicella. Sentinel sites can be limited to a geographic area, such as a county or city, or selected to be representative of the entire state population. States may also consider requesting reports from sites that already participate in other surveillance networks. Some states have initiated surveillance using sentinel or school-based surveillance even though statewide case reporting is not required. States can expand their number of sites as they develop their system with the intention of eventually having statewide surveillance.

The following data are epidemiologically important and should be collected in the course of a case investigation. Additional information may be collected at the direction of the state health department.

- Age—to monitor the impact of vaccination on disease reduction in specific age groups and any shift in disease to older persons.

- Varicella vaccination status—to determine the proportion of cases occurring in vaccinated persons and assess crude vaccine effectiveness.
- Number of varicella vaccine doses received – to monitor number of cases with one, two, or no doses of vaccine.
- Severity of disease—to assess the severity of varicella in vaccinated persons, to monitor the impact of vaccination on disease severity, and to determine if vaccine-induced immunity wanes over time (based on number of lesions)
  - Number of lesions:
    - Mild: fewer than 50 lesions
    - Mild/moderate: 50–249 lesions
    - Moderate: 250–499 lesions
    - Severe: 500 or more lesions or any complications such as bacterial superinfection, varicella pneumonitis, encephalitis, hospitalization, or death.
  - Hospitalization

Additional information to collect can include the following:

- Demographic information
  - Name
  - Address
  - Date of birth
  - Sex
  - Ethnicity
  - Race
  - Country of birth
- Reporting source
  - County
  - Earliest date reported
- Clinical data
  - Pre-existing medical conditions
  - History of varicella (to distinguish varicella from herpes zoster or to document reported second infections)
  - Medications
  - Dates of rash onset
  - Duration of rash
  - Symptoms and date of onset
  - Complications
- Vaccination status
  - Date(s) of vaccination
  - Type and manufacturer of vaccine
  - Vaccine lot number
  - If not vaccinated, reason
- Outcome (patient survived or died)
  - Date of death
- Epidemiologic data
  - Transmission setting
  - Source of transmission
  - Vaccination status of source patient

- Laboratory information
  - Virus isolation test dates and results
  - PCR test dates and results
  - DFA test dates and results
  - Serologic test dates and results

CDC has designed a worksheet to provide guidance for individual varicella case investigations (see Appendix 20).

### *Varicella Outbreaks*

Although varicella outbreaks are not nationally notifiable, states are encouraged to report varicella outbreaks to CDC on an annual basis. The information is important for understanding the epidemiology of varicella and monitoring the impact of the routine two dose varicella vaccination program. An example of the varicella outbreak reporting worksheet can be found online here (http://www.cdc.gov/vaccines/vpd-vac/varicella/outbreaks/appx.htm#a). Reporting worksheets can be faxed to CDC/NCIRD/DVD/Epidemiology Branch (404-639-8665)

The following data are epidemiologically important. Additional information may be collected at the direction of the state health department.

- Outbreak setting
- Outbreak duration
- Outbreak size (i.e., # varicella cases)
- Ages of cases
- Vaccination status of cases
- Number of laboratory confirmed cases

## VIII. Vaccination

Two varicella-containing vaccines are now available in the United States. The live attenuated single-antigen varicella vaccine (Varivax®, Merck & Co., Inc.) was licensed in March 1995. A combination varicella-containing vaccine, Measles, Mumps, Rubella, Varicella (MMRV) (ProQuad®, Merck & Co., Inc.), was licensed in 2005 for use in children 12 months through 12 years of age. Because of the thermolability of the vaccines, the manufacturer's requirements for maintaining the cold chain must be followed strictly. Vaccine that is not properly stored before administration could have suboptimal potency.[33, 50]

Prelicensure studies of one dose of varicella vaccine, using various vaccine formulations, showed vaccine efficacy ranging from 70% to 90% for all disease and greater than 95% for severe disease.[4, 51, 52] Postlicensure studies under conditions of community use have demonstrated vaccine effectiveness in the range of 80%–85% for prevention of all disease. However, several lower estimates (40%–59%), and some higher estimates (100%) have been reported.[53-59]

The efficacy of two doses of varicella vaccine was evaluated in a randomized clinical trial. Over a 10-year observation period, the estimated vaccine efficacy of two doses was 98.3% compared with 94.4% for one dose. The difference was statistically significant ($p<0.001$).[60] A second dose of vaccine reduced varicella attack rates by 3.3-fold.[60] A case control study evaluating the effectiveness of two doses found the 2-dose vaccine effectiveness to be 98.3% [61], similar to what was seen in the clinical trial. The two dose vaccine effectiveness estimate calculated from an outbreak investigation was found to be lower, 89%.[62] High two-dose vaccine coverage should greatly decrease outbreaks that have been reported among groups of school children with high vaccination coverage.

### *Recommendations for the use of varicella-containing vaccines*[33]

**Routine administration of two doses of live attenuated varicella virus–containing vaccine:**

- All children should routinely receive their first dose at 12–15 months of age. The second dose is recommended routinely when children are aged 4–6 years (i.e., before a child enters kindergarten or first grade), but can be administered at an earlier age provided the interval between the first and second dose is at least 3 months.
- Persons 13 years of age or older without evidence of varicella immunity should receive two doses of single-antigen varicella vaccine administered 4–8 weeks apart. Serologic testing of adults with an uncertain or negative history may be cost-effective.
- Healthcare workers without laboratory evidence of immunity to varicella, laboratory confirmation of disease, or provider-confirmed history of varicella or herpes zoster should receive two doses of varicella-containing vaccine.
- Documentation of vaccination or evidence of immunity to varicella should be required for children and adults entering or working in child care, school, college, other post–high school educational institutions, and healthcare settings.
- Second-dose catch-up varicella vaccination is recommended for children, adolescents, and young adults who previously received one dose.
- Prenatal assessment of women for evidence of varicella immunity is recommended. Upon completion or termination of their pregnancy, women without evidence of varicella immunity should receive a first dose of varicella vaccine before discharge from the hospital, birthing center, or healthcare facility. The second dose can be given 4 or more weeks after the first dose (e.g., at the postpartum visit). Postpartum vaccination need not be delayed because of breastfeeding.
- Asymptomatic or mildly symptomatic HIV-infected children in CDC clinical class N, A, or B with age-specific CD4+ T-lymphocyte counts of higher than 15% and without evidence of varicella immunity may receive two doses of single-antigen varicella vaccine 3 months apart. Data on the use of varicella vaccine in older HIV-infected persons are lacking. However, based on expert opinion, vaccination for HIV-infected adults with similar immune function should be considered.
- A two-dose vaccination policy is recommended for outbreak control. Persons without evidence of immunity or those who received one dose of varicella vaccine should be offered vaccine.

**Contraindications:**[33]

- Allergy to vaccine components.
- Altered T-cell immunity from a malignant condition, including blood dyscrasias, leukemia, lymphomas of any type, other malignant neoplasms affecting the bone marrow or lymphatic systems, or HIV, except as discussed above.
- For children receiving high doses of systemic steroids (i.e., at least 2 mg/kg prednisone) for 2 weeks or longer, vaccination should be delayed until steroid therapy has been discontinued for at least 1 month, in accordance with the recommendations of ACIP for live-virus vaccines.[63]
- Pregnancy. Varicella vaccination is contraindicated during pregnancy. Women should avoid pregnancy for 1 month after receiving a dose of varicella vaccine. If a pregnant woman is inadvertently vaccinated, the incident should be reported to the Varivax in Pregnancy Registry at 1-800-986-8999. In the first 10 years of data collection, no reported cases of congenital varicella syndrome or other patterns of birth defects have been reported, although an extremely low risk cannot be excluded.[64]

**Additional precautions:**

- Severe illness. Vaccination of persons with severe illness should be postponed until recovery.
- Because of the potential inhibition of the response to varicella vaccination by passively transferred antibodies, varicella vaccine should not be administered for 3-11 months, depending on dosage, after administration of blood (except washed red blood cells), plasma, or IG. In addition, varicella vaccine should not be administered for at least 5 months after administration of VZIG. Persons who have received varicella vaccine should not be given antibody-containing product for 2 weeks after vaccination unless the benefits exceed those of vaccination.
- Vaccination of leukemic children who are in remission and who do not have evidence of immunity to varicella should be undertaken only with expert guidance and with the availability of antiviral therapy in case complications occur.
- Salicylates (i.e., aspirin and related medications) should not be used for 6 weeks after receiving varicella vaccine because of the association between aspirin use and Reye syndrome following varicella disease.

## IX. Establishing or Enhancing Surveillance

Varicella surveillance is needed to facilitate public health action at the state and local level and to monitor the impact of the varicella immunization program. Several approaches may be used to monitor trends in varicella disease burden. States should consider their surveillance strengths and build varicella surveillance into an existing system where feasible.

### *Case investigation*

Although investigation of all cases of varicella may not be feasible in all settings in all states, action may be required to prevent transmission to persons without evidence of immunity to varicella who are at high risk of serious complications of varicella.[33] In addition, investigation is warranted in some specific circumstances, including deaths associated with varicella, cases with severe complications such as invasive group-A streptococcal infections, outbreaks involving exposure of persons without evidence of immunity to varicella who are at high risk of serious complications of varicella, and outbreaks in populations with high two-dose varicella vaccine coverage. For more information or for assistance with case, outbreak, and death investigations, the state health department should be contacted. Varicella postexposure prophylaxis of contacts should also be considered.[33]

### *Outbreak investigation*

Although varicella vaccination coverage has increased and disease incidence has declined, outbreaks of varicella continue to occur, increasingly among highly vaccinated populations. Elementary schools are now the most common sites for varicella outbreaks, although they continue to occur in daycare settings and in middle and high schools. Because younger children are targeted for vaccination, a higher proportion of older children and adolescents may have escaped exposure and vaccination at a younger age and thus be more vulnerable to disease. Additionally, despite low susceptibility among adults (generally less than 5%), outbreaks have been reported from a variety of adult settings, including correctional facilities, hospitals, military training facilities, refugee centers, immigration detention facilities, homeless shelters, other residential institutions, and cruise ships. Outbreak response is particularly important in settings that present the greatest risk for severe disease (e.g., healthcare settings). Additionally, with implementation of the two-dose varicella vaccine policy, investigations of outbreaks provide data to monitor the effectiveness of the varicella vaccination program.

Investigations of outbreaks of vaccine-preventable diseases help determine whether outbreaks are occurring because of failure of vaccine (lower than expected vaccine effectiveness) or failure to vaccinate (low vaccine coverage rates and therefore high susceptibility). Investigations of varicella outbreaks will

1. improve existing knowledge of the epidemiology of varicella;
2. identify virus transmission patterns;

3. describe disease burden;
4. determine risk factors for severe varicella;
5. provide additional estimates of varicella vaccine effectiveness; and
6. describe risk factors for vaccine failure.

Information about strategies for the investigation and control of varicella outbreaks can be found at: http://www.cdc.gov/vaccines/vpd-vac/varicella/outbreaks/manual.htm. Reporting of varicella outbreaks is also important to help monitor impact of the two dose varicella vaccination recommendation. A worksheet for reporting varicella outbreaks is available in Appendix 20.

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# Chapter 18: Surveillance Indicators

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## I. Role of Surveillance in Disease Elimination Programs

In routine disease control programs, traditional, passive disease surveillance systems are usually adequate to meet program demands despite their limitations. In contrast, in disease elimination or eradication programs, routine surveillance activities are inadequate once the goal is near. In advanced disease elimination and eradication programs, ***every case counts***. Without adequate surveillance, elimination of vaccine-preventable diseases cannot be achieved and sustained. This chapter describes the surveillance needs for diseases in various stages of prevention and control and discusses surveillance indicators that have been developed to evaluate the appropriateness, completeness, accuracy, and timeliness of surveillance systems.

Traditionally, communicable disease surveillance programs have relied on passive reporting, in which reports are received from physicians and other providers. For diseases and conditions for which laboratory confirmation is routinely obtained, laboratory-based reporting has virtually replaced traditional provider-based reporting in many jurisdictions, because case ascertainment is far more complete.[1, 2] However, even when supplemented by laboratory-based reports, reporting in traditional passive surveillance systems remains incomplete. Despite this limitation, these data remain useful because they are used primarily for monitoring trends in disease occurrence rather than for initiating public health action in response to each individual case.

In disease elimination programs, the role of surveillance is different. To achieve a goal of zero cases of a disease, aggressive efforts must be made to identify factors that allow cases to continue to occur despite the low incidence of disease. The occurrence of these cases may indicate the need for new prevention strategies, but in order to track the impact of any such strategies, surveillance data are essential. In addition, timely notification is necessary so that public health action can be taken to limit spread of disease.

This was illustrated during the global smallpox eradication program. The continued occurrence of cases of smallpox despite high vaccination coverage led to the development of a new strategy for smallpox eradication; i.e., a wide circle of contacts around each case-patient was identified and vaccinated, creating a wall of immunity around the remaining patients. This led ultimately to the global eradication of smallpox.[3] It could not have been achieved without recognition of the need for an additional strategy and without the ability to rapidly identify and respond to individual cases. Andrews and Langmuir wrote in 1963, "To achieve and maintain the eradication status of a specific disease within an area, it is necessary 1) to obstruct transmission until endemicity ceases, and 2) to prevent or nullify the reestablishment of the disease from carriers, relapsing cases, or imported sources of infection. Accordingly, an adequate surveillance organization must be developed to identify and cope with these threats to the achievement of disease eradication."[4]

## II. Development of Surveillance Indicators

Because of the essential role of surveillance in disease elimination, methods to monitor its quality were developed in 1988 by the Pan American Health Organization (PAHO) as part of the polio eradication effort in the Western Hemisphere. Surveillance indicators included measures of surveillance infrastructure (e.g., the number of reporting units reporting on a weekly basis), timeliness of notification (e.g., the interval between case onset and notification), adequacy of case investigation (e.g., the proportion of cases with appropriately timed laboratory specimens obtained), and timeliness of laboratory testing.[5] Although not generally done outside of evaluation projects in routine disease control programs, monitoring these attributes would undoubtedly provide useful information for any surveillance system. These attributes overlap with those recommended by CDC for evaluation of surveillance systems[6] (see Appendix 21).

### *Indicator of reporting completeness*

The unique requirements of surveillance in disease elimination programs led PAHO to also develop an indicator that allowed monitoring of the completeness of reporting. In disease elimination programs, it is critical to have some measure of the adequacy of case ascertainment as well as a measure of how well cases were investigated once they are reported as suspected cases. It is not sufficient to adequately investigate the reported cases if most of the cases are never reported. More importantly, as disease incidence declines, it becomes increasingly difficult to interpret the absence of reported cases. How can you tell if zero means zero? Does it mean there were no cases, or does it mean no one looked?

PAHO developed one successful strategy to address this problem during the polio eradication effort in Latin America. Surveillance was performed not for paralytic poliomyelitis but for a syndrome that includes both paralytic polio and other conditions, including Guillain-Barré Syndrome (GBS), among children younger than 15 years of age—that is, the surveillance system was organized to identify cases that were clinically consistent with polio (suspected cases), and then to track them as laboratory investigation was performed to either accept or rule out a diagnosis of polio due to wild poliovirus. If adequate laboratory testing was not obtained to definitively determine or rule out the diagnosis of polio, the case was classified as compatible and considered a failure of case investigation and surveillance. Because in the absence of polio, GBS and other conditions causing acute flaccid paralysis (AFP) in children occur at a fairly constant rate over time, the adequacy of ascertainment of suspected cases of polio could be monitored by tracking the incidence of AFP among children younger than 15 years of age. In countries or regions reporting rates of AFP of 1 per 100,000 children younger than 15 years of age and without confirmed or compatible cases of polio, one could be reasonably confident that the absence of reported cases of polio in fact meant the absence of polio. In contrast, if AFP rates were less than 1 per 100,000 among children in this age group, the absence of cases might reflect inadequate surveillance rather than the absence of polio. Monitoring the rate of AFP reporting in Latin America was a critical component of PAHO's effort to monitor the adequacy of polio surveillance. By tracking this closely at the regional and national level, investigators could identify and assist areas with inadequate surveillance and document resulting improvements.

Unfortunately, few other examples of vaccine-preventable diseases exist for which indicators analogous to the AFP rate are known. No external standard for determining the completeness of measles surveillance exists that would be equivalent to the rate of AFP in the surveillance of polio.[7]

While monitoring all cases of AFP is highly sensitive, it is not specific. Another part of the PAHO approach is essential—that is, classifying incompletely evaluated cases as "compatible." In a disease elimination program the aim is to capture all the true cases by having a case definition that is very sensitive; nonetheless, it is also important to exclude non-cases by adequate case investigation and laboratory testing. The PAHO strategy captured both these elements, enhancing sensitivity and specificity of the surveillance system.

## III. Surveillance Indicators in the United States

The purpose of vaccine-preventable disease surveillance indicators in the United States is to ensure adequate performance of the essential components of surveillance and case investigation, and to identify components of each that need improvement. Surveillance indicators for selected vaccine-preventable diseases were proposed by CDC and approved by the Council of State and Territorial Epidemiologists (CSTE) in 1994. Since then, the indicators have continued to evolve to maximize their usefulness. CDC currently monitors the following indicators on a regular basis.

### *Indicators for measles surveillance*

- The proportion of confirmed cases reported to the National Notifiable Disease Surveillance System (NNDSS) with complete information (clinical case definition, hospitalization, laboratory testing, vaccination history, date reported to health department, transmission setting, outbreak related, epidemiologic linkage, date of birth, and onset date)
- The interval between date of symptom onset and date of public health notification
- The proportion of confirmed cases that are laboratory confirmed
- The proportion of cases that have an imported source
- The proportion of cases for which at least one clinical specimen for virus isolation was submitted to CDC
- The number of discarded measles-like illness (MLI) reports (discontinued January 2006)

### *Indicators for mumps surveillance*

- The proportion of confirmed cases reported to NNDSS with complete information (clinical case definition, hospitalization, laboratory testing, vaccination history, date reported to health department, transmission setting, outbreak related, epidemiologic linkage, date of birth, and onset date)
- The interval between date of symptom onset and date of public health notification
- The proportion of confirmed cases that are laboratory confirmed
- The proportion of cases that have an imported source

### *Indicators for rubella surveillance*

- The proportion of confirmed cases reported to NNDSS with complete information (clinical case definition, hospitalization, laboratory testing, vaccination history, date reported to health department, transmission setting, outbreak related, epidemiologic linkage, date of birth, and onset date)
- The interval between date of symptom onset and date of public health notification
- The proportion of confirmed cases that are laboratory confirmed
- The proportion of cases that have an imported source
- The proportion of confirmed cases among women of child-bearing age with known pregnancy status

### *Indicators for* Haemophilus influenzae *type b invasive disease surveillance*

- The proportion of cases reported to NNDSS with complete information (clinical case definition—species, specimen type; vaccination history; and serotype testing)
- The proportion of cases among children younger than 5 years of age with complete vaccination history
- The proportion of cases among children younger than 5 years of age in which an isolate was serotyped

### *Indicators for pertussis surveillance*

- The proportion of cases reported to NNDSS with complete information (clinical case definition, complications, antibiotic treatment, laboratory testing, vaccination history, and epidemiologic data [e.g., outbreak/epidemiologic linkage])
- The interval between date of symptom onset and date of public health notification
- The proportion of cases meeting clinical case definition that are laboratory tested
- The proportion of case-patients with complete vaccination history

## IV. Additional Approaches and Future Directions

Although these indicators have proved useful for identifying major problems with case investigation and reporting, given the small number of cases of most vaccine-preventable diseases now reported in the United States, a critical issue remaining is the sensitivity of the surveillance system, i.e., does the absence of cases from a particular jurisdiction indicate that there were in fact no cases?

One approach to improving the completeness of reporting is to implement active surveillance, that is, to make contact and solicit reports from all providers and institutions responsible for reporting on a regular basis. Active surveillance has been shown to increase reporting of measles, rubella, salmonellosis, and hepatitis in demonstration projects but is generally too expensive to perform routinely.[8, 9]

Active surveillance is supported by the following assumptions:

- Cases are occurring in the community.
- Case-patients seek medical attention or otherwise come to the attention of institutions subject to reporting requirements.
- The condition is recognized by the provider or institution.
- Cases are not reported because filling out reporting forms or calling the health department is too much trouble.
- If the administrative reporting burden for providers is reduced, cases will be reported.

For rare diseases (i.e., most vaccine-preventable diseases in the United States) these conditions are rarely met. Indeed, previous demonstrations of the usefulness of active surveillance have focused on diseases that were relatively common or at least endemic in the population under surveillance. In many communities and states, no cases of measles or rubella have occurred in years, and in the absence of a large, ongoing outbreak, participating in active surveillance for these conditions is unlikely to be of much interest to providers.

As part of the polio eradication effort in the Western Hemisphere, PAHO instituted a system of weekly negative reporting that allowed them to monitor the surveillance infrastructure (i.e., the number of clinics and other facilities that participated in the surveillance system). Each reporting unit was to include in the weekly notifiable diseases report not only cases of disease identified, but for AFP only, a negative report if no cases were identified that week (i.e., "no cases of acute flaccid paralysis"). It was implicitly assumed that any such cases would be recognized because the patient would seek medical care. This was an attempt to gain the benefits of active surveillance within a passive surveillance system without the investment of resources needed to conduct active surveillance. However, an evaluation in one country suggested that at the local level, negative reporting was not accompanied by efforts at case finding, and substantial training was needed to make negative reporting meaningful at the local level.[10]

What approach can provide firm evidence that the absence of reported cases means the absence of disease in the population? Several methods may be useful: application of external standards, identification of imported cases, monitoring the level of reporting for suspected cases that are ruled out as cases by epidemiologic and laboratory investigation, monitoring diagnostic effort, and monitoring circulation of the organism.

### *External standards*

As discussed above, monitoring the rate of AFP among children younger than 15 years of age was found to be a powerful tool in ensuring the adequacy of surveillance during the polio eradication program in the Western Hemisphere. Unfortunately, a similar external standard does not exist for measles or for most other vaccine-preventable diseases. However, an external standard may exist for invasive disease due to *Haemophilus influenzae* type b. Data from an active laboratory-based surveillance system suggest that among children younger than 5 years of age, non–type b invasive disease occurs at a rate of about 1.6 per 100,000.[11] If this rate is relatively stable over time in different geographic areas, it can serve as an external standard for monitoring the quality of reporting of type b invasive disease. In 1991, *H. influenzae* invasive disease became nationally notifiable; cases caused by type b and non–type b strains are included in the NNDSS. Because invasive disease due to non-type b *H. influenzae* strains are not prevented by vaccination in any age group and because type b cases continue to occur among adults, the absence of reported cases of invasive *H. influenzae* disease of any type in any age group in a jurisdiction strongly suggests that surveillance is inadequate.

### *Identification of imported cases*

One indirect measure of the quality of case ascertainment at the national level is the demonstration that a surveillance system is sufficiently sensitive to detect imported cases. At the state level, if no importations are identified and reported, this may reflect either the absence of disease or the absence of effort to identify cases. Cases in persons who are not permanent residents of the United States are probably less likely to be reported and adequately investigated than cases in permanent residents for a number of reasons: visitors may not have access to medical care, may be only briefly in an area (making it difficult to complete an adequate case investigation), or may avoid contact with authorities if they are in the United States without appropriate documentation. Single cases of measles—usually with no or very little spread—are often reported, investigated, and confirmed in the United States.[12] In jurisdictions in which no US-acquired cases are reported, the demonstration of imported cases provides good evidence for a well-functioning surveillance system. This concept is listed as a measles surveillance indicator (the proportion of cases that have an imported source).

