Chapter 1: Diphtheria

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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 a sign 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. Respiratory diphtheria usually lasts several days, 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 also may 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 and lead to classic respiratory diphtheria-like illness.[2, 3] Both species 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 2005, 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, and 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 recent years, 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 the sub-Saharan belt in Africa. In the 1990s, a large epidemic of diphtheria occurred in the former Soviet Union, where diphtheria had previously been well controlled, and renewed interest in the factors associated with persistent circulation of toxigenic *C. diphtheriae*.[10, 11] During the past decade, many developing countries have achieved marked reduction in diphtheria incidence with high childhood immunization coverage.[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 did not routinely or recently receive diphtheria toxoid booster vaccinations. Rarely, outbreaks occur in well-vaccinated populations with intense exposure to toxigenic *C. diphtheriae*, but disease is usually mild, with fewer complications and no fatalities.[13]

About half of U.S. adults are estimated to have levels of diphtheria toxin antibodies below the lower limit of protection.

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 did not receive 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. 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]

Contacts of 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 contacts help to halt the spread of disease.

Information obtained through surveillance is used to assess progress towards the year 2010 disease elimination goals. This information is used to characterize infected persons or areas so that additional intervention efforts can be focused to reduce disease incidence.

V. Disease Reduction Goals

A *Healthy People 2010* goal is the elimination of indigenous diphtheria among persons younger than 35 years of age in the United States.[14]

VI. Case Definition

The following case definition for diphtheria was revised in 1995 by the Council of State and Territorial Epidemiologists (CSTE) and published in 1997.[15]

Clinical description

An upper-respiratory tract illness characterized by sore throat, low-grade fever, and an adherent membrane of the tonsil(s), pharynx, and/or nose.

Laboratory criteria for diagnosis

- Isolation of *C. diphtheriae* from a clinical specimen, or
- Histopathologic diagnosis of diphtheria

Case classification

Probable: A clinically compatible case that is not laboratory confirmed and is not epidemiologically linked to a laboratory-confirmed case.

Confirmed: A clinically compatible case that is either laboratory confirmed or epidemiologically linked to a laboratory-confirmed case.

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 may result from infection with other *Corynebacterium* species (*C. ulcerans* or *C. pseudotuberculosis*). These isolates 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* 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 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 useful if nonviable *C. diphtheriae* organisms are present in clinical specimens that are obtained after antibiotic therapy has been initiated. The state health department should be contacted to report a suspected case and to arrange for laboratory testing.

Even if the patient's culture is negative, isolation of C. diphtheriae *from close contacts may confirm the diagnosis of the case.*

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. At present, 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 of the throat and tonsils, including* Streptococcus *spp., Epstein-Barr virus and cytomegalovirus (both of which cause infectious mononucleosis syndrome),* Arcanobacter hemolyticum, Candida albicans*; anaerobic organisms (Vincent's angina), and some viruses. The patient's healthcare provider should be encouraged to perform appropriate laboratory tests to rule out these conditions.*

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 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 be obtained. 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.

Demonstration of toxin production is required to classify a case as confirmed diphtheria.

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 is required to classify a case as confirmed 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 requirement 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 specimen collection and shipping, and to arrange for PCR testing, the state health department may contact the CDC Diphtheria Laboratory at 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 basic immunity.

Submission of C. diphtheriae *isolates*

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

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 (Phone: 404-639-1231) to arrange specimen shipping.

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 CDC 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. Because in the United States diphtheria antitoxin is only available from CDC as an Investigational New Drug (IND)[18] (See Section X, "Treatment," for contact information), additional epidemiologic and clinical data are needed.

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*, or *C. pseudodiphtheriticum*). Such cases should also be reported to CDC.

Cutaneous diphtheria is no longer reportable, 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 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 at least 6 months after the third. If the interval between the third and fourth doses 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 5 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 19–64 years of age should receive a single dose of Tdap (ADACEL®) to replace a single dose of Td for active booster immunization against tetanus, diphtheria and pertussis, if they received their last dose of Td 10 or more years earlier and have not previously received a dose of Tdap.[21] Tdap is not licensed or recommended for adults 65 years of age or older; these persons should receive Td instead.