Endemic transmission of measles has been eliminated in the United States; evidence for this determination rests on the performance of the surveillance system.[13–15] Although measles is now rare throughout the Western Hemisphere, it is endemic in many countries of Western Europe and Asia. Endemic transmission of rubella has also been eliminated from the United States, although international importations continue to be identified. Importation of measles or rubella by travelers from foreign countries occurs frequently and is expected, especially from countries with endemic disease and substantial numbers of international travelers. Failure to detect such cases would suggest that, at the national level, surveillance is not sensitive enough to detect individual, US-acquired cases.

### *Monitoring cases that are ruled out*

Another approach to tracking the quality of case ascertainment is to track the number of cases of suspected disease that are reported, investigated, and ruled out as cases. This approach was employed by PAHO in the polio eradication program in the Western Hemisphere. Even though polio had become an extremely rare disease, suspected cases continued to be reported throughout the region and were aggressively evaluated, including obtaining appropriately timed laboratory specimens. In this way, thousands of cases were demonstrated not to be polio, providing a measurement of system performance. Likewise, cases of acute flaccid paralysis that were not adequately investigated were classified as compatible and indicated a failure of surveillance and case investigation.

In 1997, surveillance for discarded measles-like illness (MLI) was established and has been used to track the quality of measles surveillance and case investigation at the state level.[16] When such information was available, the simultaneous demonstration that 1) many cases were reported and 2) nearly all were ruled out as measles by appropriate investigation provided some assurance that efforts were being made to identify cases of measles and that once a case was reported, investigation was adequate. The assurance of the strength of the surveillance system provided support for the determination that indigenous transmission of measles had been eliminated in the Unites States.

With elimination of indigenous measles transmission in the United States, discarded MLI as a surveillance indicator was no longer useful and was discontinued in the United States as of January 1, 2006. Collection of MLI data was difficult in some areas, and it required collecting a good deal of information on cases that ultimately were ruled out, which, outside of special evaluation projects, might be considered an inappropriate use of limited resources. Also, in the United States, there is great variation in the delegation of responsibility for case investigation; in many states, it is delegated to city and county health departments. When cases were diagnosed at the local level and measles was almost always ruled out, requiring that every suspected case of measles be reported to the state was challenging. Therefore, although state-level staff may have recognized the usefulness of collecting this information as a performance measure, the necessary information may not have been available at their level. At present, without an external

standard, uncertainty remains regarding how many cases of suspected measles should be reported and investigated in a population in the absence of the introduction and circulation of measles virus.

### Monitoring diagnostic effort

Given the difficulties in collecting data on reported cases that are ruled out as cases, another approach to surveillance assessment could be to measure diagnostic effort. Diagnostic effort indicates the level of suspicion of a vaccine-preventable disease; if disease is suspected, appropriate laboratory testing should be done to confirm (or rule out) that suspicion. For example, this may be used for evaluation of pertussis surveillance; tracking the number of pertussis specimens submitted over time, even if none are positive, provides good evidence that the diagnosis is being considered even if no cases are found. A similar approach could be used for other vaccine-preventable diseases by tracking submission of laboratory requests for diagnostic testing (e.g., IgM antibody tests for measles, mumps, or rubella). If no testing is being done, no one is looking.

Consolidation of laboratory functions and development of standards and systems for electronic reporting of laboratory data make this approach feasible without developing new data collection systems. If testing occurs, the diagnosis is being considered, so the absence of reported cases is more likely to reflect the absence of disease. Without an external standard, how much testing is "enough" is still open to question, but this approach does capture those suspected cases that are evaluated in the private sector but are not reported as "suspected cases."

### Monitoring circulation of the organism

One adjunct to case surveillance is surveillance for the agent (the virus or bacterium that causes the disease). Molecular typing methods exist for measles, rubella, diphtheria, pertussis, and polio and have been used to supplement the information collected in case surveillance for all these diseases. Monitoring the organism can provide information about its origin, evidence of repeated introduction from multiple sources, and evidence of endemic transmission. For example, the demonstration of endemic transmission of multiple strains of toxigenic *Corynebacterium diphtheriae* in a Northern Plains Indian community provided evidence of an ongoing public health problem in the absence of reported cases.[17] Molecular epidemiology has also been critical in demonstrating the interruption of endemic transmission of measles in the United States and the increasing importance of importation of measles cases.[18] Similar methods applied to isolates of rubella virus from infants with congenital rubella syndrome and persons with rubella in the United States[19] have been instrumental in documenting the elimination of endemic transmission of rubella in this country.[20] Ultimately, as diseases progress toward eradication, monitoring circulation of the organism becomes an essential component of surveillance activities.

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# Chapter 19: Enhancing Surveillance

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## I. Surveillance Activities

Surveillance activities are critical to detecting vaccine-preventable diseases and gaining information to help control or address a problem. However, complete and accurate reporting of cases is dependent on many factors, such as reporting source, timeliness of investigation, and completeness of data. In addition, various methods for conducting surveillance are used to collect information, depending on disease incidence, specificity of clinical presentation, available laboratory testing, control strategies, public health goals, and stage of vaccination program. For vaccine-preventable diseases, passive surveillance is the most common method, although active surveillance may be needed in special surveillance situations. Active surveillance is often short-term and usually requires more funding than passive surveillance.

Common systems used for disease surveillance include national notifiable disease reporting; physician, hospital, or laboratory-based sentinel surveillance, and population-based surveillance.[1] Sentinel surveillance involves a limited number of recruited participants, such as healthcare providers or hospitals, that report specified health events that may be generalizable to the whole population.[2]

The National Notifiable Diseases Surveillance System (NNDSS)[3] is the passive surveillance system that includes all the diseases and conditions under national surveillance. Efforts are being made to integrate and enhance the surveillance systems for national notifiable diseases. A collaborative effort between CDC and state and local health departments is in progress to enhance surveillance system capabilities with the implementation of the National Electronic Disease Surveillance System (NEDSS).[4, 5, 6] NEDSS will eventually replace the National Electronic Telecommunications System for Surveillance (NETSS) and will become the electronic system used to report national notifiable diseases and conditions in the United States and territories.

Enhancing the surveillance system is only one part of improving surveillance data; data for notifiable diseases are still dependent on reporting, timeliness and completeness. This chapter outlines activities that may be useful at the state and local level to improve reporting for vaccine-preventable diseases. Some are more routinely used (encouraging provider reporting), while others, such as searching laboratory or hospital records, may be more helpful under certain circumstances.

## II. Encouraging Provider Reporting

Most infectious disease surveillance systems rely on receipt of case reports from healthcare providers and laboratories.[7–8] These data may not be complete and may not be representative of certain populations; completeness of reporting has been estimated to vary from 6% to 90% for many of the common notifiable diseases.[9] However, if the level of completeness is consistent, these data provide an important source of information regarding disease trends and characteristics of the persons affected. Some mechanisms to encourage healthcare provider reporting are described here.

### *Promoting awareness of the occurrence of vaccine-preventable diseases*

Some healthcare providers may be particularly likely to encounter patients with vaccine-preventable diseases. For example, they may see immigrants and travelers returning from areas where vaccine-preventable diseases are endemic.

### *Promoting awareness of reporting requirements*

Although there is a list of diseases designated as nationally notifiable by the Council of State and Territorial Epidemiologists in conjunction with CDC,[10–11] each state has laws or regulations stipulating which diseases are reportable.[7,11] Efforts should be made to increase healthcare providers' awareness of their responsibility to report suspected cases.[12–16]

The list of reportable diseases with detailed instructions explaining how, when, and to whom to report cases should be widely distributed within each state. Mailings, e-mail list serves, websites, in-service and other continuing education courses, and individual provider interaction may be used to accomplish this goal. However, while these are all examples of possible methods to raise awareness of reporting requirements, studies of interventions have demonstrated that telephone and other personal contact with individual healthcare providers, rather than groups, is most effective.[17] For example, interaction with healthcare providers in the Vaccines for Children program offers an opportunity to promote awareness of reporting requirements. Face-to-face communication is the most direct and dynamic means of communication, allowing feedback and responses to overcome objections and concerns.[18] A study on mandatory chronic disease reporting by physicians suggests that public health should emphasize both the legal and public health bases for reporting.[19]

### *Giving frequent and relevant feedback*

Providing regular feedback to healthcare providers and others who report cases of vaccine-preventable diseases reinforces the importance of participating in public health surveillance.[20] Feedback should be timely, informative, interesting, and relevant to the provider's practice. Ideally, it should include information on disease patterns and disease control activities in the area. Some examples of methods of providing feedback are monthly newsletters, e-mail list serves, regular oral reports at clinical conferences such as hospital grand rounds, or regular reports in local or state medical society publications.

Contact with individual providers may be most effective. Examples of positive individual interaction for giving feedback on disease reporting include the following:

- Providing feedback to the provider on the epidemiologic investigations conducted for their patients;
- Providing feedback to the provider, in addition to the laboratory, for any cases that were first reported to the health department by the laboratory (or other source);
- Using every professional interaction with the provider to at least briefly discuss surveillance issues.

### *Simplifying reporting*

Reporting should be as simple and as painless as possible for the healthcare provider. State health department personnel should be easily accessible and willing to receive telephone reports and answer questions. Reporting instructions should be simple, clear, and widely distributed to those who are responsible for disease reporting.

## III. Ensuring Adequate Case Investigation

Detailed and adequate case information is crucial for preventing continued spread of the disease or changing current disease control programs. The following steps are essential to ensuring adequate case investigation.

### *Obtaining accurate clinical information*

During a case investigation, clinical information (e.g., date of symptom onset, signs and symptoms of disease) about a case-patient is often obtained by a retrospective review of medical records and interviews with the case-patient, family, friends, caretakers, and other close associates of the case-patient. Detailed and accurate information (e.g., date of onset, laboratory results, duration of symptoms) may indicate the source of the infection and possible contacts, allowing interventions to prevent the spread of disease. This clinical information also may be aggregated by disease to study other aspects of the diseases (e.g., trends, incidence, prevalence). For vaccine-preventable diseases, vaccination history is particularly important for determining whether the case represents a vaccine failure or a failure to vaccinate. In addition to medical and school records, the state's immunization registry may be used to provide the most complete vaccination history information.

### *Obtaining appropriate laboratory specimens*

Efforts should be taken to ensure that healthcare providers obtain necessary and appropriate laboratory specimens. For example, specimens for bacterial cultures should be taken before administering antibiotics, and paired sera are often required for meaningful serologic testing. For more information on laboratory support for vaccine-preventable disease surveillance, see Chapter 22, "Laboratory Support for the Surveillance of Vaccine-Preventable Diseases."

### *Ensuring access to essential laboratory capacity*

Availability of laboratory testing needed to confirm cases of vaccine-preventable diseases must be assured. Additional testing, such as serotype, serogroup, and molecular testing provides epidemiologically important information that can support disease control and prevention activities. Healthcare providers should be encouraged to contact the local or state health department for assistance in obtaining appropriate laboratory testing.

Laboratory testing needed to confirm diagnoses of public health significance is a public responsibility and should be made available at no cost to the patient. For information on laboratory support available in individual states, contact the state health department.

### *Investigating contacts*

Identification of all case contacts and follow-up of susceptible persons may reveal previously undiagnosed and unreported cases. This investigation will also reveal persons eligible for any indicated prophylaxis, thereby facilitating disease control efforts.[21]

## IV. Improving the Completeness of Reporting

Complete reporting involves accounting for as many cases of vaccine-preventable diseases as is possible. Completeness of reporting can be enhanced in many ways,[22] including using electronic laboratory reporting,[23–28] searching hospital and laboratory records, using administrative datasets, and expanding sources of reporting.

### *Searching hospital and laboratory records*

For some vaccine-preventable diseases, a regular search of laboratory records for virus isolations or bacterial cultures may reveal previously unreported cases.[13] Likewise, hospital discharge records may also be reviewed for specific discharge diagnoses,[12, 27] such as *Haemophilus influenzae* meningitis, tetanus, and other vaccine-preventable diseases. Such searches may assist in evaluating completeness of reporting and may help improve reporting in the future.[20, 30] Identifying the source of missed cases may lead to modifications that make the surveillance system more effective and complete. Although not a substitute for timely reporting of suspected cases, such searches can supplement reporting when resources for more active surveillance are unavailable.

### *Using administrative datasets*

Administrative datasets, such as Medicare or Medicaid databases or managed care organization databases, may be useful for surveillance; when linked to immunization records, administrative records have been useful for monitoring rare adverse events following vaccination.[31-32] However, unless extensive efforts are made to validate diagnoses, misclassification is likely.[33] Most vaccine-preventable diseases are now rare, and data quality may be insufficient for these datasets to be useful adjuncts to vaccine-preventable disease surveillance.[34]

### *Expanding sources of reporting*

Notifiable disease reporting has traditionally relied on reporting by physicians. Other healthcare personnel such as infection control practitioners, school nurses, employee health nurses, laboratories, and childcare center personnel may be underutilized yet appropriate sources of case reports and surveillance information.[20, 30, 35–38] These professionals often give the first indication that a health event is occurring that affects more than one person. In general, the most complete surveillance systems at the state and local levels involve multiple sources of reporting.

## V. Strengthening Surveillance Infrastructure

Arrangements and procedures for public health surveillance and reporting may differ from department to department at both state and local levels. To ensure an effective national surveillance system, reporting institutions and organizations need to maintain and strengthen independent reporting mechanisms. Some methods for maintaining a strong surveillance infrastructure are described here.

### *Making technical assistance available*

Training and written guidance should be available to health department personnel participating in surveillance activities and should include such topics as reporting requirements, epidemiologic methods, case finding, and investigation. Likewise, the health department should make this information readily available to healthcare providers and others who are required to participate in disease reporting and surveillance.

### *Creating networking opportunities*

Meetings, conferences, and other professional interactions between public health professionals, where practices and plans for surveillance are discussed, can validate the importance of surveillance activities. In addition, those attending these meetings gain knowledge and strengthen professional interactions. These functions can help establish strong, professional links between public health professionals and private healthcare providers.

### *Monitoring surveillance indicators*

Surveillance activities have many measurable components (surveillance indicators), including timeliness of reporting, completeness of reporting, and the ability to obtain all the information needed during case investigation. Regular monitoring of surveillance indicators may identify specific areas of the surveillance and reporting system that need improvement. For more information on this topic see Chapter 18, "Surveillance Indicators."

## VI. Special Surveillance Activities

Special surveillance activities include contacting providers under active surveillance and using sentinel surveillance systems and active laboratory-based surveillance. The following provides a brief overview of these special surveillance systems.

### *Contacting providers in active surveillance catchmant areas*

Active surveillance, such as when the health department initiates contact with a healthcare provider to identify cases, involves regular (e.g., weekly) contact with healthcare providers.[14, 17, 20, 35, 39, 40] This regular contact with individual providers promotes increased awareness of reporting responsibilities and increased cooperation with the health department. Active surveillance may be limited to short-term disease control activities, such as during outbreaks, or to seasonal activities, such as during influenza season, because of the expense of sustaining an active system and the low yield when disease incidence is low. However, long-term active surveillance systems may also be put into place to determine the incidence and epidemiologic and laboratory characteristics of specific pathogens or conditions of public health concern.

### *Using sentinel surveillance systems*

Sentinel surveillance,[17, 24, 35] in which a network of healthcare providers or hospitals are recruited by the health department to regularly report specified health events, is useful for some vaccine-preventable diseases (e.g., influenza) in which the goal of surveillance is information on disease trends rather than individual case investigation. Sentinel surveillance systems may also be based in schools, child care centers, hospitals, or other institutions serving specific populations. When targeted toward communities with a high risk of disease, sentinel surveillance may be a useful adjunct to other reporting sources and may supplement disease reporting when resources for more active surveillance are unavailable.

### *Using active laboratory-based surveillance*

Active laboratory-based surveillance, in which a group of laboratories is recruited by the health department to regularly report specified laboratory results, is useful for the surveillance of vaccine-preventable diseases for which diagnosis and/or case confirmation requires laboratory testing (e.g., *Haemophilus influenzae* invasive disease). Laboratory-based surveillance systems may include both public and private laboratories; when targeted to include laboratories most likely to provide testing for vaccine-preventable diseases, laboratory-based surveillance may be a useful adjunct to other reporting sources and may supplement disease reporting when resources for other surveillance activities are scarce.[41, 42]

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# Chapter 20: Analysis of Surveillance Data

*Sandra W. Roush, MT, MPH*

## I. Background

Ongoing analysis of surveillance data is important for detecting outbreaks and unexpected increases or decreases in disease occurrence, monitoring disease trends, and evaluating the effectiveness of disease control programs and policies. This information is also needed to determine the most appropriate and efficient allocation of public health resources and personnel.

Analyses should be performed at regular intervals to identify changes in disease reporting. These analyses can be performed using standard approaches (e.g., running a standard computer program to generate a summary report). Findings of analyses should be reviewed regularly and provided as feedback to medical providers and others in the community who are asked to report cases. Often additional, special analyses are needed to answer specific questions that arise;[1] these analyses may require additional customized approaches beyond what are routinely performed.

Analyses can be done using any one of a number of database and statistical programs. Systems developed by CDC and others can assist in epidemiologic and laboratory surveillance, outbreak detection, and mapping. Local health departments should contact the state health department for information about recommended software and to identify support for setting up a surveillance database at a local level. The state health department may also give assistance in setting up useful analyses and reports that can be generated as needed.

However, although computer technology has greatly facilitated collection and analysis of surveillance data, surveillance of most vaccine-preventable diseases in the United States results in small numbers of cases, and data analysis is not complex (see examples included in this chapter). In addition, skillful interpretation of the data is needed to determine why any aberrations may be occurring or decide whether additional action is necessary. Therefore, both technologic and human factors play important roles in analysis of surveillance data. Despite the increased speed and accuracy of a sophisticated trend analysis, it must be supplemented by familiarity with the people and the disease patterns in a community and with the reporting system being used.

The mistake most commonly made in analysis and use of public health surveillance data is not related to statistical testing, improper presentation of data, or failure to perform complex multivariate analyses; the most common mistake is not looking at the data. Computer hardware and software can facilitate the epidemiologist's task, but they are no substitute for looking, thinking, discussing, and taking action.

## II. The Analytic Process

Analysis of surveillance data begins with characterizing the pattern of disease reports by person, place, and time. Patterns of disease reports should be compared at different times (e.g., the number of mumps cases reported in 2005 compared with the number of cases in 2006); in different places (e.g., the number of pertussis cases reported in one district compared with the number in another district); and among different populations (e.g., the number of measles cases reported among infants, preschool age children, school age children, adolescents, and adults). Vaccination status of case-patients should also be examined; if there is disease transmission in the community, lack of vaccination is likely to be a factor most strongly associated with illness. Analyses that examine delays in reporting, completeness of reporting of critical variables, and applying case definition criteria also are useful in evaluating the quality of case investigation and reporting and should be undertaken regularly. Missing or inaccurate data may limit the usefulness of any analysis. Erroneous or incomplete data cannot be corrected through statistical procedures.

## III. Surveillance Indicators in the United States

The following analyses of surveillance data should be performed routinely. Additional analyses may be needed under special circumstances; the state health department can provide additional guidance in routine and special analyses of surveillance data. The interpretations and possible action steps listed here are only examples to indicate some of the information that may be gained from the analysis.

### *By person*

Describe the persons with vaccine-preventable diseases (cases) who were identified by your surveillance system. Attributes of the case-patients include age group, sex, and race or ethnicity.

It may be appropriate to divide age groups based on recommended ages for vaccine administration (e.g., separating those too young to be vaccinated from those eligible for vaccination), as well as on the age distribution of persons with reported cases. Age groups should span a narrower age range for ages in which disease incidence is highest and a broader age range in which disease incidence is lower.

**Example 1. Pertussis cases by age group, 2011**

| Age group | Frequency | % | Cumulative % |
|---|---|---|---|
| younger than 6 mo | 57 | 36.1 | 36.1 |
| 6–12 mo | 41 | 25.9 | 62.0 |
| 13–18 mo | 6 | 3.8 | 65.8 |
| 19–23 mo | 6 | 3.8 | 69.6 |
| 2–5 yr | 18 | 11.4 | 81.0 |
| 6–9 yr | 17 | 10.8 | 91.8 |
| 10 yrs or older | 12 | 7.6 | 99.4 |
| Age unknown | 1 | 0.6 | 100.0 |
| **Total** | 158 | 100.0 | |

**Interpretation.** Pertussis cases are clustered among infants, with more than 60% of reported cases among those 12 months of age and younger (Figure 1). The occurrence of pertussis among infants younger than 6 months of age is extremely worrisome because these children are too young to have received three doses of pertussis vaccine. Note that it is difficult to draw any conclusions about disease incidence from these data; although these age-group divisions are logical for analysis of pertussis data, presentation of data in such unequal age groups may obscure important differences in disease incidence. Figure 2 shows the incidence of pertussis, by age group.

**Figure 1. Pertussis cases by age group, 2011**

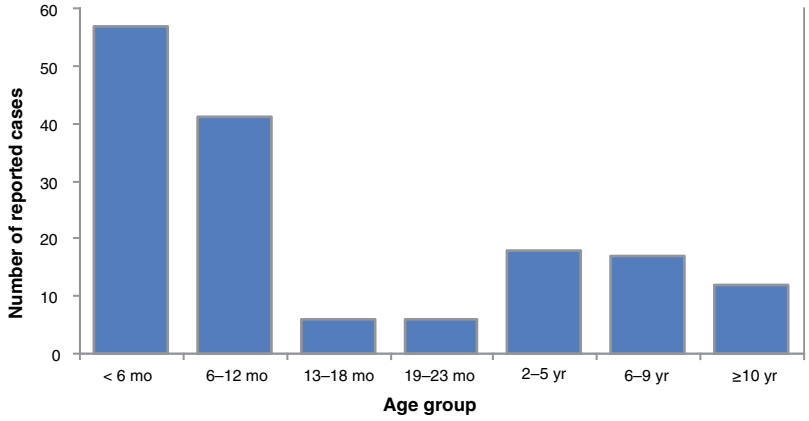
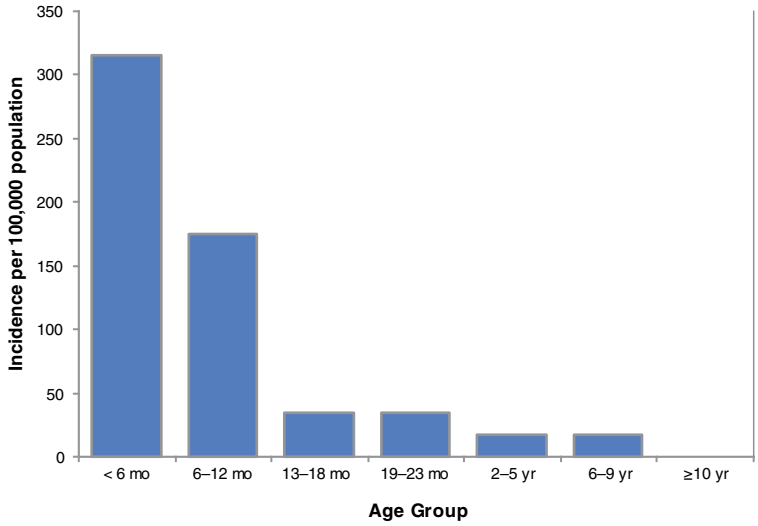


**Figure 2. Pertussis incidence by age group, 2011**




**Example 2. Rubella cases by sex**

| Sex | Frequency | % | Cumulative % |
|---|---|---|---|
| Female | 27 | 69.3 | 69.3 |
| Male | 12 | 30.7 | 100.0 |
| **Total** | 39 | 100.0 | |

**Interpretation.** Of the 39 cases of rubella, more than two-thirds are among females. Assuming the population under surveillance includes approximately equal numbers of males and females, the female predominance among cases may reflect a real difference in disease incidence among females, possibly due to differences in susceptibility or exposure, or differences in ascertainment occurring because of concerns about rubella among women of childbearing age. The occurrence of rubella among women of childbearing age is of great concern because of the risk of congenital rubella syndrome (CRS) among infants born to women infected with rubella during the first trimester of pregnancy. Because many cases of rubella are asymptomatic or mild, there likely are many more cases than were reported. Subsequent surveillance for CRS in this community is essential.

**Next steps.** Look at cases among women by age group to identify women of childbearing age.

**Example 3. Pertussis cases by Hispanic ethnicity, 2011**

| Ethnicity | Frequency | % | Cumulative % |
|---|---|---|---|
| Hispanic | 32 | 20.35 | 20.3 |
| Not Hispanic | 77 | 48.7 | 69.0 |
| Unknown | 49 | 31.0 | 100.0 |
| **Total** | 158 | 100.0 | |

**Interpretation.** Of the 158 cases of pertussis, one-fifth occurred among persons of Hispanic ethnicity, and almost half were among non-Hispanics. However, ethnicity was unknown for almost one-third of cases, suggesting that case investigation was incomplete.

Even if the data were complete, more information is needed to know how to interpret these proportions. What proportion of the population under surveillance is of Hispanic ethnicity? Do the data suggest a disproportionate burden of disease in one group? Reports indicating a disproportionate disease burden could result from low rates of vaccine coverage, increased disease incidence in certain neighborhoods or communities, or different levels of reporting,

which might be due to differences in access to medical care and diagnostic testing or differences in reporting practices among providers. (For example, public clinics may be more likely to report cases than private physicians.)

**Next steps.** Obtain missing data, if possible; calculate incidence rates by ethnicity; look for geographic clustering.

### *By place*

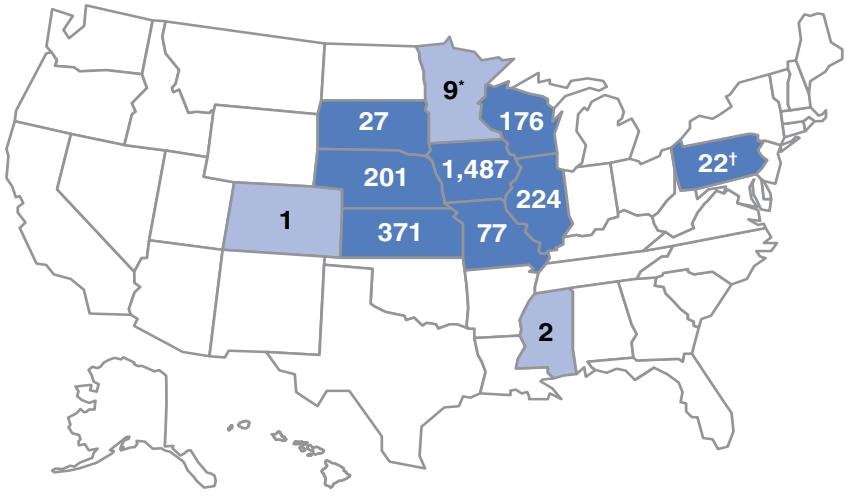
Describe the persons with vaccine-preventable diseases (cases) detected by your surveillance system by geographic location. Location may be defined as the place where the case was first reported, place of residence of the case-patient, or place of hospitalization. Location may be a state, city, county, or health district.

**Example 4. Outbreak-related mumps cases by state, Jan 1–May 2, 2006.[2]**

| State | Frequency | % | Cumulative % |
|---|---|---|---|
| Colorado | 1 | 0 | 0 |
| South Dakota | 27 | 1 | 1 |
| Nebraska | 201 | 8 | 9 |
| Kansas | 371 | 14 | 23 |
| Minnesota | 9 | 0 | 23 |
| Iowa | 1,487 | 57 | 81 |
| Missouri | 77 | 3 | 84 |
| Wisconsin | 176 | 7 | 90 |
| Illinois | 224 | 9 | 99 |
| Mississippi | 2 | 0 | 99 |
| Pennsylvania | 22 | 1 | 100 |
| **Total** | 2597 | 100.0 | |

During January 1–May 2, 11 states reported 2,597 cases of mumps related to the multistate outbreak. The majority of mumps cases (1,487 [57%]) were reported from Iowa; states with the next highest case totals were Kansas (371), Illinois (224), Nebraska (201), and Wisconsin (176) (Figure 3).

**Figure 3. Outbreak-related mumps cases by state, Jan 1–May 2, 2006**




*N = 2,597*
** Three cases related to the outbreak*
*† Twelve cases related to the outbreak*

**Interpretation.** During January 1–May 2, 11 states reported 2,597 cases of mumps related to the multistate outbreak. Eight states (Illinois, Iowa, Kansas, Missouri, Nebraska, Pennsylvania, South Dakota, and Wisconsin) reported mumps outbreaks with ongoing local transmission or clusters of cases; three states (Colorado, Minnesota, and Mississippi) reported cases associated with travel from an outbreak state. The majority of mumps cases (1,487 [57%]) were reported from Iowa; states with the next highest case totals were Kansas (371), Illinois (224), Nebraska (201), and Wisconsin (176).

### *By time*

Describe the distribution of cases over time. Look for changes in the number of cases during the defined time period. Time intervals may be in years, months, weeks, or other unit of time. Date may be defined as date of onset of illness, date of diagnosis, or date of report to the health department. Analysis by date of symptom onset gives the most accurate representation of disease occurrence. Distribution of cases over time is most clearly presented as a graph with time on the x-axis and number of cases on the y-axis.

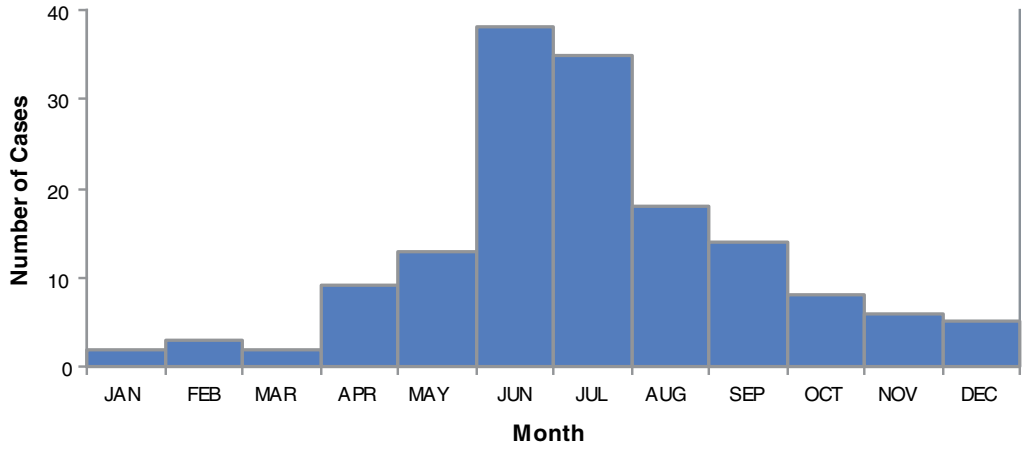
Compare the number of cases occurring in a current time period with the number reported during the same time period in each of the last 5 years. Compare the cumulative number of cases year-to-date with the cumulative number of cases year-to-date of previous years.

**Example 5. Reported pertussis cases, 2010, by month of onset**

| Month | Frequency | % | Cumulative % |
|---|---|---|---|
| Oct. 2003 | 3 | 1.9 | 1.9 |
| Nov. 2003 | 1 | 0.6 | 2.5 |
| Dec. 2003 | 1 | 0.6 | 3.2 |
| Jan. 2004 | 2 | 1.3 | 4.4 |
| Feb. 2004 | 3 | 1.9 | 6.3 |
| Mar. 2004 | 2 | 1.3 | 7.6 |
| Apr. 2004 | 9 | 5.7 | 13.3 |
| May 2004 | 13 | 8.2 | 21.5 |
| Jun. 2004 | 38 | 24.0 | 45.6 |
| Jul. 2004 | 35 | 22.2 | 67.7 |
| Aug. 2004 | 18 | 11.4 | 79.1 |
| Sep. 2004 | 14 | 8.9 | 88.0 |
| Oct. 2004 | 8 | 5.1 | 93.0 |
| Nov. 2004 | 6 | 3.8 | 96.8 |
| Dec. 2004 | 5 | 3.2 | 100.0 |
| **Total** | 158 | 100.0 | |

**Interpretation.**There is marked temporal clustering, suggesting that a large outbreak occurred during the summer of 2010. Note that in this dataset of cases reported during 2010 there are a number of cases with onset during 2009. Reports in 2011 should be reviewed to look for cases with onset in 2010 because of apparent delays in reporting. The magnitude of these delays can be monitored by tracking the interval between onset of disease and initial report. Figure 4 demonstrates the reported cases of pertussis in 2010 by month of onset, omitting the cases with onset in 2009, and including the few additional cases reported in 2011 but with onset in the latter months of 2010.

**Figure 4. Reported pertussis cases by month of onset, 2010**




**Example 6. Pertussis cases by age group and DTaP/Tdap doses, Jan–April, 2005**

| Age group | DTaP/Tdap Doses | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | Unknown | Total |
| 0–2 mo | 7 | 1 | 0 | 0 | 0 | 0 | 0 | 8 |
| 3–4 mo | 7 | 6 | 1 | 0 | 0 | 0 | 0 | 14 |
| 5–6 mo | 2 | 6 | 1 | 0 | 0 | 0 | 1 | 10 |
| 7–18 mo | 5 | 6 | 9 | 10 | 4 | 0 | 0 | 34 |
| 19 mo.–6 yr | 1 | 2 | 4 | 8 | 10 | 2 | 0 | 27 |
| 7 yrs or older | 1 | 0 | 1 | 1 | 0 | 10 | 9 | 22 |
| Total | 23 | 21 | 16 | 19 | 14 | 12 | 10 | 115 |

**Interpretation.** Many of the children reported with pertussis were undervaccinated. Cases among infants younger than 6 months of age are not preventable by vaccination because these infants are too young to have received three doses of pertussis vaccine, the minimum needed to confer protection. In order to be up-to-date, children 3–4 months of age should have received at least one dose; 5–6 months, at least 2 doses; 7–18 months, at least 3 doses; 19 months to 3 years of age, 4 doses; and those 7 years of age and older should have received five doses. Many of these cases were among children who were not age-appropriately immunized, suggesting that there may be a wider problem with immunization coverage among young children in this community. It is often extremely difficult to verify vaccination of adults, which may account for the high proportion of cases with unknown vaccination status among children 7 years of age and older.

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# Chapter 21: Surveillance for Adverse Events Following Immunization Using the Vaccine Adverse Event Reporting System (VAERS)

*Elaine R. Miller, RN, MPH; Penina Haber, MPH; Beth Hibbs, RN, MPH; Karen Broder, MD*

## I. Public health importance

Vaccination is one of the ten great public health achievements of the 20th century.[1] Vaccines have reduced the incidence of many vaccine-preventable diseases in the United States by more than 98% compared with the prevaccine era.[2,3] This historic decrease in disease rates is shown in Table 1.

Vaccinations are usually administered to healthy persons and often are mandated; therefore, they are held to a higher standard of safety than other medical products.[4] However, as with all medical products, no vaccine is perfectly safe or effective. Vaccines can cause minor adverse effects such as fever or local reactions at the injection site. Rarely, they can cause serious adverse effects such as febrile seizures or severe allergic reactions. Adverse events (AE) can also occur coincidentally after vaccines (i.e. they would have occurred in the absence of vaccination). To reduce the occurrence of vaccine AE and maintain public confidence in vaccines, it is important to improve the understanding of vaccine safety. Robust vaccine safety monitoring may foster the discovery of adverse events associated with vaccination, and thus the development and use of safer vaccines and recommendations to minimize the risk of AE after vaccination (e.g., define new recommendations, contraindications and precautions).[5] One way to enhance our understanding of vaccine safety is to improve surveillance for vaccine AE.

**Table 1. Decline in vaccine-preventable disease morbidity in the United States during the 20th century[2,3]**

| Disease | Baseline 20th century total cases | 2009 total cases | % Decrease |
|---|---|---|---|
| Smallpox | 48,164 | 0 | 100 |
| Diphtheria | 175,885 | 0 | 100 |
| Pertussis | 147,271 | 16,858 | >88 |
| Tetanus | 1,314 | 18 | >98 |
| Poliomyelitis (paralytic) | 16,316 | 1 | >99 |
| Measles | 503,282 | 71 | >99 |
| Mumps | 152,209 | 1991 | >98 |
| Rubella | 47,745 | 3 | >99 |
| Congenital rubella | 823 (estimated) | 2 | >99 |
| *Haemophilus influenzae* disease (<5 years of age) | 20,000 (estimated) | 213 (serotype b or unknown serotype) | >98 |

## II. Background

Vaccines, like other pharmaceutical products, undergo extensive testing and review for safety, immunogenicity, and efficacy in trials with animals and humans before they are licensed in the United States. Because these trials usually include a placebo control or comparison group, it is possible to ascertain which local or systemic reactions were actually caused by the vaccine. However, prelicensure trials are relatively small— usually limited to a few thousand subjects— and usually last no longer than a few years. In addition, they may be conducted in populations less demographically, racially, and ethnically diverse than those in which the vaccine is ultimately used. Persons with certain health conditions, such as pregnancy, may be excluded

from the trials. Prelicensure trials usually do not have the ability to detect rare AE or AE with delayed onset. Postlicensure or postmarketing surveillance— the continuous monitoring of vaccine safety in the general population after licensure— is needed to identify and evaluate risk for such AE after vaccination.[4]

With the passage of the National Childhood Vaccine Injury Act of 1986 (NCVIA) healthcare providers who administer vaccines are required by law to report certain AE following specific vaccinations.[6] The NCVIA's purposes were to compensate persons who may have been injured by vaccines and to reduce threats to the stability of the immunization program (e.g., liability concerns, inadequate supply of vaccine, rising vaccine costs).[7] The NCVIA stipulates the vaccines, the AE, and the time of occurrence after vaccination for which reporting by healthcare providers is required (Table 2). It also requires that any event listed in the manufacturer's package insert as a contraindication to subsequent doses of the vaccine be reported by healthcare providers. In 1990, the Department of Health and Human Services (DHHS) directed that a single system be established for the collection and analysis of reports of AE following immunization.[8] This led to the establishment of the Vaccine Adverse Event Reporting System (VAERS), which is cosponsored by CDC and FDA. Spontaneous reporting systems for AE such as VAERS exist in many countries; some monitor vaccines separately from other drug products, but many are joint programs. These programs form the cornerstone of drug and vaccine safety monitoring efforts around the world.

**Table 2. VAERS Table of Reportable Events Following Vaccination*~**

| Vaccine/Toxoid | Event and interval from vaccination |
|---|---|
| Tetanus in any combination; DTaP, DTP, DTP-Hib, DT, Td, TT, Tdap, DTaP-IPV, DTaP-IPV/Hib, DTaP-HepB-IPV | A. Anaphylaxis or anaphylactic shock (7 days)<br>B. Brachial neuritis (28 days)<br>C. Any acute complications or sequelae (including death) of above events (interval— not applicable)<br>D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert) |
| Pertussis in any combination; DTaP, DTP, DTP-Hib, Tdap, P, DTaP-IPV, DTaP-IPV/Hib, DTaP-HepB-IPV | A. Anaphylaxis or anaphylactic shock (7 days)<br>B. Encephalopathy or encephalitis (7 days)<br>C. Any acute complications or sequelae (including death) of above events (interval— not applicable)<br>D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert) |
| Measles, mumps and rubella in any combination; MMR, MR, M, MMRV, R | A. Anaphylaxis or anaphylactic shock (7 days)<br>B. Encephalopathy or encephalitis (15 days)<br>C. Any acute complications or sequelae (including death) of above events (interval— not applicable)<br>D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert) |
| Rubella in any combination; MMR, MMRV, MR, R | A. Chronic arthritis (42 days)<br>B. Any acute complications or sequelae (including death) of above event (interval— not applicable)<br>C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert) |
| Measles in any combination; MMR, MMRV, MR, M | A. Thrombocytopenic purpura (7-30 days)<br>B. Vaccine-strain measles viral infection in an immunodeficient recipient (6 months)<br>C. Any acute complications or sequelae (including death) of above events (interval— not applicable)<br>D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert) |

**Table 2. VAERS Table of Reportable Events Following Vaccination*~**

| Vaccine/Toxoid | Event and interval from vaccination |
|---|---|
| Oral Polio (OPV) | A. Paralytic polio<br>• in a non-immunodeficient recipient (30 days)<br>• in an immunodeficient recipient (6 months)<br>• in a vaccine-associated community case (interval— not applicable)<br>B. Vaccine-strain polio viral infection<br>• in a non-immunodeficient recipient (30 days)<br>• in an immunodeficient recipient (6 months)<br>• in a vaccine-associated community case (interval— not applicable)<br>C. Any acute complication or sequelae (including death) of above events (interval— not applicable)<br>D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert) |
| Inactivated Polio -IPV, DTaP-IPV, DTaP-IPV/HIB, DTaP-HepB-IPV | A. Anaphylaxis or anaphylactic shock (7 days)<br>B. Any acute complication or sequelae (including death) of the above event (interval— not applicable)<br>C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert) |
| Hepatitis B in any combination- HepB, HepA-HepB, DTaP-HepB-IPV, Hib-HepB | A. Anaphylaxis or anaphylactic shock (7 days)<br>B. Any acute complications or sequelae (including death) of the above event (interval— not applicable)<br>C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert) |
| *Hemophilus influenzae* type b in any combination (conjugate)- Hib, Hib-HepB, DTP-Hib, DTaP-IPV/Hib | Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert) |
| Varicella in any combination- VAR, MMRV | Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert) |
| Rotavirus (monovalent or pentavalent) RV1, RV5 | Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert) |
| Pneumococcal conjugate (7-valent or 13-valent) PCV7, PCV13 | Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert) |
| Hepatitis A in any combination- HepA, HepA-HepB | Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert) |
| Influenza— trivalent inactivated influenza, live attenuated influenza-TIV, LAIV | Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert) |
| Meningococcal - MCV4, MPSV4 | Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert) |
| Human Papillomavirus (Quadrivalent or Bivalent)- HPV4, HPV2 | Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert) |

* ***Effective date: November 10, 2008.*** *The Reportable Events Table (RET) reflects what is reportable by law (42 USC 300aa-25) to the Vaccine Adverse Event Reporting System (VAERS) including conditions found in the manufacturers package insert. In addition, healthcare professionals are encouraged to report any clinically significant or unexpected events (even if not certain the vaccine caused the event) for any vaccine, whether or not it is listed on the RET. Manufacturers are also required by regulation (21CFR 600.80) to report to the VAERS program all adverse events made known to them for any vaccine.*

**~ See the end of this chapter for the Reportable Events Table definitions**

**For a list of vaccine abbreviations, see** http://www.cdc.gov/vaccines/recs/acip/vac-abbrev.htm

**For a link to the Reportable Events Table online, see** http://www.vaers.hhs.gov/reportable.htm

## III. Objectives of VAERS

The objectives of VAERS are to:

1. Detect new, unusual, or rare vaccine AE
2. Assess the safety of newly licensed vaccines
3. Identify vaccine lots with increased numbers or types of reported AE
4. Identify potential risk factors in vaccinees for particular types of AE
5. Monitor trends in known AE, particularly increases
6. Rapidly respond to vaccine safety concerns or public health emergencies

### *Scope of reports sought*

The Reportable Events Table (Table 2) lists the events mandated for healthcare providers to report to VAERS. In addition, healthcare providers should submit reports to VAERS for all clinically significant AE occurring after vaccination, in all age groups, even if the causal relationship to vaccination is uncertain. Such events include (but may not be limited to) all deaths, any life-threatening illness, an illness requiring a hospitalization, prolongation of a hospital stay, or any illness resulting in a permanent disability, and congenital anomalies, as well as less serious AE of concern to the reporter. The VAERS form requests information about the adverse event(s), the type of vaccine(s) received, the timing of vaccination before the AE, demographic information about the recipient, concurrent medical illness or medications, and prior medical history and history of prior AE (see Appendix 22). The VAERS form allows description of the AE in a narrative format by the reporter. AE should be described as clearly as possible, with accurate timing with respect to vaccination. Additional medical records or discharge summaries are requested to be submitted by the VAERS staff during follow-up for reports of serious AE.

## IV. Reporting to VAERS

Anyone can report any vaccine AE to VAERS. As described above, healthcare providers are mandated by law to report certain AE after vaccination, and they are encouraged to report any clinically significant event occurring after vaccination, even if they are not certain the event is causally related to a vaccine(s). As previously stated, a table listing required vaccine reportable events is available at http://www.vaers.hhs.gov/reportable.htm and is reprinted in this chapter (Table 2). Reports are also accepted from vaccine manufacturers, public health providers, patients, parents and caregivers. Persons who are not healthcare providers are encouraged to consult with a healthcare provider to ensure that information is complete and accurate and to ensure that their provider is aware of the AE. Manufacturers are required to report to VAERS all adverse events made known to them for any US licensed vaccine.

Reporting to VAERS can be done in one of three ways, but online reporting (i.e., web-based reporting) is strongly preferred since it allows for quicker receipt and processing of the information:

- Online through a secure website: https://vaers.hhs.gov/esub/step1 (exit site)

  Or

- Fax, a completed VAERS form to 877-721-0366

  Or

- Mail, a completed VAERS form to:

  VAERS
  P.O. Box 1100
  Rockville, MD 20849-1100

A VAERS reporting form, which can be copied for reporting purposes, is printed in Appendix 22. The form can also be downloaded from http://vaers.hhs.gov/resources/vaers_form.pdf or can be requested by telephone at 800-822-7967. The Vaccine Information Statements (VIS) (available at http://www.cdc.gov/vaccines/pubs/vis/default.htm) developed by CDC for all U.S.-licensed vaccines and given to patients at the time of vaccination also contain instructions

on how to report AE to VAERS. Detailed instructions for completing the reporting form are provided below. Local health departments should follow the reporting instructions provided by their state immunization program.

### Completion of VAERS form and submission of reports

Instructions for completing the VAERS form are on the back of the form.

***Note:*** *Report AE associated with vaccines on the VAERS form. Do not use MEDWATCH forms to report vaccine AE.*

Do not report events associated with tuberculosis screening tests (Tine, PPD, or Mantoux), immune globulins, or other nonvaccine medical products to VAERS. These events should be reported to the FDA's MEDWATCH program at 800-FDA-1088 (800-332-1088) or at http://www.fda.gov/medwatch/.