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[22] 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.[19–22]

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. Detailed recommendations can be obtained from the state health department and CDC. 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 to obtain antitoxin and assistance with arrangements for its transport, and should also contact the local and state health departments.

Antibiotics

Persons with suspected diphtheria should also receive antibiotics to eradicate carriage of *C. diphtheriae,* to limit transmission, and to prevent further production of diphtheria toxin.[23] Treatment with erythromycin or penicillin is administered as a 14-day course.

Local health departments should assure the availability of laboratory capacity for isolation of C. diphtheriae.

Vaccination

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

Contacting CDC

During office hours, 8:00 a.m.–4:30 p.m. Eastern time, contact staff at the Meningitis and Vaccine-Preventable Diseases Branch, NCIRD, CDC, at 404-639-3158 or the DEOC at 404-639-7100 for diphtheria antitoxin at any time.

XI. Enhancing Surveillance

Because diphtheria has occurred only rarely in the United States in recent years, many clinicians may not consider the diagnosis. 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. Even 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 that were endemic for *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*. Hi may be either encapsulated (typeable) or unencapsulated (nontypeable). Six antigenically distinct capsular types of Hi (types a–f) that can cause invasive disease in persons of any age have been identified. Nontypeable strains may also cause invasive disease but are less virulent than encapsulated strains and cause only infrequently serious infection in children.

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.

Because Hib has become a rare cause of invasive disease in the United States, the need to correctly identify the serotype of Hi isolate from any invasive disease has increased.

Before the introduction of effective vaccines, *H. influenzae* serotype b (Hib) was the cause of more than 95% of invasive Hi 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

Before the introduction of Hib conjugate vaccines for infants in late 1990, an estimated 20,000 children younger than 5 years of age (approximately 1 in 200 children) developed invasive Hib disease each year in the United States; nearly two-thirds of all cases occurred among children younger than 18 months. By 2000, the incidence of all Hi invasive disease among children younger than 5 years of age reported to CDC declined by 96%—from 41 cases per 100,000 in 1987 to 1.6 cases per 100,000 in 2000.[2–5] Laboratory-based surveillance data from the Active Bacterial Core surveillance (ABCs) system, which included serotype information on all invasive Hi isolates, provided direct evidence of a decline in Hib disease. From 1989 to 2000, there was a 99% reduction in Hib invasive disease among children younger than 5 years of age, which coincided with the introduction and use of Hib conjugate vaccines among infants and children.[2–5] Continued monitoring of Hi invasive disease through ABCs demonstrated a decrease in invasive Hib rates in children younger than 5 years of age, with the average incidence from 2000 to 2004 being 0.14 cases per 100,000.[6–10]

Because Hib has become a rare cause of invasive disease in the United States, the need to correctly identify the serotype of Hi isolate from any invasive disease has increased. Serotyping by slide agglutination can sometimes be inaccurate, especially since it is not performed routinely in most laboratories. One study found that 28 (70%) of 40 Hi isolates from ABCs sites that had been reported as "Hib" to CDC were actually nontypeable Hi isolates.[11] Another study found discrepancies between the results of slide agglutination subtyping performed at state health departments and those of polymerase chain reaction (PCR) capsule typing performed at CDC for 56 (40%) of 141 isolates.[12] Accurate serotype data on all Hi isolates from children younger than 5 years of age is critical for monitoring Hib vaccine effectiveness. These studies emphasize the importance of quality control and quality assurance in laboratory serotyping.

III. Importance of Rapid Case Identification

Rapid case identification is important for early administration of Hib vaccine and, if needed, for chemoprophylaxis to household and childcare classroom contacts of case-patients.[13] In addition, early notification of Hi invasive disease cases in children younger than 5 years is needed to obtain the Hi isolate before it is discarded so that it can be serotyped. 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

Surveillance is the ongoing, systematic collection, analysis, interpretation, and dissemination of data about a health-related event for use in public health action to reduce morbidity and mortality and to improve health. Surveillance serves at least eight public health functions. These include supporting case detection and public health interventions, estimating the impact of a disease or injury, portraying the natural history of a health condition, determining the distribution and spread of illness, generating hypotheses and stimulating research, evaluating prevention and control measures, and facilitating planning.[14]

Hib surveillance information is used to monitor the effectiveness of immunization programs and vaccines and to assess progress toward disease elimination. It is important that states report data in a timely manner so that national trends of disease can be determined.