**Reporting responsibilities**

Local health departments may request reporting forms from their state immunization program or report AEs online at www.vaers.hhs.gov. Clinic staff at the local level are responsible for completing a VAERS report when an AE is suspected or occurs following immunization. As much of the requested information as possible should be obtained. Although reporting priority may be given to serious or unexpected events or unusual patterns of expected non serious events, all clinically significant AE should be reported. Each report should be reviewed for completeness, accuracy, and legibility before it is sent to VAERS or to the State Health Coordinator (SHC) or VAERS Coordinator, with specific attention to the following:

- *Dates*— All dates should make chronological sense. For example, the vaccine date cannot precede the birth date, or the report date cannot precede the vaccine date. All date fields require entry of the full month, day, and year.
- *Patient name*— Verify that the patient's first and last names are correct. This check assists in identification of duplicate reports.
- *Reporter information (upper right corner of form)*— The reporter name and complete mailing address are required. Verification letters and requests for missing or follow-up information are sent to this address. Any person reporting other than manufacturer or state immunization program staff is sent a mailed letter from VAERS verifying receipt of the form and is requested to supply any critical information that was missing from the VAERS report. State Immunization program staff are sent quarterly reports via Epi-X (http://www.cdc.gov/epix/) which acknowledge report receipt and request missing information. In order to receive reports via Epi-X, SHC must first contact Epi-X at epiXhelp@cdc.gov to obtain a digital certificate to gain access to the secure system.
- Some SHCs prefer to receive and submit verification letters, requests for missing information, and related correspondence; they may delete the original reporter's name and address and insert the SHC name and address. If you do not receive a verification letter within a reasonable amount of time (e.g., 1 month), check with your SHC. As stated previously, reports submitted by States receive verification letters and requests for missing information via Epi X quarterly reports
- *Critical boxes*— Certain items on the VAERS form are crucial to the analysis of VAERS data and have been designated as critical boxes (data fields). Persons reporting will be asked to supply this information later if it is missing. Critical boxes are differentiated by a square around their respective item numbers on the form as follows:
  - Box 3: Date of birth
  - Box 4: Age of patient at the time of vaccination
  - Box 7: Narrative description of AE, symptoms, etc.
  - Box 8: Indicates whether a report is regarded as serious or non serious, and identifies the most serious reports for 60-day and annual follow-up
    - Serious (serious status is based on the Code of Federal regulations (see http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=600.80)

        - Patient died and date of death
        - Life-threatening illness (based on the judgment of the reporter)
        - Resulted in permanent disability
        - Required hospitalization and number of days hospitalized
        - Resulted in prolongation of hospitalization
      - Nonserious
        - Required emergency department or doctor visit
        - None of the above
    - Box 10: Date of vaccination (and time, if known)
    - Box 11: Date of onset of AE (and time, if known)
    - Box 13: All vaccines given on the date listed in Box 10, including name of vaccine, vaccine manufacturer, vaccine lot number, route and site of administration and number of previous doses given. Accurate lot information is needed to examine events occurring within specific vaccine lots.
- *Timely reporting*— All reports from the public health domain are to be sent to VAERS as they occur, especially reports of any serious event. Programs are discouraged from sending batches of reports. VAERS data are downloaded on a daily basis by the FDA and CDC. Timely reporting is essential to timely assessment of vaccine safety concerns and follow-up investigation.

**State Health Coordinator (SHC) or VAERS Coordinator responsibilities**
The SHC or VAERS coordinator receives VAERS reports from local health departments or immunization projects and is responsible for the following activities:

- Registers with Epi-X at epiXhelp@cdc.gov so that they can receive quarterly report summaries of the VAERS reports that they submitted.
- Reviews each report for completeness (especially the critical boxes), obtains any other necessary information, and clarifies any questions about the report.
- Assigns an identifying immunization project number using the 2-letter state postal abbreviation, 2- or 4-digit representation for year, and the state numbering sequence. For example, the 57th report received in Arizona in 2011 begins with AZ, followed by 11, followed by 057, and should look like this: AZ11057. This number is entered into box 24 of the VAERS report.
- Sends the original report with the identifying number to VAERS and keeps a copy. As with local reporting, the cases should be forwarded rapidly to VAERS and not sent in a batch.
- Any further correspondence about a report must include the 6-digit VAERS ID number, which is assigned by the VAERS system. Reports are entered into the VAERS database under this number. It is also helpful to have the patient's name and date of birth, if available, to help identify the specific report. VAERS maintains the confidentiality of patients' personal identifying information, consistent with the requirements of the NCVIA.
- Completes the quarterly update report that is sent by VAERS via Epi-X to each SHC. (Although these follow-up requests are sent quarterly, the case reports are scanned upon receipt at VAERS and available to CDC and FDA for evaluation in near real time upon request.) This report contains a list of all initial reports received during the quarter, by VAERS ID number and SHC project number, and serves as an acknowledgment of those reports. Specific missing or incomplete information for these reports is noted and completed in the appropriate boxes. The quarterly update report also lists reports for which VAERS requests recovery status at 60 days postvaccination and at 1 year postvaccination. The SHC submits to VAERS any requested missing information, as well as follow-up recovery status information for each listed report at 60 days and 1 year postvaccination. The SHC may update any other pertinent information about these individuals, such as vaccination information or date of birth. Reponses to quarterly report questions can be submitted to VAERS by mail, fax, or email.
- Update VAERS with any personnel, fax, phone, or address changes. This is done by means of a quarterly e-mail request from VAERS to the state health department.

## V. Evaluation of VAERS

VAERS reports are received and processed by staff at the VAERS contract site. Upon receipt by VAERS, reports are entered into a database, and trained staff use a standard set of coding terms from the Medical Dictionary for Regulatory Affairs (MedDRA) (http://www.meddramsso.com/) to code the adverse event(s); a report may include more than one AE. FDA and CDC medical officers and vaccine safety experts review reports of deaths and other serious events and conduct other analyses to address specific safety concerns and to evaluate trends in reporting. FDA also conducts analysis of reports by vaccine lots. Although all serious reports are reviewed, it is primarily by analyzing all reports in aggregate that possible causal relationships between vaccines and AE can be properly detected and assessed. When vaccine safety concerns are detected in VAERS they almost always require further assessment in other systems such as the Vaccine Safety Datalink (VSD) (see below).

Approximately 28,000 US reports of AE following immunization (AEFI) are now received by VAERS each year (CDC, unpublished data). All reports are accepted and entered without case-by-case determination of whether the AE could have been caused by the vaccine in question. To put the number of reports of AE in perspective, it should be noted that each year over 220 million doses of vaccine are distributed in the United States (CDC unpublished data). Additionally, the type and severity of events reported vary from minor local reactions or fever to death. Of the US primary reports received between 2006 and 2010, 0.6% reported death as the outcome; 7.7% reported a serious nonfatal adverse event (as defined above), and 91.7% reported non-serious events (CDC unpublished data).

From 2006 through 2010, vaccine providers submitted 37% of US VAERS reports, vaccine manufacturers submitted 27%; patients or parents submitted 10%, and 26% came from other or unknown sources (CDC unpublished data).

Direct reporting to VAERS or to the SHC by healthcare providers is strongly encouraged, as these reports usually arrive on a more timely basis than those submitted first submitted to manufacturers. Manufacturers are not required to provide these reports to VAERS immediately upon receipt unless serious or unexpected events have occurred. As a result, evaluation of non-serious vaccine-associated events may be delayed.

### *Usefulness*

1. Detect new, unusual, or rare vaccine AE
2. Assess the safety of newly licensed vaccines
3. Identify potential risk factors in vaccinees for particular types of AE
4. Rapidly respond to vaccine safety concerns or public health emergencies
5. Identify vaccine lots with increased numbers or types of reported AE
6. Monitor trends in known AE, particularly increases

The data from VAERS have been used by FDA, CDC, and the National Vaccine Injury Compensation Program at the Health Resources and Services Administration (HRSA), vaccine policy bodies, including the Advisory Committee on Immunization Practices (ACIP) (http://www.cdc.gov/vaccines/recs/acip/default.htm), and other stakeholders. Below are some recent examples of how VAERS data has contributed to public health, listed by some of the major objectives of VAERS:

1. To detect new, unusual, or rare AE: The classic example is that VAERS detected an unexpected number of intussusception reports after an earlier rotavirus vaccine Rotashield®.[9] Further investigation in other systems verified this association and the Rotashield® vaccine is no longer licensed.[10-12]
2. Assess the safety of newly licensed vaccines: VAERS has been used to assess the safety profile of the human papillomavirus vaccine; these findings have supported the indications and recommendations.[13]

3. Identify potential risk factors in vaccinees for particular types of AE: VAERS contributed data to support severe combined immunodeficiency syndrome (SCID) as a new contraindication for rotavirus vaccine.[14, 15]
4. Rapidly respond to vaccine safety concerns or public health emergencies: VAERS provided first national data during 2009-10 H1N1 response. The first 2 months of data was published 3 months after the start of the program.[16]

VAERS data have also been used by the Institute of Medicine (IOM) Vaccine Safety Committee (http://www.iom.edu/Activities/PublicHealth/ImmunizationSafety.aspx) in an extensive assessment of the causal relations between common childhood vaccines and AE. IOM established an independent expert committee that reviewed hypotheses about existing and emerging immunization safety concerns during 2001–2004. A focused report has been published regarding each hypothesis addressed. These IOM reports summarize the current epidemiologic evidence (including information obtained from VAERS) for causality between an immunization and a hypothesized health effect, the biologic mechanisms relevant to the adverse event hypothesis, and the significance of the issue in a broader societal context. Hypotheses reviewed and published include the following: Measles-Mumps-Rubella Vaccine and Autism,[17] Thimerosal-Containing Vaccines and Neurodevelopmental Disorders,[18] Multiple Immunizations and Immune Dysfunction,[19] Hepatitis B Vaccine and Demyelinating Neurological Disorders,[20] SV40 Contamination of Polio Vaccine and Cancer,[21] Vaccinations and Sudden Unexpected Death in Infancy,[22] Influenza Vaccines and Neurological Complications,[23] and Vaccines and Autism.[24] Executive summaries for each of these reports are available free of charge at the IOM Vaccine Safety Committee website listed above. These references may be useful to providers or public health officials who are called on to answer the public's questions on vaccine safety and the occurrence of AE. Another IOM report is expected to be released in late 2011 and will review adverse health effects associated with eight vaccines.

### *Reporting sensitivity*

Like all passive surveillance systems, VAERS is subject to varying degrees of underreporting. The sensitivity of VAERS is affected by the likelihood that parents and/or vaccinees detect an AE, parents and/or vaccinees bring the event to the attention of their health-care provider(s), parents and/or healthcare providers suspect an event is related to prior vaccination, parents and/or healthcare providers are aware of VAERS, and that parents and/or health-care providers report the event. The completeness of reporting of AE associated with certain vaccines varies according to the severity of the event and the specificity of the clinical syndrome to the vaccine.[25,26] Stimulated reporting also occurs due to media attention on specific AE.

Table 3 shows the reporting efficiency to VAERS for various AE from two studies published in 1995 and 2001. The reporting efficiency is the proportion of occurrences of an event after administration of a particular vaccine that are reported to VAERS.[27] For example, the reporting efficiency for paralytic poliomyelitis following oral polio vaccine (severe event, very specific vaccine association, and very rare) was 68%; the reporting efficiency for rash following MMR vaccine was <1% (mild event, many causes).

**Table 3 Reporting efficiency To VAERS for various adverse events[25,26]**

| Event * | Reporting efficiency % |
|---|---|
| OPV and vaccine-associated paralytic polio | 68% |
| Rotashield® rotavirus vaccine and intussusception | 47% |
| MMR + MR and seizures | 37% |
| DTP and seizures | 24% |
| MMR and thrombocytopenia | 4% |
| DTP and hypotonic hyporesponsive episodes | 3% |
| MMR and rash | <1% |

### *Limitations of VAERS*

The limitations of VAERS, which are common to many passive reporting systems, should be considered in interpreting VAERS data.

**Dose distribution data.** An important limitation is that vaccine dose distribution data used to calculate reporting rates are not age or state specific. Dose distribution information, derived from biologics surveillance data provided by vaccine manufacturers, also does not track the amount of vaccine actually administered. This biologics surveillance data is proprietary and is not available to the public. The only exception is for annual influenza vaccine. Data on the number of doses of influenza vaccine administered is calculated by CDC and made available to the public, but is not product specific by brand or manufacturer.

**Quality of information.** Since there are no strict guidelines for reporting, and because anyone may submit reports to VAERS, the accuracy and amount of information vary significantly between reports.

**Underreporting.** Underreporting may occur for several reasons. These include limitations in detection of an event, lack of recognition of association between vaccine and event, or failure to submit a report. Underreporting can affect the ability of VAERS to detect very rare events, although clinically serious events are more likely to be reported than non-serious events.[25]

**Biased and stimulated reporting.** Reports to VAERS may not be representative of all AE that occur. Events that occur within a few days to weeks of vaccine administration are more likely to be submitted to VAERS than events with a longer onset interval. Media attention to particular types of medical outcomes can stimulate reporting, as occurred after the initial 1999 Morbidity and Mortality Weekly Report (*MMWR*) publication describing reports of intussusception associated with a previously licensed rotavirus vaccine, Rotashield®.[9]

**Confounding by drug and disease.** Many reports to VAERS describe events that may have been caused by medications or underlying disease processes. Many AE reports encompass clinical syndromes that are poorly defined, not clearly understood, or represent diagnoses of exclusion (e.g., sudden infant death syndrome).

**Inability to determine causation.** VAERS reports are usually not helpful in assessing whether a vaccine actually caused the reported AE because they lack either unique laboratory findings or clinical syndromes necessary to draw such conclusions.[4] Often multiple vaccines are administered at the same visit, making attribution of causation to a single vaccine or antigen difficult. Additionally, there is lack of an unvaccinated group for comparison. Therefore, reports to VAERS are useful for generating hypotheses, but controlled studies are necessary to confirm any hypotheses generated by VAERS observations.[5]

## VI. Enhancing surveillance

Several activities can be undertaken to improve the quality of VAERS as a surveillance system.

### *Improving quality of information reported*

At the state and local levels, VAERS forms (including the electronic submission form) should be reviewed for completeness and accuracy. The reporter should be contacted if any information is missing. For death and serious outcomes after vaccination, the VAERS staff will attempt to obtain additional documentation (e.g., hospital discharge summaries, laboratory reports, death certificates, autopsy reports). The VAERS staff contacts reporters, health care providers and parents or vaccine recipients routinely to obtain missing information or to correct inaccurate information for all reports of deaths, serious AE, and other selected clinically significant events.

### *Evaluation of system attributes*

An unpublished survey was been conducted to assess the knowledge, attitudes, and practices of both private and military healthcare providers about reporting to VAERS. Data from 2005 indicated that although 90% of pediatricians had knowledge of VAERS, only 55% of internal medicine physicians were familiar with it. Approximately 40% of healthcare providers had

identified at least one adverse event after immunization, but only 19% stated that they had ever reported to VAERS. Vaccine Information statements (VIS) were the most common source used to learn about VAERS.[28] CDC is supporting efforts to further evaluate providers perceptions and behaviors about VAERS and about reporting AE after vaccination.

### *Promoting awareness*

Current outreach and education efforts to promote VAERS include general information brochures in English and Spanish (http://vaers.hhs.gov/resources/vaersmaterialspublications) and an online public use data set (http://vaers.hhs.gov/data/index) and search engine (http://wonder.cdc.gov/vaers.html). Continuing Education articles for healthcare professionals are periodically published or posted on the VAERS website. A Surveillance Summary for VAERS data covering 1991–2001 was published in 2003 and is available at http://www.cdc.gov/MMWR/preview/MMWRhtml/ss5201a1.htm. A bibliography of VAERS and vaccine safety publications is available at (http://vaers.hhs.gov/resources/biblio).

The VAERS contact information is provided on all VISs that are to be handed out at each vaccination visit to persons receiving a vaccine that is covered by the Vaccine Injury Compensation Program (i.e., is listed on the Vaccine Injury Table). VIS use is strongly encouraged for all vaccines, including those not covered by the Vaccine Injury Compensation Program.

VAERS data, without identifying information, are available to the public through the VAERS website (http://vaers.hhs.gov/) for downloading raw data files or via search engine on the CDC WONDER site (http://wonder.cdc.gov/vaers.html) and are updated monthly.

Despite its limitations, VAERS is useful in that it generates signals that trigger further investigations. VAERS can detect unusual increases in previously reported events, and it indicates the number of suspected adverse reactions reported nationwide. As previously stated, the sentinel role of VAERS is particularly significant for newly licensed vaccines, as evidenced in 1999 by the detection of intussusception following a previously licensed rhesus–human rotavirus reassortant tetravalent vaccine, Rotashield®.[9] Although manufacturers are now routinely asked to conduct or sponsor postlicensure studies designed to collect additional safety data for large numbers of vaccine recipients, the need for a national postlicensure surveillance system remains. Like pre-licensure studies, postlicensure studies may not be large enough to detect novel very rare AE, or may take several years to accumulate enough data to assess a rare occurrence. The major strengths of VAERS are:1) it is national in scope and therefore can be used during public health emergencies (as was done during the H1N1 influenza vaccine program), 2) it is timely, 3) it can detect new AE in addition to monitoring prespecified AE found in the pre licensure trials, and 4) it is a national system and anyone can report.

## VII. The National Vaccine Injury Compensation Program

The National Childhood Vaccine Injury Act of 1986 (NCVIA) established the National Vaccine Injury Compensation Program (VICP) to provide compensation for certain AE following immunization. VICP is a "no-fault" system to compensate individuals whose injuries may have been caused by any routinely recommended childhood vaccines. **VICP is separate from VAERS. Reporting an event to VAERS does not result in the filing of a claim to the VICP. A claim for compensation must be filed directly with VICP.** The Vaccine Injury Compensation Program website (http://www.hrsa.gov/vaccinecompensation/table.htm) lists specific injuries or conditions and time frames following vaccination that may be compensated under the VICP.[6, 29]

The toll-free number for the Vaccine Injury Compensation Program is 800-338-2382. Further information can be obtained by visiting their website at http://www.hrsa.gov/vaccinecompensation/ or by writing to National Vaccine Injury Compensation Program, Parklawn Building, Room 11C-26, 5600 Fishers Lane, Rockville, MD 20857.

## VIII. Other Vaccine Safety Monitoring Activities

In addition to VAERS, several other systems exist to monitor the safety of vaccines. Some of these systems are listed below.

The Vaccine Safety Datalink (VSD) project (http://www.cdc.gov/vaccinesafety/activities/vsd.html) is a collaborative effort between CDC's Immunization Safety Office and 10 managed care organizations (MCOs) to monitor immunization safety and address the gaps in scientific knowledge about AE following immunization.[30] The VSD links computerized vaccination and medical records for approximately 9.2 million persons (3% of the total U.S. population). Because these programs have enrollees numbering from thousands to millions, large cohorts may be assembled to examine less frequent AE. Denominator data and control groups are also readily available. Hence the VSD provides a way of testing hypotheses related to vaccine safety. VSD also has implemented a system to conduct near real-time monitoring for specific AE after vaccines in the VSD population.

The Clinical Immunization Safety Assessment (CISA) Network, consisting of six academic centers with vaccine safety expertise working in partnership with CDC (http://www.cdc.gov/vaccinesafety/Activities/CISA.html) is designed to improve scientific understanding of vaccine safety issues at the individual patient level. The CISA network's goal are to study mechanisms of vaccine AE, study individual risk factors for AE, serve as a resource to provide consultation for difficult vaccine safety issues, and to assist in developing vaccine safety guidance.

The Vaccine Analytic Unit (VAU) (http://www.cdc.gov/vaccinesafety/Activities/brighton.html) complements the other CDC vaccine safety surveillance systems (VAERS, VSD, and CISA). VAU works in collaboration with the U.S. Department of Defense (DoD) and with input from the FDA to evaluate longer term safety of vaccines administered to young adults of military age. The VAU uses data from the Defense Medical Surveillance System (DMSS) for its investigations. The DMSS is a unique source of active surveillance data, and contains medical, vaccination and deployment information for US military personnel (active component is approximately 1.4 million individuals).

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## Appendix: Reportable Events Table Definitions

**Anaphylaxis and anaphylactic shock.** Anaphylaxis and anaphylactic shock mean an acute, severe, and potentially lethal systemic allergic reaction. Most cases resolve without sequelae. Signs and symptoms begin minutes to a few hours after exposure. Death, if it occurs, usually results from airway obstruction caused by laryngeal edema or bronchospasm and may be associated with cardiovascular collapse.

**Brachial neuritis** is defined as dysfunction limited to the upper extremity nerve plexus (i.e., its trunks, division, or cords) without involvement of other peripheral (e.g., nerve roots or a single peripheral nerve) or central (e.g., spinal cord) nervous system structures. A deep, steady, often severe aching pain in the shoulder and upper arm usually heralds onset of the condition. The pain is followed in days or weeks by weakness and atrophy in upper extremity muscle groups. Sensory loss may accompany the motor deficits, but is generally a less notable clinical feature.

**Encephalopathy.** For purposes of the Reportable Events Table, a vaccine recipient shall be considered to have suffered an encephalopathy only if such recipient manifests, within the applicable period, an injury meeting the description below of an acute encephalopathy, and then a chronic encephalopathy persists in such person for more than 6 months beyond the date of vaccination.

1. An acute encephalopathy is one that is sufficiently severe so as to require hospitalization (whether or not hospitalization occurred).
   a. For children less than 18 months of age who present without an associated seizure event, an acute encephalopathy is indicated by a "significantly decreased level of consciousness" (see "2" below) lasting for at least 24 hours. Those children less than 18 months of age who present following a seizure shall be viewed as having an acute encephalopathy if their significantly decreased level of consciousness persists beyond 24 hours and cannot be attributed to a postictal state (seizure) or medication.
   b. For adults and children 18 months of age or older, an acute encephalopathy is one that persists for at least 24 hours and is characterized by at least two of the following:
      i. A significant change in mental status that is not medication related: specifically a confusional state, or a delirium, or a psychosis;
      ii. A significantly decreased level of consciousness, which is independent of a seizure and cannot be attributed to the effects of medication; and
      iii. A seizure associated with loss of consciousness.
   c. Increased intracranial pressure may be a clinical feature of acute encephalopathy in any age group.
2. A "significantly decreased level of consciousness" is indicated by the presence of at least one of the following clinical signs for at least 24 hours or greater:
   a. Decreased or absent response to environment (responds, if at all, only to loud voice or painful stimuli);

b. Decreased or absent eye contact (does not fix gaze upon family members or other individuals); or
c. Inconsistent or absent responses to external stimuli (does not recognize familiar people or things).

The following clinical features alone, or in combination, do not demonstrate an acute encephalopathy or a significant change in either mental status or level of consciousness as described above: Sleepiness, irritability (fussiness), high-pitched and unusual screaming, persistent inconsolable crying, and bulging fontanelle. Seizures in themselves are not sufficient to constitute a diagnosis of encephalopathy. In the absence of other evidence of an acute encephalopathy, seizures shall not be viewed as the first symptom or manifestation of the onset of an acute encephalopathy.

1. **Chronic Encephalopathy** occurs when a change in mental or neurologic status, first manifested during the applicable time period, persists for a period of at least 6 months from the date of vaccination. Individuals who return to a normal neurologic state after the acute encephalopathy shall not be presumed to have suffered residual neurologic damage from that event; any subsequent chronic encephalopathy shall not be presumed to be a sequelae of the acute encephalopathy. If a preponderance of the evidence indicates that a child's chronic encephalopathy is secondary to genetic, prenatal or perinatal factors, that chronic encephalopathy shall not be considered to be a condition set forth in the Table. An encephalopathy shall not be considered to be a condition set forth in the Table if it is shown that the encephalopathy was caused by an infection, a toxin, a metabolic disturbance, a structural lesion, a genetic disorder or trauma (without regard to whether the cause of the infection, toxin, trauma, metabolic disturbance, structural lesion or genetic disorder is known).
2. **Chronic Arthritis.** For purposes of the Reportable Events Table, chronic arthritis may be found in a person with no history in the 3 years prior to vaccination of arthropathy (joint disease) on the basis of:
   a. Medical documentation, recorded within 30 days after the onset, of objective signs of acute arthritis (joint swelling) that occurred between 7 and 42 days after a rubella vaccination; and
   b. Medical documentation (recorded within 3 years after the onset of acute arthritis) of the persistence of objective signs of intermittent or continuous arthritis for more than 6 months following vaccination.
   c. Medical documentation of an antibody response to the rubella virus.

The following shall not be considered as chronic arthritis: musculoskeletal disorders such as diffuse connective tissue diseases (including but not limited to rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease, polymyositis/dermatomyositis, fibromyalgia, necrotizing vasculitis and vasculopathies and Sjogren's syndrome), degenerative joint disease, infectious agents other than rubella (whether by direct invasion or as an immune reaction), metabolic and endocrine diseases, trauma, neoplasms, neuropathic disorders, bone and cartilage disorders and arthritis associated with ankylosing spondylitis, psoriasis, inflammatory bowel disease, Reiter's syndrome, or blood disorders.

**Arthralgia** (joint pain) or stiffness without joint swelling shall not be viewed as chronic arthritis.

**Sequela** The term "sequela" means a condition or event, which was actually caused by a condition listed in the Reportable Events Table (http://vaers.hhs.gov/resources/vaersmaterialspublications

# Chapter 22: Laboratory Support for the Surveillance of Vaccine-Preventable Diseases

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## I. Surveillance of Vaccine-Preventable Diseases

Surveillance for vaccine-preventable diseases (VPDs) requires the close collaboration of clinicians, public health professionals, and laboratorians. Public health surveillance relies on both clinical and laboratory reports of VPDs; therefore, appropriate specimen collection, transport, and laboratory testing are essential. This chapter provides guidelines on specimen collection for each VPD and interpretation of laboratory results.

Each public health professional dealing with vaccine-preventable diseases should identify sources of laboratory support for his or her clinical and public health practice. Table 1 lists appropriate tests for VPDs and provides names and contact information for laboratories and laboratory personnel. In addition to the guidelines presented in this chapter, state health department personnel can provide additional guidance on specimen collection, transport, and other related information.

**Table 1. Contact persons for VPD surveillance laboratory support**

| Disease | Test name | Lab contact name | Lab contact/Phone | Lab contact fax | Name of lab | Notes |
|---|---|---|---|---|---|---|
| **Diphtheria** | Culture | Dr. M. Lucia Tondella or Ms. Pam Cassiday | mlt5@cdc.gov 404-639-1239 pxc1@cdc.gov 404-639-1231 | 404-639-4421 | CDC Pertussis and Diphtheria Laboratory | |
| | Toxigenicity testing | Dr. M. Lucia Tondella or Ms. Pam Cassiday | mlt5@cdc.gov 404-639-1239 pxc1@cdc.gov 404-639-1231 | 404-639-4421 | CDC Pertussis and Diphtheria Laboratory | |
| | PCR | Dr. M. Lucia Tondella or Ms. Pam Cassiday | mlt5@cdc.gov 404-639-1239 pxc1@cdc.gov 404-639-1231 | 404-639-4421 | CDC Pertussis and Diphtheria Laboratory | |
| | Serology (antibodies to diphtheria toxin) | Dr. M. Lucia Tondella or Ms. Pam Cassiday | mlt5@cdc.gov 404-639-1239 pxc1@cdc.gov 404-639-1231 | 404-639-4421 | CDC Pertussis and Diphtheria Laboratory | This test is currently not available at CDC. |
| ***Haemophilus influenzae*** | Culture | Dr. Leonard Mayer | lwm1@cdc.gov 404-639-2841 | 404-639-4421 | CDC Meningitis Laboratory | |
| | Serotyping | Dr. Leonard Mayer | lwm1@cdc.gov 404-639-2841 | 404-639-4421 | CDC Meningitis Laboratory | |
| | Antigen detection | Dr. Leonard Mayer | lwm1@cdc.gov 404-639-2841 | 404-639-4421 | CDC Meningitis Laboratory | |
| | Subtyping | Dr. Leonard Mayer | lwm1@cdc.gov 404-639-2841 | 404-639-4421 | CDC Meningitis Laboratory | |
| **Hepatitis A** | | Ruth Jiles | rxg0@cdc.gov 404-639-2339 | 404-639-1563 | CDC Hepatitis Reference Laboratory | |
| **Hepatitis B** | | Ruth Jiles | rxg0@cdc.gov 404-639-2339 | 404-639-1563 | CDC Hepatitis Reference Laboratory | |

**Table 1. Contact persons for VPD surveillance laboratory support**

| Disease | Test name | Lab contact name | Lab contact/Phone | Lab contact fax | Name of lab | Notes |
|---|---|---|---|---|---|---|
| **Influenza** | Culture/viral isolation | Dr. Michael Shaw | mws2@cdc.gov<br>404-639-1405 | 404-639-2350 | CDC Influenza Surveillance and Diagnosis Laboratory | |
| | Antigen detection | Dr. Michael Shaw | mws2@cdc.gov<br>404-639-1405 | 404-639-2350 | CDC Influenza Surveillance and Diagnosis Laboratory | |
| | RT-PCR/ real time RT-PCR | Dr. Michael Shaw | mws2@cdc.gov<br>404-639-1405 | 404-639-2350 | CDC Influenza Surveillance and Diagnosis Laboratory | |
| | Serology | Dr. Michael Shaw | mws2@cdc.gov<br>404-639-1405 | 404-639-2350 | CDC Influenza Surveillance and Diagnosis Laboratory | |
| **Measles** | IgM antibody | Dr. Paul Rota | par1@cdc.gov<br>404-639-4181 | 404-639-4187 | CDC MMR & Herpes Virus Laboratory | |
| | IgG antibody | Dr. Paul Rota | par1@cdc.gov<br>404-639-4181 | 404-639-4187 | CDC MMR & Herpes Virus Laboratory | |
| | Culture | Dr. Paul Rota | par1@cdc.gov<br>404-639-4181 | 404-639-4187 | CDC MMR & Herpes Virus Laboratory | |
| | PCR | Dr. Paul Rota | par1@cdc.gov<br>404-639-4181 | 404-639-4187 | CDC MMR & Herpes Virus Laboratory | |
| **Meningococcal disease** | Culture | Dr. Leonard Mayer | lwm1@cdc.gov<br>404-639-2841 | 404-639 4421 | CDC Meningitis Laboratory | |
| | SASG | Dr. Leonard Mayer | lwm1@cdc.gov<br>404-639-2841 | 404-639 4421 | CDC Meningitis Laboratory | |
| | PCR | Dr. Leonard Mayer | lwm1@cdc.gov<br>404-639-2841 | 404-639 4421 | CDC Meningitis Laboratory | |
| | Susceptibility testing | Dr. Leonard Mayer | lwm1@cdc.gov<br>404-639-2841 | 404-639 4421 | CDC Meningitis Laboratory | |
| | Molecular genotyping (PFGE, MLST, etc.) | Dr. Leonard Mayer | lwm1@cdc.gov<br>404-639-2841 | 404-639 4421 | CDC Meningitis Laboratory | |
| **Mumps** | Culture | Dr. Paul Rota | par1@cdc.gov<br>404-639-4181 | 404-639-4187 | CDC MMR & Herpes Virus Laboratory | |
| | IgM antibody | Dr. Paul Rota | par1@cdc.gov<br>404-639-4181 | 404-639-4187 | CDC MMR & Herpes Virus Laboratory | |
| | IgG antibody | Dr. Paul Rota | par1@cdc.gov<br>404-639-4181 | 404-639-4187 | CDC MMR & Herpes Virus Laboratory | |
| **Pertussis** | Culture | Dr. M. Lucia Tondella<br>or<br>Ms. Pam Cassiday | mlt5@cdc.gov<br>404-639-1239<br>pxc1@cdc.gov<br>404-639-1231 | 404-639-4421 | CDC Pertussis and Diphtheria Laboratory | |
| | PCR | Dr. M. Lucia Tondella<br>or<br>Dr. Kathy Tatti | mlt1@cdc.gov<br>404-639-1239<br>ket2@cdc.gov<br>404-639-3797 | 404-639-4421 | CDC Pertussis and Diphtheria Laboratory | |

**Table 1. Contact persons for VPD surveillance laboratory support**

| Disease | Test name | Lab contact name | Lab contact/Phone | Lab contact fax | Name of lab | Notes |
|---|---|---|---|---|---|---|
| **Pneumococcal disease** | Culture | Dr. Bernard Beall or Dr. Gloria Carvalho | bbeall@cdc.gov 404-639-1237 mcarvalho@cdc.gov 404-639-3558 | 404-639-2070 | CDC Streptococcus Laboratory | |
| | PCR | Dr. Bernard Beall or Dr. Gloria Carvalho | bbeall@cdc.gov 404-639-1237 mcarvalho@cdc.gov 404-639-3558 | 404-639-2070 | CDC Streptococcus Laboratory | |
| | Susceptibility testing | Dr. Bernard Beall or Dr. Gloria Carvalho | bbeall@cdc.gov 404-639-1237 mcarvalho@cdc.gov 404-639-3558 | 404-639-2070 | CDC Streptococcus Laboratory | |
| | Serotyping, (conventional or PCR-based) | Dr. Bernard Beall or Dr. Gloria Carvalho | bbeall@cdc.gov 404-639-1237 mcarvalho@cdc.gov 404-639-3558 | 404-639-2070 | CDC Streptococcus Laboratory | Provide typing of isolates of *S. pneumoniae* only in the setting of an outbreak. PCR-based serotyping can be performed using commercially available supplies. |
| | Genotyping | Dr. Bernard Beall or Dr. Gloria Carvalho | bbeall@cdc.gov 404-639-1237 mcarvalho@cdc.gov 404-639-3558 | 404-639-2070 | CDC Streptococcus Laboratory | |
| | Antibiotic resistance | Dr. Bernard Beall | bbeall@cdc.gov 404-639-1237 | 404-639-4215 | CDC Streptococcus Laboratory | |
| **Poliomyelitis** | Culture | Dr. Steve Oberste | soberste@cdc.gov 404-639-5497 | 404-639-4011 | CDC Polio/ Picornavirus Laboratory | |
| | Intratypic differentiation | Dr. Steve Oberste | soberste@cdc.gov 404-639-5497 | 404-639-4011 | CDC Polio/ Picornavirus Laboratory | |
| | Serology | Dr. Steve Oberste | soberste@cdc.gov 404-639-5497 | 404-639-4011 | CDC Polio/ Picornavirus Laboratory | |
| **Rotavirus** | Antigen EIA | Dr Jon Gentsch | jgentsch@cdc.gov 404-639-2860 | 404-639-3645 | CDC Gastroenteritis Virus Laboratory | |
| | Intratypic differentiation | Dr Jon Gentsch | jgentsch@cdc.gov 404-639-2860 | 404-639-3645 | CDC Gastroenteritis Virus Laboratory | |
| | Serology | Dr Jon Gentsch | jgentsch@cdc.gov 404-639-2860 | 404-639-3645 | CDC Gastroenteritis Virus Laboratory | |
| | Culture | Dr Jon Gentsch | jgentsch@cdc.gov 404-639-2860 | 404-639-3645 | CDC Gastroenteritis Virus Laboratory | |
| **Rubella** | IgG antibody | Dr. Joe Icenogle | jicenogle@cdc.gov 404-639-4557 | 404-639-1516 | CDC MMR & Herpes Virus Laboratory | |
| | IgM antibody | Dr. Joe Icenogle | jicenogle@cdc.gov 404-639-4557 | 404-639-1516 | CDC MMR & Herpes Virus Laboratory | |

**Table 1. Contact persons for VPD surveillance laboratory support**

| Disease | Test name | Lab contact name | Lab contact/Phone | Lab contact fax | Name of lab | Notes |
|---|---|---|---|---|---|---|
| **Rubella cont'd** | Culture | Dr. Joe Icenogle | jicenogle@cdc.gov 404-639-4557 | 404-639-1516 | CDC MMR and Herpes Virus Laboratory | |
| | PCR | Dr. Joe Icenogle | jicenogle@cdc.gov 404-639-4557 | 404-639-1516 | CDC MMR and Herpes Virus Laboratory | |
| **Congenital rubella syndrome** | IgG antibody | Dr. Joe Icenogle | jicenogle@cdc.gov 404-639-4557 | 404-639-1516 | CDC MMR & Herpes Virus Laboratory | |
| | IgM antibody | Dr. Joe Icenogle | jicenogle@cdc.gov 404-639-4557 | 404-639-1516 | CDC MMR & Herpes Virus Laboratory | |
| | Culture | Dr. Joe Icenogle | jicenogle@cdc.gov 404-639-4557 | 404-639-1516 | CDC MMR & Herpes Virus Laboratory | |
| | PCR | Dr. Joe Icenogle | jicenogle@cdc.gov 404-639-4557 | 404-639-1516 | CDC MMR & Herpes Virus Laboratory | |
| | Serology | Dr. Joe Icenogle | jicenogle@cdc.gov 404-639-4557 | 404-639-1516 | CDC MMR & Herpes Virus Laboratory | |
| **Varicella** | DFA | Dr. Scott Schmid | sschmid@cdc.gov 404-639-0066 | 404-639-4056 | National VZV Laboratory | |
| | Culture | Dr. Scott Schmid | sschmid@cdc.gov 404-639-0066 | 404-639-4056 | National VZV Laboratory | |
| | Viral typing/ strain identification | Dr. Scott Schmid | sschmid@cdc.gov 404-639-0066 | 404-639-4056 | National VZV Laboratory | |

## II. General Guidelines for Specimen Collection and Laboratory Testing

Specimen collection and shipping are important steps in obtaining laboratory diagnosis or confirmation for VPDs. Guidelines have been published for specimen collection and handling for viral and microbiologic agents.[1–3] Information is also available on using CDC laboratories as support for reference and disease surveillance;[4, 5] this includes the form required for submitting specimens to CDC (See Appendix 23, Form #CDC 0.5034) and information on general requirements for shipment of etiologic agents (Appendix 24). Although written to guide specimen submission to CDC, this information may be applicable to the submission of specimens to other laboratories.

## III. Disease-specific Guidelines for Specimen Collection and Laboratory Testing

This chapter provides a quick reference summary of the laboratory information from Chapters 1–17 of this manual. Table 2 lists confirmatory and other useful tests for surveillance of vaccine-preventable diseases, and Table 3 summarizes specimen collection procedures for laboratory testing. Because some specimens require different handling procedures, be sure to check with the diagnostic laboratory prior to shipping. When in doubt about what specimens to collect, timing of specimen collection, or where or how to transport specimens, call the state health department and the state laboratory.

### Table 2. Confirmatory and other useful tests for the surveillance of vaccine-preventable diseases

| Disease | Confirmatory tests | Other useful tests |
|---|---|---|
| **Diphtheria** | Culture<br>Toxigenicity testing | PCR<br>Serology (antibodies to diphtheria toxin) |
| ***Haemophilus influenzae*** | Culture | Serotyping (identification of capsular type of encapsulated strains)<br>Antigen detection<br>Subtyping |
| **Hepatitis A** | IgM anti-HAV (positive) | Total anti-HAV (marker of immunity)<br>PCR |
| **Hepatitis B** | IgM anti-HBc (acute infection)<br>HBsAg (acute or chronic infection)* | Anti-HBs (marker of immunity)<br>Total anti-HBc (marker of past or present infection) |
| **Influenza** | Culture<br>Antigen detection (EIA, IFA, EM)<br>Serology<br>PCR | |
| **Measles** | IgM<br>Paired sera for IgG | Culture (for molecular epi)<br>PCR |
| **Meningococcal disease** | Culture | Serogroup-specific PCR<br>Slide agglutination serogrouping<br>PCR |
| **Mumps** | Culture<br>IgM<br>IgG | IgG (for immunity testing) |
| **Pertussis** | Culture<br>PCR | Serology |
| **Pneumococcal disease** | Culture<br>PCR | Antibiotic resistance<br>- serotyping<br>- PCR deduction of serotypes<br>- strain identification (MLST,PFGE) |
| **Poliomyelitis** | Culture-from stool, pharynx, or CSF | Intratypic differentiation (wild vs. vaccine type)<br>Paired serology<br>CSF analysis |
| **Rotavirus** | Culture<br>Paired serology | Nucleic acid electrophoresis<br>PCR genotyping |
| **Rubella** | Paired sera for IgG<br>IgM<br>Culture | PCR |
| **Tetanus** | There are no lab findings characteristic of tetanus | Serology (for immunity testing) |
| **Varicella** | Culture<br>Serology | Viral typing/strain identification<br>DFA |

* *Confirmation of HBsAg positive results by HBsAg neutralization assay should be performed as specified in test package insert.*

### Table 3. Specimen collection for laboratory testing for VPDs

| Disease | Test name | Specimens to take | Timing for specimen collection | Transport requirements | Collection requirements | Other notes |
|---|---|---|---|---|---|---|
| **Diphtheria** | Culture | Swab of nose, throat, membrane | ASAP, when diphtheria is suspected | < 24 hrs: Amies' or similar transport medium<br>≥24 hrs: silica gel sachets | State health departments may call CDC diphtheria lab at 404-639-1231 or 404-639-1239. | ALERT lab that diphtheria is suspected, so that tellurite-containing media will be used. |
| | PCR | Swabs (as above), pieces of membrane, biopsy tissue | Take these specimens at same time as those for culture. | Silica gel sachet; or a sterile dry container at 4°C | State health departments may call CDC diphtheria lab at 404-639-1231 or 404-639-1239. | ALERT lab that diphtheria is suspected, so that specific PCR assay will be used. |

**Table 3. Specimen collection for laboratory testing for VPDs**

| Disease | Test name | Specimens to take | Timing for specimen collection | Transport requirements | Collection requirements | Other notes |
|---|---|---|---|---|---|---|
| **Diphtheria cont'd** | Toxigenicity testing (Elek test) | Isolate from culture (above) | After *C. diphtheriae* has been isolated | Transport medium such as Amies medium, or silica gel sachets | State health departments may call CDC diphtheria lab at 404-639-1231 or 404-639-1239. | |
| | Serology (antibodies to diphtheria toxin) | Serum | Before administration of antitoxin | Frozen (-20°C) | | Collect paired sera, taken 2–3 weeks apart. This test is currently not available at CDC. |
| ***Haemophilus influenzae* type b** | Culture | Blood | ASAP | Blood culture bottles w/broth or lysis-centrifugation tube | Collect 3 separate samples in a 24-hr period. | Request that lab conduct serotyping on any *H. influenzae* isolate from any normally sterile site. |
| | Culture | CSF | ASAP | Sterile, screw-capped tube | | Request that lab conduct serotyping on any *H. influenzae* isolate from any normally sterile site. |
| | Culture | Other normally sterile site | ASAP | | | |
| | Serotyping | Isolate from culture (above) | | | Highest priority are isolates from persons <15 years. | |
| | Antigen detection | Any normally sterile site | ASAP | | | |
| **Hepatitis A** | IgM anti-HAV | Serum | ASAP after symptom onset (detectable up to 6 months) | All sera to be tested for serologic markers of HAV and HBV infection can be kept at ambient temperatures, refrigerated, or frozen for short term (<48 hours). For longer than 48 hours storage, sera should be frozen or refrigerated. | Non-hemolyzed | |
| | Total anti-HAV | Serum | No time limit | | Non-hemolyzed | Measures both IgM and IgG. |
| **Hepatitis B** | IgM anti-HBc | Serum | ASAP after symptom onset (Detectable up to 6 months) | | Non-hemolyzed | |
| | HBsAg | Serum | | | Non-hemolyzed | HBsAg-positive results should be confirmed by HBsAg neutralization assay as specified in the package insert for each assay. |
| | Anti-HBs | Serum | 1–2 months after vaccination | | Non-hemolyzed | |

**Table 3. Specimen collection for laboratory testing for VPDs**

| Disease | Test name | Specimens to take | Timing for specimen collection | Transport requirements | Collection requirements | Other notes |
|---|---|---|---|---|---|---|
| **Influenza** | Culture/viral isolation | Nasal wash, nasopharyngeal aspirates, nasal/ throat swabs, transtracheal aspirate, bronchoalveolar lavage | Within 72 hours of onset of illness | Transport specimens at 4°C if tests are to be performed within 72 hours; otherwise, freeze at -70°C until tests can be performed. | | |
| | Antigen detection and RT–PCR | Nasal wash, nasopharyngeal aspirate, nasal/ throat swabs, gargling fluid, transtracheal aspirates, bronchoalveolar lavage | Within 72 hours of onset of illness | Transport specimens at 4°C if tests are to be performed within 72 hours; otherwise, freeze at -70°C until tests can be performed. | | Save an aliquot of the clinical sample for confirmation and isolation. Viral isolates may be further characterized by WHO/CDC. |
| | Serology | Paired sera | Acute: within 1 week of onset Convalescent: 2–3 weeks after acute | Store at 4°C or frozen. | . | Fourfold rise is a positive result. Consider vaccination history. |
| **Measles** | Culture/PCR | Nasopharyngeal aspirates, throat swabs, urine, heparinized blood | Collect at same time as samples for serology (best within 3 days of rash onset) | | | PCR for molecular typing. Do not collect if after 10 days from rash onset. |
| | IgM antibody | Serum | ASAP, and repeat 72 hours after onset if first negative | | | IgM is detectable for at least 30 days after rash onset. |
| | IgG antibody | Paired sera | Acute: ASAP after rash onset (7 days at the latest)<br>Convalescent: 14–30 days after acute | | | |
| **Meningococcal disease** | Culture* | Blood | ASAP | TI medium is preferred.<br>Blood culture bottles w/broth or lysis-centrifugation tube | | Request that lab conduct serogrouping on any *N. meningitidis* isolate from any normally sterile site. |
| | Culture* | CSF | ASAP | TI medium is preferred.<br>Sterile, screw-capped tube | | Request that lab conduct serogrouping on any *N. meningitidis* isolate from any normally sterile site. |
| | Culture* | Other normally sterile site | ASAP | TI medium is preferred. | | |
| | Serogrouping | Isolate from culture (above) | | Slant, frozen, lyophilized or silica gel pack. | | |
| | PCR | Any normally sterile site | ASAP | Sent frozen on blue ice packs. | | |

**Table 3. Specimen collection for laboratory testing for VPDs**

| Disease | Test name | Specimens to take | Timing for specimen collection | Transport requirements | Collection requirements | Other notes |
|---|---|---|---|---|---|---|
| **Mumps** | Culture | Buccal /parotid swabs, CSF | | | Massage the salivary/parotid gland area for 30 seconds prior to swab collection. | |
| | IgM antibody | Serum | ASAP; antibodies peak about a week after onset | | | |
| | IgG antibody | Paired sera | Acute: within several days of onset<br>Convalescent: 2 weeks after acute | | | |
| **Pertussis** | Culture | Posterior nasopharyngeal swab or aspirate | Within the first 2 weeks of cough onset | Swabs: half-strength charcoal horse blood agar at 4°C<br>Aspirates: in catheter trap at 4°C | Use Dacron or calcium alginate (not cotton) swabs with flexible shaft or aspiration by catheter attached to catheter trap. | Inoculate selective primary isolation media such as charcoal horse blood agar or Bordet-Gengou as soon as possible.<br>A negative culture does NOT rule out pertussis. |
| | PCR | Nasopharyngeal swab or aspirate | Within the first 2 weeks of cough onset | Short term at 4°C; long term -20°C or below | Use Dacron (not calcium alginate or cotton) swabs with flexible shaft or aspiration by catheter attached to catheter trap. | PCR should be validated with culture when possible. |
| | Serology | Acute and convalescent sera | Acute: within the first 2 weeks of cough onset<br>Convalescent: 3–9 weeks after acute | -20°C | | Results are presumptive and should be validated with culture. Serologic results are currently not accepted as laboratory confirmation for purposes of national surveillance. |
| **Pneumococcal disease** | Culture | Normally sterile site | As soon as possible after onset of clinical illness but before administration of antibiotics | Blood culture bottles w/broth or lysis-centrifugation tube or, if from another sterile site, a sterile, screw-capped tube | Collect 2 separate blood samples in a 24-hr period. Most other sterile specimens (e.g., CSF) are collected only once. | |
| | PCR | Normally sterile site | ASAP, soon after administration of antibiotics is a viable option. | Send specimen frozen on blue ice packs. | PCR | |
| | PCR deduction of serotype | Culture-negative sterile site specimen | Specimen frozen immediately | | PCR deduction of serotype | |
| | Susceptibility testing | Pure culture | | Slant, frozen, or silica packet | Susceptibility testing | |
| | Serotyping | Pure culture | | Slant, frozen, or silica packet | Serotyping | |

**Table 3. Specimen collection for laboratory testing for VPDs**

| Disease | Test name | Specimens to take | Timing for specimen collection | Transport requirements | Collection requirements | Other notes |
|---|---|---|---|---|---|---|
| **Poliomyelitis** | Culture | Stool, pharyngeal swab, CSF | Acute | Sterile, screw-capped container | No carrier for stool; saline buffer for swabs | Maintain frozen or transport rapidly to lab; avoid desiccation of swab specimens. |
| | Intratypic differentiation | Isolate from culture (above) | | | | Maintain frozen or transport rapidly to lab; avoid desiccation of swab specimens. |
| | Serology | Paired sera | Acute: ASAP<br>Convalescent: 3 weeks after acute | | | |
| **Rotavirus gastroenteritis** | EIA, PCR genotyping | Stool, sera if stool not available | First to fourth day of illness optimal (stool); third to seventh day (serum) | Sterile, screw-capped container | Bulk stool, whole serum | Keep frozen or transport rapidly to lab; avoid multiple freeze–thaw cycles. |
| | Culture, RNA electrophoresis, EM | Stool | First to fourth day of illness optimal | Sterile, screw-capped container | Bulk stool, whole serum | Keep frozen or transport rapidly to lab; avoid multiple freeze–thaw cycles. |
| | Serology | Paired sera | Acute: ASAP<br>Convalescent: 3 weeks after acute | Sterile, screw-capped container | Whole serum | |
| **Rotavirus-associated seizures** | PCR | CSF | ASAP after symptoms begin | Sterile, screw-capped container | No carrier | Keep frozen or transport rapidly to lab; avoid multiple freeze–thaw cycles. |
| **Rubella** | IgM antibody | Serum | Within 7–10 days of onset of rash | | | |
| | IgG antibody | Paired sera | Acute: within 7–10 days of onset of illness<br>Convalescent: 2–3 weeks after acute | | | |
| | Culture/PCR | Nasopharyngeal swab/wash, throat, urine | Within 4 days of onset of rash | Viral transport media | | Maintain frozen (except urine) or transport rapidly to lab; avoid desiccation of swab specimens. |
| **Congenital rubella syndrome (CRS)** | IgM antibody | Serum | As soon as possible, within 6 months of birth | | | |
| | IgG antibody | Paired sera | | | | Confirmation is by documenting persistence of serum IgG titer beyond the time expected from passive transfer of maternal IgG antibody. |
| | Culture/PCR | Nasopharyngeal swab/wash, urine, blood, cataracts | As soon as possible; every 1–3 months until cultures are repeatedly negative | Viral transport media | | Maintain frozen (except urine) or transport rapidly to lab; avoid desiccation of swab specimens. |

**Table 3. Specimen collection for laboratory testing for VPDs**

| Disease | Test name | Specimens to take | Timing for specimen collection | Transport requirements | Collection requirements | Other notes |
|---|---|---|---|---|---|---|
| **Varicella** | Serology | Serum | Immune status: collect anytime except during acute illness<br>Paired serologic diagnosis: acute within 7–10 days of onset; convalescent 2–3 weeks after acute | | Single IgG assay is useful to assess immune status.<br>Paired serum is used to identify recent infection, but is not the method of choice when rapid diagnosis is needed. | |
| | Direct immuno-fluorescent antibody (DFA) | Scraping/swab from base of vesicle | Acute illness 2–3 days after rash onset and fresh vesicles | | | Used for rapid diagnosis. |
| | Culture | Fluid from vesicles, nasal or throat swabs, serum, spinal fluid, urine, bronchial tree washing or inflamed joints | Acute illness 2–3 days after rash onset and fresh vesicles | | | Definitive diagnosis, but not useful for rapid diagnosis. |
| | Viral typing/ strain identification | Viral isolate (from culture) | Within 2–3 days of rash onset | Storage more than a few hours must be kept on dry ice or frozen at -70°C or below | | Merck and Co., Inc., offers a free viral identification service using PCR analysis (1-800-672-6372). |

* Neisseria meningitidis *culture cannot be performed on specimens sent to CDC, but CDC is available to provide advice and answer questions on culture methods.*

## *A. Diphtheria (see Chapter 1)*

Diagnostic tests used to confirm infection include isolation of *Corynebacterium diphtheriae* on culture and toxigenicity testing. Although no other tests for diagnosing diphtheria are commercially available, CDC can perform a polymerase chain reaction (PCR) test on clinical specimens to confirm infection with a potentially toxigenic strain. PCR can detect nonviable *C. diphtheriae* organisms from specimens taken after antibiotic therapy has been initiated.

Although PCR for the diphtheria toxin gene and its regulatory element, as performed by the CDC Pertussis and Diphtheria Laboratory, provides supportive evidence for the diagnosis, data are not yet sufficient for PCR to be accepted as a criterion for laboratory confirmation. At present, a case that is PCR positive without the isolation of the organism or histopathologic diagnosis or without epidemiologic linkage to a laboratory-confirmed case should be classified as a probable case.

**Isolation of *C. diphtheriae* by culture**

Isolation of *C. diphtheriae* by bacteriological culture is essential for confirming diphtheria. The following should be considered:

- A clinical specimen for culture should be obtained as soon as possible when diphtheria (involving any site) is suspected, even if treatment with antibiotics has already begun.
- Specimens should be taken from the nose and throat, and from the diphtheritic membrane. If possible, swabs also should be taken from beneath the membrane.
- The laboratory should be alerted to the suspicion of diphtheria because isolation of *C. diphtheriae* requires special culture media containing tellurite.
- Isolation of *C. diphtheriae* from close contacts may confirm the diagnosis of the case, even if the patient's culture is negative.

All suspected cases and their close contacts should supply specimens from the nose and throat (i.e., both a nasopharyngeal and a pharyngeal swab) for culture.

**Biotype testing**
After *C. diphtheriae* has been isolated, the biotype (substrain) should be determined. The four biotypes are intermedius, belfanti, mitis, and gravis.

**Toxigenicity testing**
In addition to determining biotype, toxigenicity testing using the Elek test should be performed to determine if the *C. diphtheriae* isolate produces toxin. These tests are not readily available in many clinical microbiology laboratories; isolates should be sent to a reference laboratory proficient in performing the tests.

**Polymerase chain reaction testing**
Additional clinical specimens for PCR testing at CDC should be collected at the time specimens are collected for culture. Because isolation of *C. diphtheriae* is not always possible (many patients have already received several days of antibiotics by the time a diphtheria diagnosis is considered), PCR can provide additional supportive evidence for the diagnosis of diphtheria. The PCR assay allows for detection of the regulatory gene for toxin production (*dtxR*) and the diphtheria toxin gene (*tox*).[6] Clinical specimens (swabs, pieces of membrane, biopsy tissue) can be transported to CDC with cold packs in a sterile empty container or in silica gel sachets. For detailed information on specimen collection and shipping and to arrange for PCR testing, the state health department may contact the CDC Pertussis and Diphtheria Laboratory at 404-639-1231 or 404-639-1239.

**Serologic testing**
Measurement of the patient's serum antibodies to diphtheria toxin before administration of antitoxin may help in assessing the probability of the diagnosis of diphtheria. The state health department or CDC can provide information on laboratories that offer this test (few laboratories have the capability to accurately test antibody levels). If antibody levels are low, diphtheria cannot be accurately ruled out, but if levels are high, *C. diphtheriae* is less likely to produce serious illness.

**Submission of *C. diphtheriae* isolates**
All isolates of *C. diphtheriae* from any body site (respiratory or cutaneous), whether toxigenic or nontoxigenic, should be sent to the CDC Pertussis and Diphtheria Laboratory for reference testing. Clinical specimens from patients with suspected diphtheria to whom diphtheria antitoxin has been released for treatment should also be sent to the CDC Pertussis and Diphtheria Laboratory for culture and PCR testing. To arrange for shipping of specimens, contact your state health department.

## *B.* Haemophilus influenzae *type b (Hib) invasive disease (see Chapter 2)*

**Culture**
Confirming a case of Hib disease requires culturing and isolating the bacterium from a normally sterile body site. Normally sterile site specimens include cerebrospinal fluid (CSF), blood, joint fluid, pleural effusion, pericardial effusion, peritoneal fluid, subcutaneous tissue fluid, placenta, and amniotic fluid. Most hospital and commercial microbiologic laboratories have the ability to isolate *H. influenzae* (Hi) from cultured specimens. All Hi isolates should also be tested for antimicrobial susceptibility according to guidelines in M02-A11 Performance Standards for Antimicrobial Disk Susceptibility Tests (January 2012) from the Clinical Laboratory Standards Institute.[7]

**Serotype testing (serotyping)**
Serotyping distinguishes encapsulated strains, including Hib, from unencapsulated strains, which cannot be typed. The six encapsulated types (designated a–f) have distinct capsular polysaccharides that can be differentiated by slide agglutination with type-specific antisera.

To monitor the occurrence of invasive Hib disease, microbiology laboratories should perform serotype testing of all *H. influenzae* isolates,[8, 9] particularly those obtained from children younger than 5 years of age. To monitor the disease burden and long-term vaccine effectiveness,

Hi isolates from children aged 5–14 years should also be serotyped and reported. Even though Hib disease has declined, laboratories should continue routine serotyping. Contact your state health department if serotyping is not available at your laboratory. State health departments with questions about serotyping should contact the CDC Meningitis and Vaccine Preventable Disease Branch laboratory at 404-639-3158.

**Antigen detection**
Because the type b capsular antigen can be detected in body fluids, including urine, blood, and CSF of patients, clinicians often request a rapid antigen detection test for diagnosis of Hib disease. Antigen detection may be used as an adjunct to culture, particularly in the diagnosis of patients who have received antimicrobial agents before specimens are obtained for culture. Methods for antigen detection include latex agglutination (LA) and counterimmunoelectrophoresis. LA is a rapid and sensitive method used to detect Hib capsular polysaccharide antigen in CSF, serum, urine, pleural fluid, or joint fluid. Counterimmunoelectrophoresis is more specific but less sensitive than LA, but takes longer and is more difficult to perform.

If the Hib antigen is detected in CSF but a positive result is not obtained from culture or sterile site, the patient should be considered as having a probable case of Hib disease and reported as such. Because antigen detection tests can be positive in urine and serum of persons without invasive Hib disease, persons who are identified exclusively by positive antigen tests in urine or serum should not be reported as cases. PCR assays for Hib in clinical specimens are available for research purposes only.[10–12] Isolation of the bacterium is needed to confirm Hi invasive disease, determine the serotype, and test for antimicrobial susceptibility.

**Subtyping**
Although not widely available, subtyping the Hib bacterium by pulsed-field gel electrophoresis (PFGE),[13, 14] multilocus sequence typing (MLST), and 16S rRNA gene sequence typing can be performed for epidemiologic purposes. Some subtyping methods, such as outer membrane proteins, lipopolysaccharides, or enzyme electrophoresis, are no longer recommended or performed because they were unreliable or too labor intensive. The state health department may direct questions about subtyping to the CDC Meningitis and Vaccine Preventable Disease Branch laboratory at 404-639-3158.

## *C. Hepatitis A (see Chapter 3)*

Diagnostic tests used to confirm hepatitis A virus infection include serologic testing, and occasionally, PCR-based assays to amplify and sequence viral genomes.

**Serologic testing**
The diagnosis of acute hepatitis due to hepatitis A virus (HAV) is confirmed during the acute or early convalescent phase of infection by the presence of IgM anti-HAV in serum.

Serum for IgM anti-HAV testing should be obtained as soon as possible after onset of symptoms because IgM anti-HAV generally disappears within 6 months after onset of symptoms.

IgG anti-HAV appears in the acute or convalescent phase of infection, remains for the lifetime of the person, and confers enduring protection against disease.

The antibody test for total anti-HAV measures both IgG anti-HAV and IgM anti-HAV. The presence of total anti-HAV and absence of IgM anti-HAV indicates immunity consistent with either past infection or vaccination. Commercial diagnostic tests are widely available for the detection of IgM and total (IgM and IgG) anti-HAV in serum.

**CDC laboratory special studies**
Occasionally, molecular virologic methods such as PCR-based assays are used to amplify and sequence viral genomes. These assays may be helpful to investigate common-source outbreaks of hepatitis A. Providers with questions about molecular virologic methods should consult with their state health department or the Division of Viral Hepatitis, Laboratory Branch, CDC.

## *D. Hepatitis B (see Chapter 4)*

Diagnostic tests used to confirm hepatitis B virus (HBV) infection include serologic testing, genotyping and subtyping (in outbreak investigations), and occasionally PCR-based assays to amplify/quantify and determine the sequence of viral genomes.

**Serologic testing**

Several well-defined antigen–antibody systems are associated with HBV infection, including HBsAg and anti-HBs; hepatitis B core antigen (HBcAg) and antibody to HBcAg (anti-HBc); and hepatitis B e antigen (HBeAg) and antibody to HBeAg (anti-HBe). Serologic assays are commercially available for all of these except HBcAg because no free HBcAg circulates in blood.

The presence of HBsAg is indicative of ongoing HBV infection and potential infectiousness. In newly infected persons, HBsAg is present in serum 30–60 days after exposure to HBV. Anti-HBc develops in all HBV infections, appearing at onset of symptoms or liver test abnormalities in acute HBV infection, rising rapidly to high levels, and persisting for life. Acute or recently acquired infection can be distinguished by presence of the immunoglobulin M (IgM) class of anti-HBc, which persists for approximately 6 months. IgM anti-HBc may not be present in newly infected children younger than 2 years of age, especially if they acquired their infection through perinatal transmission.

In persons who recover from HBV infection, HBsAg is eliminated from the blood, usually in 2–3 months, and anti-HBs develops during convalescence. The presence of anti-HBs indicates immunity from HBV infection. After recovery from natural infection, most persons will be positive for both anti-HBs and anti-HBc, whereas only anti-HBs develops in persons who are successfully vaccinated against hepatitis B. Persons who do not recover from HBV infection and become chronically infected remain positive for HBsAg (and anti-HBc), although a small proportion (0.3% per year) of these persons may eventually clear HBsAg and develop anti-HBs.

In some cases, anti-HBc is the only serologic marker detected. Isolated anti-HBc can occur after HBV infection in persons who have recovered but whose anti-HBs levels have waned or in persons in whom anti-HBs failed to develop. Certain chronically infected persons may be positive for anti-HBc alone, with HBsAg levels that are below levels detectable by commercially available tests. Infants who are born to HBsAg-positive mothers and who do not become infected may also have detectable anti-HBc for up to 24 months after birth from passively transferred maternal antibody.

The diagnosis of acute hepatitis due to hepatitis B virus infection is serologically confirmed by a positive test for IgM antibody to hepatitis B core antigen (anti-HBc). If testing for IgM antiHBc is not available, the diagnosis of acute hepatitis B can also be confirmed by a positive test for hepatitis B surface antigen (HBsAg) with a negative test for hepatitis A antibody (anti-HAV) (Table 4). Confirmation of HBsAg-positive results by HBsAg neutralization assay should be done as needed according to the manufacturer's instructions in the package insert. In addition to acute HBV infection, both perinatal HBV infection and chronic HBV infection are reportable vaccine-preventable conditions. Chronic infection with HBV is confirmed by a positive test for HBsAg accompanied by a negative test for IgM anti-HBc or by two positive HBsAg test results that are at least 6 months apart. A diagnosis of perinatal HBV infection is confirmed by a positive test for HBsAg in an infant aged 1–24 months born in the United States or in U.S. territories to an HBsAg-positive mother.

**Table 4. Interpretation of hepatitis B serologic tests**

| Serologic Markers | | | | Interpretation |
|---|---|---|---|---|
| HBsAg* | Total Anti-HBc† | IgM Anti-HBc§ | Anti-HBs¶ | |
| - | - | - | - | Susceptible, never infected |
| + | - | - | - | Acute infection, early incubation** |
| + | + | + | - | Acute infection |
| - | + | + | - | Acute resolving infection |
| - | + | - | + | Past infection, recovered and immune |
| + | + | - | - | Chronic infection |
| - | + | - | - | False positive (i.e., susceptible), past infection, or 'low level' chronic infection |
| - | - | - | + | Immune if titer is >10 mIU/ml |

* *Hepatitis B surface antigen*
† *Antibody to hepatitis B core antigen*
§ *Immunoglobulin M*
¶ *Antibody to hepatitis B surface antigen*
** *Transient HBsAg positivity (lasting <18 days) might be detected in some patients during vaccination.*

**Genotyping and subtyping**
Genotyping and subtyping of HBsAg has occasionally been used to investigate outbreaks of hepatitis B, but this procedure is not routinely available in commercial laboratories.

**Molecular analysis**
Molecular virologic methods such as PCR-based assays are available from CDC and commercial laboratories for detection and sequencing of HBV DNA. Although results for HBV DNA are not currently included in the definition for acute hepatitis B, they are included for the chronic HBV definition. Testing for HBV DNA is most commonly used for the purpose of evaluating a patient with diagnosed HBV infection who is receiving or being considered for treatment; these tests are not typically used for the initial diagnosis of infection.

PCR-based methods for amplifying and sequencing the HBV genome, done in conjunction with epidemiologic studies, may be helpful for investigating common-source outbreaks of hepatitis B infection. In addition, these assays are essential for detecting the emergence of vaccine-resistant strains. For example, detection of HBV variants or "escape mutants" among vaccinated infants of HBsAg-positive women is important to determine their potential role in vaccine failures.[15] Healthcare professionals with questions about molecular virologic methods or those who identify HBsAg-positive events among vaccinated persons should consult with their state health department or the Epidemiology Branch, Division of Viral Hepatitis, CDC, 404-718-8500.

## *E. Influenza (see Chapter 6)*

Methods available for the diagnosis of influenza include virus isolation (standard methods and rapid culture assays), molecular detection (reverse transcriptase–polymerase chain reaction [RT–PCR]), detection of viral antigens (enzyme immunoassays [EIA], immunofluorescent antibody [IFA], and commercially available rapid diagnostic kits), and less frequently, electron microscopy and serologic testing.

**Virus isolation**
Virus isolation is the gold standard for influenza diagnosis. The following guidelines should be considered:

- Appropriate samples include nasal washes, nasopharyngeal aspirates, nasal and throat swabs, transtracheal aspirates, and bronchoalveolar lavage.
- Samples should be taken within 72 hours of onset of illness to maximize the probability of isolating virus.
- Rapid culture assays that use immunologic methods to detect viral antigens in cell culture are available. These assays can provide results in 18–40 hours, compared with an average of 4.5 days to obtain positive results from standard culture.

**Molecular testing methods**
RT–PCR, including real-time RT–PCR, can be used to detect the presence of influenza virus in a clinical specimen or to characterize an influenza virus grown in tissue culture or embryonated eggs.

RT–PCR testing can be performed under biosafety level 2 conditions, even for viruses such as avian influenza A(H5N1), which require biosafety level 3 with enhancements for viral culture.

**Antigen detection assays**
Several methods exist for the diagnosis of influenza infection directly from clinical material:

- Cells from the clinical sample can be stained using an immunofluorescent antibody to look for the presence of viral antigen. Nasal washes, nasopharyngeal aspirates, nasal and throat swabs, gargling fluid, transtracheal aspirates, and bronchoalveolar lavage are suitable clinical specimens.
- Commercially available kits to test for the presence of viral antigens fall into three groups: the first detects only influenza type A viruses, while the second detects both influenza type A and B viruses but does not differentiate between virus types; and the third detects both influenza type A and B viruses and distinguishes between the two. Results of these rapid antigen detection tests can be available in less than 1 hour.
- Other less frequently used methods include immunostaining and visualization of viral antigens by electron microscopy.
- When direct antigen detection methods are used for the diagnosis of influenza, it is important to collect and reserve an aliquot of the clinical sample for possible further testing. The medium used to store the specimen for some rapid testing methods is inappropriate for viral culture; in this case, it is necessary to collect two separate samples. These additional or reserved samples may be used to confirm direct test results by culture and to subtype influenza A isolates.

**Serologic testing**
Serologic diagnosis of influenza infection requires paired serum specimens. The acute-phase sample should be collected within 1 week of the onset of illness, and the convalescent-phase sample should be collected approximately 2–3 weeks later.

Hemagglutination inhibition (HI) tests are the preferred method of serodiagnosis. A positive result is a fourfold or greater rise in titer between the acute- and convalescent-phase samples when tested at the same time. Serologic test results are usually available in 24 hours.

While serologic testing can be useful in certain situations where viral culture is not possible or in special studies, serologic diagnosis of influenza is not used for national surveillance because of the lack of standardized testing methods and interpretation.

## *F. Measles (see Chapter 7)*

**Serologic testing**
Serologic testing for antibodies to measles is widely available. Generally, in a previously susceptible person exposed to either vaccine- or wild-type measles virus, the IgM response begins around the time of rash onset and can be detected for 1–2 months. The IgG response starts more slowly, at about 5–10 days after rash onset, but typically persists for a lifetime. The diagnosis of acute measles infection can be made by detecting IgM antibody to measles in a single serum specimen or by detecting a rise in the titer of IgG antibody in two serum specimens obtained approximately 2 weeks apart. Uninfected persons are IgM negative but will either be IgG negative or IgG positive, depending upon their previous infection or vaccination histories.

*Recommendations for serologic testing for measles*

- An enzyme immunoassay (EIA) test for IgM antibody to measles in a single serum specimen, obtained at the first contact with the suspected measles case-patient, is the recommended method for diagnosing acute measles.
- A single-specimen test for IgG is the most commonly used test for immunity to measles because IgG antibody is long-lasting.
- Testing for IgG along with IgM is recommended for suspected measles cases.

- Paired sera (acute and convalescent) may be tested for a rise in IgG antibody to measles to confirm acute measles infection.
- When a patient with suspected measles has been recently vaccinated (6–45 days prior to rash onset), neither IgM nor IgG antibody responses can distinguish measles disease from the response to vaccination. In this instance, a viral specimen should be obtained so CDC can attempt to distinguish between vaccine virus and wild-type virus (Table 5).

**Table 5. Interpretation of measles enzyme immunoassay results***

| IgM Result | IgG Result | Previous infection history | Current infection | Comments |
|---|---|---|---|---|
| + | – or + | Not vaccinated, no prior history of measles | Recently received first dose of measles vaccine | Seroconversion. IgG response depends on timing of specimen collection. |
| + | – or + | Not vaccinated, no prior history of measles | Wild-type measles | Seroconversion. Classic clinical measles. IgG response depends on timing of specimen collection. |
| + | – or + | Previously vaccinated, primary vaccine failure | Recently received second dose of measles vaccine | Seroconversion. IgG response depends on timing of specimen collection. |
| – | + | Previously vaccinated, IgG+ | Recently received second dose of measles vaccine | IgG level may stay the same or may boost. |
| + | + | Previously vaccinated, IgG+ | Wild-type measles | May have few or no symptoms (e.g., no fever or rash). |
| + | + | Recently vaccinated | Exposed to wild-type measles | Cannot distinguish between vaccine or wild-type virus; evaluate on epidemiologic grounds.† |
| – | + | Distant history of natural measles | Vaccine | IgG level may stay the same or may boost. |
| + (at least in some patients) | + | Distant history of natural measles | Wild-type measles | May have few or no symptoms. |

* *These results are those expected when using the capture IgM and indirect IgG enzyme immunoassays and may not apply to different assays due to different techniques and sensitivities/specificities.*

† *However, in this circumstance, IgM testing will be helpful. If negative, it could rule out wild-type measles infection.*

*Tests for IgM antibody.* Although multiple possible methods exist for testing for IgM antibody, EIA is the most consistently accurate test and is therefore the recommended method. There are two formats for IgM tests. The first and most widely available is the indirect format, which requires a specific step to remove IgG antibodies. Problems with removal of IgG antibodies can lead to false-positive[16] or, less commonly, false-negative results.

The second format, IgM capture, does not require the removal of IgG antibodies. This is the preferred reference test for measles. One direct-capture IgM EIA is commercially available.

EIA tests for measles are often positive on the day of rash onset. However, in the first 72 hours after rash onset, up to 30% of tests for IgM may give false-negative results. Tests that are negative in the first 72 hours after rash onset should be repeated (Table 3); serum should be obtained for repeat testing 72 hours after rash onset. IgM is detectable for at least 28 days after rash onset and frequently longer.[17]

When a laboratory IgM test result is suspected of being false-positive (Table 3), additional tests may be performed. False-positive IgM results for measles may be due to the presence of rheumatoid factor in serum specimens. Serum specimens from patients with other rash illness, such as parvovirus B19, rubella, and roseola, have been observed to yield false-positive

reactions in some IgM tests for measles. False-positive tests may be suspected when thorough surveillance reveals no source or spread of cases, when the case does not meet the clinical case definition, or when the IgG result is positive within 3 days of rash onset. In these situations, confirmatory tests may be done at the state public health laboratory or at CDC. IgM results by tests other than EIA can be validated with EIA. Indirect EIA tests may be validated with capture EIA.

*Tests for IgG antibody.* Because tests for IgG require two serum specimens and a confirmed diagnosis cannot be made until the second specimen is obtained, IgM tests are generally preferred. However, if the IgM tests remain inconclusive, a second (convalescent-phase) serum specimen, collected 14–30 days after the first (acute-phase) specimen, can be used to test for an increase in the IgG titer. These tests can be performed in the state laboratory or at CDC. A variety of tests for IgG antibodies to measles are available; these include EIA, hemagglutination inhibition, indirect fluorescent antibody tests, and plaque reduction neutralization. Complement fixation, although widely used in the past, is no longer recommended. The "gold standard" test for serologic evidence of recent measles virus infection is plaque reduction neutralization test of IgG in acute- and convalescent-phase paired sera.

Paired IgG testing for laboratory confirmation of measles requires the demonstration of a fourfold rise in titer of antibody against measles. The tests for IgG antibody should be conducted on both acute- and convalescent-phase specimens at the same time. The same type of test should be used on both specimens. The specific criteria for documenting an increase in titer depend on the test. EIA values are not titers, and increases in EIA values do not directly correspond to rises in titer.

**Virus isolation**

Isolation of measles virus in culture or detection of measles virus by RT–PCR in clinical specimens confirms the diagnosis of measles. However, since culture and RT–PCR can take weeks to perform, they are rarely useful in confirming an actual diagnosis of measles. Also, a negative culture or RT–PCR result does not rule out measles because the tests are greatly affected by the timing of specimen collection and the quality and handling of the clinical specimens. If positive, these tests can be useful adjuncts to diagnosing acute measles when serology results are inconclusive. If measles virus is cultured or detected by RT–PCR, the viral genotype can be used for molecular epidemiology and to distinguish between measles disease caused by a wild-type measles virus and a response to measles vaccination, caused by a vaccine strain.

Viral culture and RT–PCR are important for molecular epidemiologic surveillance to help determine: 1) the origin of the virus, 2) which viral strains are circulating in the United States, and 3) whether these viral strains have become endemic in the United States. Isolation of measles virus is technically difficult and is generally performed in research laboratories.

Specimens (urine, nasopharyngeal aspirates, heparinized blood, or throat swabs) from clinically suspected cases of measles obtained for virus culture should be shipped to the state public health laboratory or to CDC at the direction of the state health department as soon as measles is confirmed. Specimens should be properly stored while awaiting case confirmation (see Appendix 7). Clinical specimens for virus isolation should be collected at the same time as samples for serologic testing. Because virus is more likely to be isolated when the specimens are collected within 3 days of rash onset, collection of specimens for virus isolation should not be delayed until laboratory confirmation is obtained. Clinical specimens should ideally be obtained within 7 days of rash onset and should not be collected if more than 10 days have passed after rash onset.

## *G.* Neisseria meningitiditis*, Meningococcal disease (see Chapter 8)*

*Neisseria meningitidis* is a gram-negative, encapsulated, aerobic diplococcus. Thirteen different meningococcal serologic groups have been defined, five of which (A, B, C, Y, and W135) cause the great majority of disease. The distinction between serogroups is based on the immunochemistry of the capsular polysaccharide, but more recently polymerase chain reaction (PCR) of capsule biosynthesis genes has been used for serogroup determination of isolates.[18] Serogroup A, C, Y, and W135 polysaccharides all elicit a serogroup-specific immune response,

which allows for serogroup-specific vaccines. The serogroup B capsular polysaccharide is poorly immunogenic, thus making it challenging to develop a vaccine to protect against this serogroup. Vaccine development efforts for serogroup B are focusing on outer membrane proteins (OMPs) or other surface molecules rather than the capsular polysaccharide.[19]

**Identification of *N. meningitidis***

The case definition for confirmed meningococcal disease requires isolation of *N. meningitidis* from a normally sterile site. Typically, the isolate comes from blood or cerebrospinal fluid (CSF), but it can also be from joint, pleural, or pericardial fluid. Aspirates or skin biopsies of purpura or petechiae can yield meningococci in cases of meningococcemia. The typical media used to grow the organism are chocolate agar or Mueller-Hinton medium in an atmosphere containing 5% carbon dioxide.[20] Gram staining for *N. meningitidis* is commonly used and continues to be a reliable and rapid method for presumptive identification. Intracellular gram-negative diplococci in CSF can be considered meningococci until proven otherwise.

In addition to bacteriology for definitive detection and identification, latex agglutination can be used for rapid detection of meningococcal capsular polysaccharides in CSF; however, false-negative or false-positive results can occur. Antigen agglutination tests on serum or urine samples are unreliable for the diagnosis of meningococcal disease.[21]

Real-time PCR detects DNA of meningococci in blood, CSF, or other clinical specimens. A major advantage of PCR is that it allows for detection of *N. meningitidis* from clinical samples in which the organism could not be detected by culture methods, such as when a patient has been treated with antibiotics before a clinical specimen is obtained for culture. Even when the organisms are nonviable following antimicrobial treatment, PCR can still detect *N. meningitidis* DNA.[18] Because of the severity of meningococcal disease, it is critical to treat the patient as soon as infection is suspected and not delay to obtain a culture or laboratory results.

**Susceptibility testing**

Routine antimicrobial susceptibility testing of meningococcal isolates is not recommended. *N. meningitidis* strains with decreased susceptibility to penicillin G have been identified sporadically from several regions of the United States, Europe and Africa.[22] Most of these isolates with reduced penicillin susceptibility remain moderately susceptible (minimum penicillin inhibitory concentration of between 0.12 µg/mL and 1.0 µg/mL). High-dose penicillin G remains an effective treatment against moderately susceptible meningococci. Surveillance of susceptibility patterns in populations should be conducted to monitor trends in *N. meningitidis* susceptibility.

**Testing during outbreaks**

Phenotypic and genotypic methods are used to investigate meningococcal diversity. Capsular polysaccharide (serogroup), porin protein PorB (serotype), and porin protein PorA (serosubtype) are all phenotypic characteristics that can be used to distinguish meningococci from one another.[19] Outbreaks of meningococcal disease are usually caused by the same or closely related strains.[23] Molecular genotyping techniques such as pulsed-field gel electrophoresis (PFGE), 16S rRNA gene sequencing, or multilocus sequence typing (MLST) are used for subtype characterization of an outbreak clone.[24, 25] This subtyping helps to better define the extent of the outbreak. It is crucial to have rapid and reliable results in determining the meningococcal serogroup in an outbreak because public health response will differ for vaccine-preventable or nonvaccine-preventable disease. Molecular genotyping provides important tools for understanding the overall epidemiology of meningococcal disease, but different methods may be more useful in certain settings. PFGE or 16S rRNA gene typing seem to be most useful for outbreak and short-time-period epidemiology, whereas MLST has become the "gold standard" for long-term, global tracing of meningococcal population changes.

## H. Mumps (see Chapter 9)

Acute mumps infection can be confirmed by the presence of serum mumps IgM, a significant rise in IgG antibody titer in acute- and convalescent-phase serum specimens, positive mumps virus culture, or detection of virus by RT–PCR.

Serum should be collected as soon as possible after onset of parotitis for IgM testing or as the acute-phase specimen for determining seroconversion. The convalescent-phase specimen for IgG detection should be obtained about 2 weeks later. IgM antibodies are detectable within 5 days after onset of symptoms, reach a maximum level about a week after onset of symptoms, and remain elevated for several weeks or months.[26, 27] The timing of the IgM response to mumps infection in vaccinated persons is highly variable and may be delayed. Virus may be isolated from the buccal mucosa from 6 days before until 10 days after salivary enlargement. Urine is less likely than oral specimens to contain sufficient virus for culture or detection; therefore, buccal swabs are preferred.[28] However, maximal viral shedding occurs 1–3 days prior to onset and through day 5 following onset of symptoms. Virus may be cleared more rapidly from vaccinated persons who become infected, so early collection of viral samples is critical. Prior immunization against mumps or previous natural infection may be documented by the presence of serum IgG mumps-specific antibodies by EIA. The level of IgG, as measured by EIA, that provides immunity has not been established.

**Serologic testing for IgM antibody**
The serologic tests available for laboratory confirmation of mumps acute infections and immunity vary among laboratories. The state health department can provide guidance on available laboratory services and preferred tests.

*Enzyme immunoassay.* EIA is a highly specific test for diagnosing acute mumps infection At the direction of the state health department, healthcare providers and state and local health departments may send serum specimens from persons with suspected mumps cases to the CDC Measles, Mumps, Rubella & Herpes Virus Laboratory Branch for IgM detection by EIA.

*Immunofluorescence assay (IFA).* IFA assays have the advantage of being relatively inexpensive and simple. The reading of IFA IgM tests requires considerable skill and experience since nonspecific staining may cause false-positive readings.

***Note:*** *Commercially available IFA antibody assays and EIA kits for detection of mumps IgM are currently not FDA approved. Each laboratory must validate these tests independently.*

**Viral cultures**
Mumps virus can be isolated from fluid collected from the parotid duct, other affected salivary gland ducts, throat, CSF and urine, although urine is unlikely to yield virus and therefore not recommended. Parotid duct swabs yield the best sample, particularly when the salivary gland area is massaged approximately 30 seconds prior to collection of the buccal/parotid duct fluid. An effort should be made to obtain the specimen as soon as possible after parotitis or meningitis onset. Because few laboratories perform mumps virus culture, it is rarely used for clinical diagnosis in uncomplicated cases. Successful isolation should always be confirmed by immunofluorescence with a mumps-specific monoclonal antibody or by molecular techniques. Molecular typing of virus isolates provides epidemiologically important information and is now recommended (see below).

**Molecular typing**
Molecular techniques such as RT–PCR can be used to detect mumps RNA for mumps confirmation in appropriately collected specimens. Molecular epidemiologic surveillance makes it possible to build a sequence database that will help track transmission pathways of mumps strains circulating in the United States. In addition, typing methods are available to distinguish wild-type mumps virus from vaccine virus. Specimens for molecular typing should be obtained as soon as possible after the onset of parotitis, ideally from the day of onset to 3 days later (not more than 10 days after parotitis). Specific instructions for specimen collection and shipping may be obtained from CDC by contacting the Measles, Mumps, Rubella & Herpes Virus Branch at 404-639-1156/3512. Specimens for virus isolation and molecular typing should be sent to CDC as directed by the state health department.

## *I. Pertussis (see Chapter 10)*

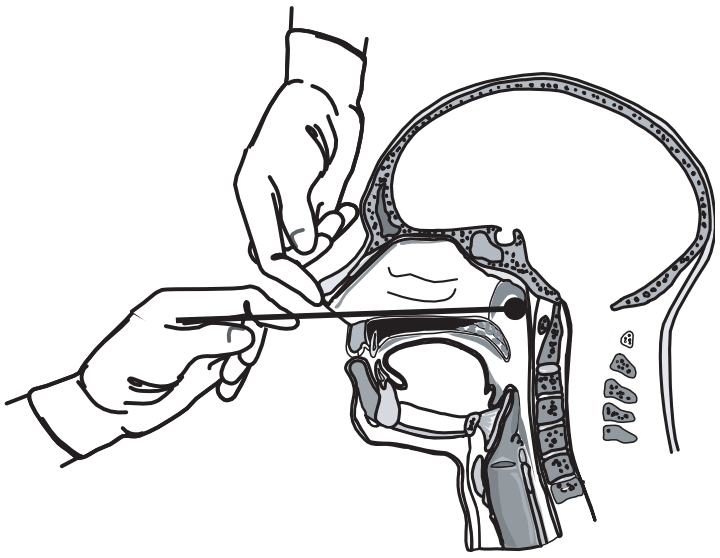
### Culture

The preferred laboratory test for diagnosis of pertussis is isolation of *Bordetella pertussis* by bacterial culture.

Isolation of the *B. pertussis* bacterium is required to test for antimicrobial resistance and for molecular typing by PFGE. Although bacterial culture is specific for the diagnosis, it is relatively insensitive. Under optimal conditions 80% of suspected cases in outbreak investigations can be confirmed by culture; in most clinical situations isolation rates are much lower.[29] The timing of specimen collection can affect the isolation rate, as can inadequately collected specimens and concurrent use of effective antimicrobial agents. Because patients can remain culture positive even while taking effective antibiotics (e.g., when strains are resistant to the antibiotic), nasopharyngeal swab for culture should be obtained regardless of concurrent use of an antibiotic.

Fastidious growth requirements make *B. pertussis* difficult to isolate. Isolation of the organism using direct plating is most successful during the catarrhal stage (i.e., first 1–2 weeks of cough). All persons with suspected pertussis disease should have a nasopharyngeal aspirate or swab obtained from the posterior nasopharynx for culture. *B. pertussis* recovery rates from nasopharyngeal aspirates are similar to or higher than rates of recovery from nasopharyngeal swabs;[29–32] rates of recovery from throat and anterior nasal swabs are unacceptably low. Therefore, specimens should be obtained from the posterior nasopharynx (Figure 1), not the throat, by using Dacron® or calcium alginate swabs, not cotton. Specimens should be plated directly onto selective culture medium or placed in transport medium. Regan-Lowe agar or freshly prepared Bordet-Gengou medium generally is used for culture; half-strength Regan-Lowe can be used as the transport medium. Success in isolating the organism declines if the patient has received prior antibiotic therapy effective against susceptible *B. pertussis* (erythromycin or trimethoprim–sulfamethoxazole), if there is a delay in specimen collection beyond the first 2 weeks of illness, or if the patient has been vaccinated. A positive culture for *B. pertussis* confirms the diagnosis of pertussis. For this reason, access to a microbiology laboratory that is prepared to perform this service for no cost or for limited cost to the patient is a key component of pertussis surveillance.

**Figure 1: Proper technique for obtaining a nasopharyngeal specimen for isolation of *B. pertussis***



**Polymerase chain reaction**
PCR testing of nasopharyngeal swabs or aspirates can be a rapid, sensitive, and specific method for diagnosing pertussis.[33] However, false-positive results may be obtained because of contamination in the laboratory or during specimen collection.[33, 34] PCR is currently available in some laboratories; the assay varies among laboratories and is not standardized. Direct comparison with culture is necessary for validation. Even if a laboratory has validated its PCR method, the result should be considered presumptive, and isolation of *B. pertussis* by culture should always be attempted to ensure that the disease is truly pertussis. *B. pertussis* isolates can then be evaluated for erythromycin susceptibility and by PFGE, which can help define the molecular epidemiology of strains circulating in the United States. Calcium alginate swabs are not acceptable for collecting specimens for PCR.

**Serologic testing**
Although serologic testing has proved useful in clinical studies, it is not yet standardized. Also, the lack of association between antibody levels and immunity to pertussis makes results of serologic testing difficult to interpret. For these reasons, serologic testing is not widely available. In Massachusetts, it is used for clinical diagnosis and reporting.[35] Elsewhere, with few exceptions, it is not known if serologic testing has been appropriately validated or standardized. Therefore, serologic testing should not be relied upon to confirm cases for the purpose of national reporting. Cases meeting the clinical case definition that are serologically positive, but not culture positive or PCR positive, should be reported as probable cases.

**Direct fluorescent antibody testing**
DFA testing of nasopharyngeal secretions may be useful as a screening test for pertussis. A positive DFA result may increase the probability that the patient has pertussis, but it has limited specificity (frequent false-positive results) and is not a confirmatory test. A monoclonal DFA test is available but the sensitivity and specificity are variable.

**Elevated white blood cell count**
An elevated white blood cell count with a lymphocytosis (i.e., increase in lymphocyte count) is usually present in cases of pertussis. The absolute lymphocyte count can reach 20,000/mm or higher. However, there may be no lymphocytosis in very young infants, vaccinated children, or adults with mild cases of pertussis. The white blood cell count is not a confirmation test.

**Pulsed-field gel electrophoresis**
Pulsed-field gel electrophoresis (PFGE) is a type of DNA fingerprinting. This technique has been useful tool for distinguishing epidemiologically related strains (e.g., strains from the same household or small community), while showing diversity within larger geographic areas such as cities, counties, and states.[36, 37]

Questions about performing PFGE on *B. pertussis* isolates, as well as questions about isolating *B. pertussis*, performing erythromycin susceptibility testing, and performing PCR can be directed to the Pertussis and Diphtheria Laboratory at CDC. Call Dr. M. Lucia Tondella at 404-639-1239, or Ms. Pam Cassiday at 404-639-1231. If needed, *B. pertussis* isolates can be sent to:

CDC, Pertussis and Diphtheria Laboratory
Attention: Pam Cassiday
DASH Unit 12
1600 Clifton Road NE
Atlanta, GA 30333

## *J. Pneumococcal infection (see Chapter 11)*

**Culture**
*Streptococcus pneumoniae* is a gram-positive, lancet-shaped diplococcus that commonly inhabits the throat as normal flora. *S. pneumoniae* commonly causes lower and upper respiratory diseases, including pneumonia, meningitis and acute otitis media. Diagnosis of invasive pneumococcal infection is confirmed by culture and isolation of *S. pneumoniae* from

a normally sterile body site (e.g., blood, CSF, pleural fluid, or peritoneal fluid). Alternatively, diagnosis can be confirmed from culture-negative specimens from normally sterile sites using real-time PCR.

**Antibiotic resistance**
The Clinical Laboratory Standards Institute (CLSI) recommends that clinical laboratories test all isolates of *S. pneumoniae* from CSF for resistance to penicillin, cefotaxime or ceftriaxone, meropenem, and vancomycin.[38] For organisms from other sources, laboratories should consider testing for resistance to erythromycin, penicillin, trimethoprim-sulfamethoxazole, clindamycin, cefepime, cefotaxime or ceftriaxone, a fluoroquinolone, meropenem, tetracycline, and vancomycin. Pneumococci resistant to vancomycin have never been described; a strain with a vancomycin minimum inhibitory concentration of 2 µg/ml or greater or zone diameter less than 17 mm should be submitted to a reference laboratory for confirmatory testing, and if resistant, should be reported to the state health department. Because pneumococci are fastidious organisms, some susceptibility testing methods used for other organisms are not appropriate for pneumococci; see the CLSI document for testing recommendations.[38]

**Serotyping**
Current pneumococcal vaccines are based upon capsular polysaccharides. There are currently 91 known capsular serotypes. Since only subsets of capsular serotypes are included in pneumococcal vaccines, serotyping allows the measurement of vaccine efficacy and can provide data for development of expanded-serotype vaccines.[39] CDC and its partners perform active, population-based surveillance for invasive pneumococcal serotypes in specific areas that represent about 30 million people in the United States. CDC does not provide serotyping outside of this surveillance except in specific situations, and this must first be cleared with Dr. Bernard Beall or a representative of the CDC Respiratory Diseases Branch Epidemiology section. Since typing sera are expensive and serotyping is technically difficult, detailed protocols for variations of a simple PCR-based method for serotype deduction are provided at http://www.cdc.gov/ncidod/biotech/strep/pcr.htm and in several publications.[40–43]

## *K. Poliomyelitis (see Chapter 12)*

**Virus isolation**
The likelihood of poliovirus isolation is highest from stool specimens, intermediate from pharyngeal swabs, and very low from blood or spinal fluid. Isolation of poliovirus from stool specimens contributes to the diagnostic evaluation but does not constitute proof of a causal association between the isolated viruses and paralytic poliomyelitis.[44] Isolation of virus from CSF is diagnostic but is rarely accomplished. To increase the probability of poliovirus isolation, at least two stool specimens and two throat swabs should be obtained 24 hours apart from patients with suspected poliomyelitis as early in the course of the disease as possible (i.e., immediately after poliomyelitis is considered as a possible differential diagnosis), but ideally within the first 15 days after onset of paralytic disease. Specimens should be sent to the state or other reference laboratories for primary isolation. Laboratories should forward isolates to CDC for intratypic differentiation to determine whether the poliovirus isolate is wild or vaccine-derived.

Isolation of wild poliovirus constitutes a public health emergency, and appropriate control efforts must be immediately initiated (in consultation among healthcare providers, the state and local health departments, and CDC).

**Serologic testing**
Serology may be helpful in supporting or ruling out the diagnosis of paralytic poliomyelitis. An acute-phase serum specimen should be obtained as early in the course of disease as possible, and a convalescent-phase specimen should be obtained at least 3 weeks later. A fourfold rise in titer between the acute- and convalescent-phase specimens suggests poliovirus infection. Nondetectable antibody titers in both specimens may help rule out poliomyelitis but may be falsely negative in immunocompromised persons, who are also at highest risk for

paralytic poliomyelitis. In addition, neutralizing antibodies appear early and may be at high levels by the time the patient is hospitalized, so that a fourfold rise may not be demonstrated. Vaccinated persons would also be expected to have measurable titers; therefore, vaccination history is important for interpretation of serologic tests. One of the limitations of serology is the inability to distinguish between antibody induced by vaccine-related poliovirus and antibody induced by wild virus. Serologic assays to detect anti-poliovirus antibodies are available in most commercial and state public health laboratories.

## *L. Rotavirus (see Chapter 13)*

Laboratory testing is necessary to confirm group A rotavirus infection and to ensure reliable surveillance and clinical therapy. Because rotavirus is shed in such high concentrations in stool, fecal specimens are preferred for diagnosis of rotavirus. Methods available to diagnose rotavirus infection include detection of viral antigens (EIA, immunochromatography, electron microscopy, and immunostaining) and molecular detection by RT–PCR and nucleotide sequencing.[45] Serologic testing, although less commonly used, can detect a rise in serum IgG and IgA antibodies for recent infections.

### Detection of viral antigens

The most widely available method of antigen detection in stool is EIA, which detects an antigen common to all group A rotaviruses.[45] Several inexpensive commercial EIA kits are available and provide rapid and highly sensitive results (90%–100%). Because EIA is rapid, inexpensive and highly sensitive, it is the most appropriate method for clinical diagnosis and surveillance.

Serotyping and subgrouping can be carried out using EIA methods. Monoclonal antibody–based EIA techniques have been invaluable in defining four globally common rotavirus serotypes (G1–G4) that represent more than 90% of the circulating strains and make up four of the five serotypes in the Rotateq® vaccine.[46] Two subgroups can also be differentiated by EIA techniques based on the reactivity of different monoclonal antibodies with the major capsid antigen that is common to all group A rotaviruses.

Another less frequently used method more appropriate for a research setting is visualization of viral particles by electron microscopy.

### Molecular detection

Several molecular methods can be used to detect rotavirus infection in a clinical specimen and to characterize the virus, but these are used most commonly in research settings. Molecular methods for detection of viral RNA include RT–PCR, nucleotide sequencing, hybridization, and silver staining.[45, 47]

- In recent years, multiplexed, semi-nested RT–PCR genotyping and nucleotide sequencing have become widely used to identify the most common and several uncommon rotavirus G and P genotypes. Hybridization can be used to confirm the results of RT–PCR genotyping.[45, 47]
- Nucleotide sequencing has been used extensively to identify uncommon strains and genetic variants that cannot be identified by RT–PCR genotyping and to confirm the results of genotyping methods.[45, 47]
- Nucleic acid hybridization is a less commonly used method to genotype rotaviruses.
- Electrophoresis and silver staining of viral RNA extracted from fecal specimens is a commonly used method for detection of rotavirus in research settings.

### Virus isolation

Rotavirus can be isolated directly from fecal specimens by inoculation of cell cultures in the presence of trypsin-containing growth medium. This procedure is more appropriate for research laboratories.

### Serologic testing

Routine diagnostic testing for rotavirus infection is primarily based on fecal specimen testing, although rotavirus antigen has been identified in serum samples of patients within 3–7 days of disease onset. Rotavirus diagnosis using serum specimens may prove especially valuable when fecal specimens are not available.[46] Serologic methods most commonly used to detect recent

infections are EIA methods that detect a rise in serum IgG and IgA antibodies. In vaccine trials, the immunogenicity of rotavirus vaccines has been assessed by measuring rotavirus-specific IgG, IgA and neutralizing antibodies to vaccine strains.

### *M. Rubella (see Chapter 14)*

Diagnostic tests used to confirm acute or recent rubella infection or congenital rubella syndrome (CRS) include serologic testing and virus isolation.

**Serologic testing**

Sera should be collected as early as possible (within 7–10 days) after onset of illness, and again at least 7–14 days (preferably 2–3 weeks) later. IgM antibodies may not be detectable before day 5 after rash onset. In case of a negative rubella IgM and IgG in specimens taken before day 5, serologic testing should be repeated. Virus may be isolated from 1 week before to 2 weeks after rash onset. However, maximum viral shedding occurs up to day 4 after rash onset.

False-positive serum rubella IgM tests have occurred in persons with parvovirus infections or positive heterophile test (indicating infectious mononucleosis) or with a positive rheumatoid factor (indicating rheumatologic disease).[48, 49] When a false-positive rubella IgM is suspected, a rheumatoid factor, parvovirus IgM, and heterophile test should be done to rule out a false-positive rubella IgM test result.

The serologic tests available for laboratory confirmation of rubella infections and immunity vary among laboratories. The following tests are widely available and may be used for screening for rubella immunity and/or laboratory confirmation of disease. The state health department can provide guidance on available laboratory services and preferred tests.

- *Enzyme immunoassay.* Most of the diagnostic testing done for rubella antibodies use some variation of the EIA, which is sensitive, widely available, and relatively easy to perform. EIA is the preferred testing method for IgM, using the capture technique; indirect assays are also acceptable.
- *Hemagglutination inhibition (HI) test.* HI once was the gold standard and most commonly used technique for confirmation of rubella infections. It allows for either screening or diagnosis (if paired acute- and convalescent-phase sera are tested). A fourfold rise or greater in HI antibody titer in paired sera is diagnostic of recent infection. The test may be modified to detect rubella-specific IgM antibody, indicative of primary infection.
- *Latex agglutination (LA) test.* The 15-minute LA test appears to be sensitive and specific for screening when performed by experienced laboratory personnel.
- *Immunofluorescent antibody (IFA) assay.* IFA is a rapid and sensitive assay. Commercial assays for both IgG and IgM are available in the United States. Care must be taken with the IgM assay to avoid false-positive results due to complexes with rheumatoid antibody.

**Virus isolation**

Rubella virus can be isolated from nasal, throat, urine, and cataract specimens from persons with rubella or CRS. The best results come from throat swabs. Efforts should be made to obtain clinical specimens for virus isolation from all case-patients (or from at least some patients in each outbreak) at the time of the initial investigation. Virus may be isolated from 1 week before to 2 weeks after rash onset. However, maximum viral shedding occurs up to day 4 after rash onset.

**Molecular typing**

Rubella virus isolates are very important for surveillance. Molecular epidemiologic surveillance provides important information on the origin of the virus, which virus strains are circulating in the United States, and whether these strains have become endemic in the United States.

In obtaining specimens for rubella molecular typing, collect throat swabs within 4 days of rash onset. Specimens for molecular typing from CRS patients should be collected as soon as possible after diagnosis. Appropriate specimens from CRS patients for molecular typing include throat/nasal swabs, urine, and cataracts from surgery. Specimens for virus isolation should be sent to CDC for molecular typing as directed by the state health department.

**Reverse transcription polymerase chain reaction**
In the United Kingdom, RT–PCR has been evaluated extensively for its usefulness in detection of rubella virus in clinical specimens.[50, 51] Clinical specimens obtained for virus isolation and sent to CDC are routinely screened by RT–PCR.

## *N. Congenital rubella syndrome (see Chapter 15)*

Diagnostic tests used to confirm CRS include serologic assays and isolation of the virus. Laboratory confirmation can be obtained by any of the following methods:

- Demonstration of rubella-specific IgM antibodies in the infant's cord blood or serum. In infants with CRS, IgM antibody persists for at least 6–12 months. In some instances, IgM may not be detected until at least 1 month of age; thus, infants with symptoms consistent with CRS who test negative shortly after birth should be retested at 1 month of age.[52]
- Documentation of persistence of serum rubella IgG titer beyond the time expected from passive transfer of maternal IgG antibody.
- Isolation of rubella virus. (Virus may be shed from the throat and urine for a year or longer, but best results come from specimens collected at or before 5 months of age.)
- Detection of rubella virus by RT–PCR.

## *O. Varicella (see Chapter 17)*

Laboratory testing for varicella is not routinely required but is indicated to confirm the diagnosis in severe or unusual cases or to determine varicella susceptibility. Because varicella is the most common disease confused with smallpox, rapid laboratory confirmation of varicella zoster virus (VZV) diagnosis is required in cases of vesicular/pustular rash illness that fall into the category of "moderate risk" for smallpox according to the CDC algorithm. As disease continues to decline, laboratory confirmation will become standard practice. Diagnostic tests used to confirm recent varicella infection include virus isolation and identification, in addition to serologic tests.

**Rapid varicella zoster virus identification**
Rapid virus identification techniques are indicated for a case with severe or unusual disease to initiate specific antiviral therapy. The direct fluorescent antibody (DFA) test is the method of choice for rapid clinical diagnosis. This test is sensitive, specific, and widely available. Results are available within several hours. Specimens are best collected by unroofing a vesicle, preferably a fresh fluid-filled vesicle, and then rubbing the base of a skin lesion with a polyester swab. Crusts from lesions are also excellent specimens. Other specimen sources such as nasopharyngeal secretions, saliva, blood, urine, bronchial washings, and cerebrospinal fluid are considered less desirable sources than skin lesions since positive test results from such specimens are much less likely. Because viral proteins persist after cessation of viral replication, DFA may be positive when viral cultures are negative.

**PCR**
PCR is a powerful technique that permits the rapid amplification of specific sequences of viral DNA that would otherwise be present in clinical specimens at concentrations well below detectable limits. Carefully designed primers that target selected small stretches of viral DNA can be used to replicate small quantities of viral DNA extracted from clinical samples. If a PCR product of the expected size is produced, it is evidence that the virus was present in the lesion. This technique has been extended for VZV by amplifying pieces of varicella DNA that include a mutation in the base sequence that distinguishes the vaccine strain from wild-type varicella strains. Highly specific cutting enzymes (restriction endonucleases) can be selected that will cut the fragment from either wild-type strains or vaccine strain, but not both. This provides a convenient means for discriminating between them. More recently, it has been possible to apply these methods to real-time PCR machines that permit direct, single-step discrimination of vaccine strain from wild-type strains on the basis, for example, of the difference in temperature at which the strands from vaccine versus wild-type DNA fragments re-anneal on cooling. This type of approach has reduced the time required to identify a vaccine adverse event from 2 days to several hours.

**Virus strain identification**
Strain identification can distinguish wild-type VZV from the vaccine (Oka/Merck) strain using PCR and restriction fragment length polymorphism (RFLP) analysis. Such testing is important in situations when it is necessary to distinguish wild-type from vaccine-type virus in suspected vaccine adverse events. More recently, rapid real-time PCR methods using Light Cycler® or TaqMan® technology have made it possible to discriminate vaccine strain from wild-type VZV in a single tube assay requiring only a few hours. Postvaccination situations for which specimens should be tested include: 1) rash with more than 50 lesions occurring 7 or more days after vaccination, 2) suspected secondary transmission of the vaccine virus, 3) herpes zoster in a vaccinated person, or 4) any serious adverse event. The National VZV Laboratory at CDC has the capacity to distinguish wild-type VZV from Oka strain using both conventional and real-time PCR methods. Call the National VZV laboratory at 404-639-0066, 404-639-3667, or email vzvlab@cdc.gov for details about collection and submission of specimens for testing.

**Virus culture**
The diagnosis of VZV infection may be confirmed by culture (isolation) of VZV. Although the virus is difficult to culture, virus isolation should be attempted in cases of severe disease, especially in immunocompromised persons, in order to confirm the diagnosis of varicella. Newer, more sensitive and rapid culture techniques can provide results within 2 to 3 days. Infectious VZV is usually recoverable from fluid from varicella lesions for 2 to 3 days and from zoster lesions for 7 days or longer. VZV may be cultured from other sites such as blood and CSF, especially in immunocompromised patients. Viable VZV cannot be recovered from crusted lesions.

**Serologic testing**
Serologic tests are available for IgG (acute and convalescent) and IgM antibodies to VZV for confirmation of disease. Testing using commercial kits for IgM antibody is not recommended since available methods lack sensitivity and specificity; false-positive IgM results are common in the presence of high IgG levels. The National VZV Laboratory at CDC has developed a reliable IgM capture assay. Call 404-639-0066, 404-639-3667, or email vzvlab@cdc.gov for details about collection and submission of specimens for testing.

**Testing susceptibles**
Single serologic IgG tests may be used to identify the immune status of persons whose history of varicella is negative or uncertain, and who may be candidates for varicella zoster immune globulin (VZIG) or vaccination. Paired acute- and convalescent-phase antibody tests are used in situations of mild or atypical presentation of disease when immediate therapy is not indicated and when, for clinical reasons, a confirmed diagnosis of the acute illness is important, e.g., a suspected second infection due to varicella. Recent evidence suggests that the latex agglutination method may result in false-positive tests that could mistakenly categorize a susceptible person as immune; less sensitive commercial ELISAs are recommended for the purpose of screening.[53] Routine testing for varicella immunity following vaccination is not recommended.

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# Chapter 23: National Surveillance of Vaccine-Preventable Diseases

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## I. Background

The national reporting system for infectious diseases in the United States was initially an archival system designed to document trends in disease occurrence rather than to provide epidemiologically important information needed for prevention and control of diseases.[1, 2] As national immunization programs developed, so did the need for surveillance of vaccine-preventable diseases. The first major support for immunization at the federal level came after the licensure of inactivated poliomyelitis vaccine (IPV) in 1955. During the 2 weeks following the announcement of the results from the successful field trial of this polio vaccine, approximately 4 million doses of vaccine were administered, mostly to elementary schoolchildren. On April 25, 1955, an infant with paralytic poliomyelitis was admitted to a Chicago hospital 9 days after being vaccinated with IPV. The next day, five additional cases of paralytic poliomyelitis were reported from California among children who had received vaccine produced by the same manufacturer of the vaccine administered to the child in Chicago. In each case, paralysis first developed in the limb in which vaccine had been given. On April 27, 1955, the Surgeon General asked the manufacturer to recall all remaining lots of vaccine. The following day, the Poliomyelitis Surveillance Unit was established at the Communicable Disease Center (now the Centers for Disease Control and Prevention [CDC]).

State health officers were asked to designate a polio reporting officer responsible for reporting cases of poliomyelitis among vaccinated persons; later, cases among their family members and other contacts were included. Case reports were transmitted by telephone or telegraph to the Poliomyelitis Surveillance Unit, where the data were collated, analyzed, and disseminated via poliomyelitis surveillance reports. The first report was mailed out on May 1, 1955—only 3 days after the surveillance activity was initiated. The report was prepared and distributed daily for 5 weeks, weekly for the remainder of the summer and fall, and once every 3–4 weeks during the winter.

During the first days of the surveillance program, as more cases were reported, the data demonstrated with increasing certainty that the problem was confined to vaccine produced by a single manufacturer. Production procedures were reviewed and other manufacturers were encouraged to continue vaccine production. Without the surveillance program and the rapid clarification of the scope of the problem that was provided by the analysis of national surveillance data, the manufacture of poliomyelitis vaccine might have been halted in the United States.

This episode highlights several important aspects of modern public health surveillance. Data were collected, analyzed, and disseminated rapidly to allow policy makers to base their decisions on the best information available. Morbidity data were not collected for publication in archival tables but rather to characterize an important public health problem and to facilitate effective public health action.

## II. National Surveillance Activities for Vaccine-Preventable Diseases

In cooperation with state health departments, CDC coordinates national surveillance for diseases and conditions included in the National Notifiable Diseases Surveillance System (NNDSS),[3] including, but not limited to, measles, mumps, rubella, congenital rubella syndrome, diphtheria, tetanus, pertussis, poliovirus infection (nonparalytic), paralytic poliomyelitis, *Haemophilus influenzae* invasive disease, invasive pneumococcal disease, meningococcal disease, hepatitis A, hepatitis B, novel influenza A virus infections, influenza-associated pediatric mortality, and varicella. In the NNDSS, CDC is notified by state health departments of cases of diseases and conditions under national surveillance, as designated

by the Council of State and Territorial Epidemiologists (CSTE); these data are reported in the *Morbidity and Mortality Weekly Report* (*MMWR*). In general, CDC encourages state health departments to submit provisional data through NNDSS before completing case investigations; however, cases are included for publication in the *MMWR* as described in the case status print criteria approved by CSTE.[4]

Development of computer data systems during the 1980s allowed electronic reporting to supplant the previous system of reporting aggregate data to NNDSS by telephone. Beginning in 1989, state health departments were able to report data electronically to NNDSS via the National Electronic Telecommunications System for Surveillance (NETSS).[5] In 2000, states began receiving federal funding to plan and implement integrated electronic systems for disease surveillance; this has developed into the National Electronic Disease Surveillance System (NEDSS).[6] Electronic reporting and data management were developed to provide timely access to demographic and epidemiologic information on each case-patient notification in NNDSS.

CDC publishes NNDSS data weekly in the *MMWR*, and yearly in the *Annual Summary of Notifiable Diseases*. NNDSS data, together with data collected through supplemental surveillance systems, are analyzed by CDC staff and are disseminated through surveillance reports, articles in the *MMWR*, *MMWR Surveillance Summaries*, and other published articles.

## III. Vaccine-Preventable Diseases Reported to NNDSS

State and local public health officials rely on healthcare providers, laboratories, and other public health personnel to report the occurrence of notifiable diseases to state and local health departments. In the United States, requirements for reporting diseases are mandated by state laws or regulations, and the list of reportable diseases in each state differs.[7, 8] CDC and CSTE have established a policy under which state health departments send notifications of cases of selected diseases to CDC through the NNDSS. CDC, in collaboration with the states, has developed the National Electronic Disease Surveillance System (NEDSS).[6] Electronic reporting and data management through NEDSS were developed to provide timely access to demographic and epidemiologic information on each case in the NNDSS. CDC has developed the NEDSS Base System, a platform used by some states to enter, update, and search for demographic and notifiable disease data; other states have developed NEDSS-compatible electronic data systems to collect and transmit surveillance data.

### *Diphtheria*

Reports of diphtheria cases from state health departments to NNDSS are supplemented by additional cases identified through requests received by CDC for diphtheria antitoxin. Clinical data on the severity of illness, patient's vaccination status, outcome, and final diagnosis are obtained for all suspected diphtheria cases. A surveillance worksheet is available to provide guidance for case investigation (Appendix 3).

### *Measles*

Since 1978, substantial effort has been invested in measles surveillance at state and local levels. In 1979, a standard clinical case definition for measles was adopted, and cases were further classified as suspected, probable, or confirmed. Since 1983, only confirmed cases have been included in published reports. In 2000, experts agreed that indigenous transmission of measles had been eliminated in the United States.[9]

In 1985, the National Immunization Program (NIP), CDC, developed the Rapid Surveillance Helper (RASH) system to electronically collect supplemental data on measles cases. RASH has now been supplanted by electronic reporting of supplemental data via NETSS and NEDSS. Data on patient vaccination status, complications, setting of transmission, laboratory confirmation, importation status, and molecular epidemiology of cases are collected (Appendix 8).

### *Mumps*

No supplemental surveillance system for mumps existed before development of the NETSS extended record for collecting epidemiologic information on mumps cases. Data on patient

vaccination status, complications, setting of transmission, laboratory confirmation, importation status, and molecular epidemiology of cases are collected (Appendix 10).

### *Pertussis*

In 1979, the Supplementary Pertussis Surveillance System (SPSS) was developed to allow health departments to collect detailed clinical, demographic, and laboratory information on each case of pertussis.

Supplemental data on pertussis cases, including expanded patient vaccination history information, are now reported electronically via NETSS or NEDSS (Appendix 11). Information is collected on patient age, diphtheria-tetanus-pertussis vaccination history, and selected clinical characteristics, including duration of cough and occurrence of complications such as pneumonia, seizures, encephalopathy, hospitalization, and death. Results of confirmatory laboratory tests and information on antimicrobial therapy are also collected. Reports of encephalopathy and death are confirmed by telephone.

### *Poliomyelitis*

Detailed demographic, clinical, and epidemiologic data are collected on all suspected cases of paralytic poliomyelitis reported to CDC (Appendix 14). Experts who are not affiliated with CDC review suspected cases and determine whether they meet the case definition for paralytic poliomyelitis. Since the adoption of a new case classification system in the 1980s, paralytic poliomyelitis cases have been classified as sporadic, epidemic, imported, or occurring in immunologically abnormal persons, and as being related to wild virus or vaccine virus.[10] Poliovirus infection (asymptomatic) was added to the list of nationally notifiable diseases and conditions in 2007.[11]

### *Rubella and congenital rubella syndrome*

No supplemental surveillance system for rubella existed before the development of the NETSS extended record. Data on patient vaccination status, complications, setting of transmission, laboratory confirmation, importation status, and molecular epidemiology of cases are collected in NNDSS (Appendix 16).

The National Congenital Rubella Syndrome Registry (NCRSR) collects additional clinical and laboratory information on cases of suspected congenital rubella syndrome in the United States (Appendix 17). The registry, established in 1969, includes data only on cases classified as confirmed or compatible. Cases reported through the registry, as well as cases reported through NNDSS, are classified as indigenous (exposure within the United States) or imported (exposure outside the United States). Registry cases are tabulated by year of birth, while cases reported to NNDSS are tabulated by year of notification.

### *Tetanus*

In 1965, the Supplemental Tetanus Surveillance System was developed to allow state health departments to collect supplemental clinical and epidemiologic information on reported cases of tetanus. Case notifications are now sent electronically to NNDSS via NETSS or NEDSS. Information is collected on the clinical history, presence, and nature of associated risk factors, patient vaccination status, wound care, and clinical management (Appendix 18).

## IV. Interpretation Issues

Reporting of vaccine-preventable diseases by physicians and other providers to passive surveillance systems is far from complete. There is little evidence that reporting by physicians has improved greatly in the years since 1922–1923, when periodic community surveys in Hagerstown, Maryland, identified 560 cases of measles among the 7,424 residents. Sixty-four percent of these patients were seen by physicians, but only 40% of these cases were reported to the health department; overall, only 26% of cases were reported to local health authorities.[12] A 1992 study showed that only an estimated 11.6% of pertussis cases in the United States were reported.[13] Although reporting of sporadic cases of measles is thought to be more complete

than that estimated for pertussis, in 1991 an investigation of reporting during an urban outbreak suggested that only 45% of measles patients treated in hospitals were reported.[14] In a review of measles reporting completeness in the US, hospital-based reporting for measles was found to be in the range of 45%-58%.[15] A literature review of articles on surveillance data for measles, pertussis, mumps, and rubella in industrialized countries further illustrates that reporting is incomplete.[16]

The completeness of reporting to supplemental surveillance systems has been evaluated by using capture–recapture methods.[17, 18] After comparing congenital rubella syndrome cases reported to the NCRSR with those identified by the Birth Defects Monitoring Program during 1970–1985, Cochi and colleagues determined that only 22% of these cases were reported to the NCRSR.[19] By comparing the number of deaths reported to CDC surveillance systems with the number reported on death certificates to CDC's National Center for Health Statistics, Sutter and colleagues estimated that only 40% of tetanus-related deaths during 1979–1984, and 33% of pertussis-related deaths during 1985–1988 were reported to CDC supplemental surveillance systems.[13, 20] Likewise, during 1985–1988, an estimated 32% of pertussis-related hospitalizations were reported to SPSS, and during 1985–1991, only 41% of measles-related hospitalizations were reported to RASH.

Those cases reported to a surveillance system may not be representative of all cases. A comparison of hospitalized pertussis patients reported to SPSS with hospital data collected by the Commission on Professional and Hospital Activities' (CPHA) Professional Activities Survey revealed that the case-patients reported to CDC were more likely to have pneumonia, seizures, and encephalitis than were those identified in the CPHA sample. The average hospitalization was longer for those case-patients reported to SPSS than for those in the CPHA sample, suggesting that more severe cases were more likely to be reported to CDC.[13]

To improve specificity and enhance comparability of state-reported cases of vaccine-preventable diseases, case definitions for surveillance have been developed. A standard case definition of paralytic poliomyelitis was introduced in 1958, and a clinical case definition of measles was adopted in 1979. Standard case definitions for surveillance of all vaccine-preventable diseases were first published in 1990,[21] revised in 1997,[22] and have been subsequently updated as needed.[23] However, implementation of uniform case definitions for reporting to local/state health departments and notification to CDC has been incomplete.

## V. Future Directions

To maximize the usefulness of vaccine-preventable diseases surveillance data at the state level, supplemental surveillance systems need to be fully integrated with state notifiable disease data systems, and the data must be fully utilized. Development of systems of distributed data entry, with electronic reporting from healthcare providers, laboratories, and local health departments, is under way in some states and will allow the benefits of rapid analysis of pertinent public health data to be realized at the local or county health department level.

There has been increasing interest in alternative approaches to traditional morbidity surveillance systems.[24, 25] Hospital discharge data sets may be useful for some purposes, although their usefulness in providing timely data for disease control purposes is limited. Ultimately, interoperable electronic health records throughout the U.S. healthcare delivery system (e.g., physicians' offices and clinics) may provide public health data that are more meaningful, timely, accurate, and complete.[26-28] The development of such systems is perhaps most advanced in large health maintenance organizations, hospitals, and large group practices, but rarely available in smaller practices. Aside from the other technological barriers, maintaining patient confidentiality remains a primary concern, and data quality must be assured.

The use of both current and new data sources needs to be improved. Laboratory-based reporting is a valuable adjunct to traditional provider reports[29-32] It is essential for the surveillance of some conditions for which the case definition is based on results of laboratory testing (e.g., Hib) and for certain conditions for which clinical diagnosis is unreliable (e.g., rubella). Laboratory-based reports in such situations may be the only source of accurate information. Improved links

between laboratories and communicable disease surveillance activities within state and local health departments are needed. In the future, enhanced interoperable electronic links with commercial laboratories, and ultimately large group practices, hospitals, and clinics, may provide more complete and timely data than are now available.

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# Chapter 24: State-Specific Surveillance of Vaccine-Preventable Diseases

## Special Notice

TThis *Manual for the Surveillance of Vaccine-Preventable Diseases* provides general guidance to state and local health department personnel who are involved in surveillance activities for vaccine-preventable diseases. The manual provides answers to commonly asked questions regarding the surveillance and reporting of vaccine-preventable diseases. However, specific laws and regulations and logistics of disease reporting are unique to each state or jurisdiction.

It should also be noted that immunization information systems (IISs, or immunization registries) have become an increasingly useful source of surveillance data for patient vaccination histories. IISs vary by state, but when available, they should be included among the sources of information used to collect and report on vaccination history for cases of vaccine-preventable diseases.

Each state or jurisdiction is encouraged to publicize and disseminate its own specific guidelines for surveillance and reporting of vaccine-preventable diseases along with the information in this manual.