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. The elimination of Hib disease among children younger than 5 years of age in the United States has been proposed as an objective for the year 2010.[15]

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VI. Case Definition

The following case definition for *H. influenzae* (invasive disease) has been approved by the Council of State and Territorial Epidemiologists (CSTE) and was published in May 1997.[16]

Clinical case definition

Invasive disease caused by *H. influenzae* can produce any of several clinical syndromes, including meningitis, bacteremia, epiglottitis, or pneumonia.

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, counterimmunoelectrophoresis, or other methods 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 Hi 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.[17]

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 monitor the occurrence of invasive Hib disease, microbiology laboratories should perform serotype testing of all *H. influenzae* isolates,[11, 18] particularly those obtained from children younger than 5 years of age. To monitor disease burden and long-term vaccine effectiveness, Hi isolates from children ages 5–14 years should also be serotyped and reported. 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. Methods for antigen detection include latex agglutination (LA) and counterimmunoeletrophoresis. 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; this test takes longer and is more difficult to perform.

If the Hib antigen is detected in CSF and no bacteria are isolated from culture of a sterile site, the patient should be considered to have a probable case of Hib disease and be reported as such. Because antigen detection tests can be positive in urine and serum of persons without invasive Hib disease, a case that is identified exclusively by positive antigen tests in urine or serum should not be reported as a true case. Polymerase chain reaction (PCR) assays for Hib in clinical specimens are available for research purposes only.[19–21] 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),[22, 23] 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, 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 Hi 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.[24] 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 infants 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 Hi invasive disease in children younger than 5 years of age. The second highest priority for completion of forms should be cases of Hi 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 Hi
  - 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 lists the Hib conjugate vaccines that are currently available. Two combination vaccines that include the Hib conjugate vaccine have been licensed by the FDA following immunogenicity and safety studies (Table 2). These combination vaccines decrease the number of injections needed for protection against vaccine-preventable diseases.

Table 1. Hib conjugate vaccines currently available*

Licensed vaccine	Trade name	Manufacturer/Distributor
PRP-T	ActHIB®	sanofi pasteur
PRP-OMP	PedvaxHIB®	Merck & Co., Inc

* *In April 2007, Wyeth discontinued production of HibTITER® (HbOC).*

Table 2. Combination vaccines containing Hib conjugate vaccines

Licensed vaccine	Trade name	Manufacturer/Distributor
PRP-T + DTaP*	TriHIBit®	sanofi pasteur
PRP-OMP + HepB	COMVAX™	Merck & Co., Inc
PRP-T + DTaP+IPV	Pentacel®	sanofi pasteur

* *On July 15, 1997, TriHIBit® was licensed for use only for the fourth dose of the DTaP and Hib vaccination series among children 15–18 months of age, to be administered at least 6 months following the third DTP or DTaP dose.*

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

Vaccine	Age at 1st dose (months)	Primary series	Booster
PRP-T (ActHIB®)	2–6	3 doses, 2 months apart	12–15 months
	7–11	2 doses, 2 months apart	12–18 months
	12–14	1 dose	2 months later
	15–59	1 dose	NR
PRP-OMP (PedvaxHIB)	2–6	2 doses, 2 months apart	12–15 months
	7–11	2 doses, 2 months apart	12–15 months
	12–14	1 dose	2 months later
	15–59	1 dose	NR

* *In April 2007, Wyeth discontinued production of HibTITER® (HbOC).*
NR = Not required

The recommended schedule for Hib conjugate vaccine administration to previously unvaccinated children is shown in Table 3.[13] Based on the recommended schedule, infants should receive three primary doses of Hib conjugate vaccine with PRP-T at ages 2, 4, and 6 months, or two primary doses of PRP-OMP at 2 and 4 months. A booster dose should be administered at age 12–15 months with any of the conjugate vaccines. Any type of licensed Hib vaccine may be used interchangeably to complete the series, and the number of doses needed to complete the series is determined by the type of vaccine used: four doses are required if either HbOC or PRP-T was administered to a child at least once.[25–27]

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.

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 Hib vaccines protect against serotype b organisms only, 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 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 available for serotype testing of *H. influenzae* isolates. Hospital laboratories unable to perform serotype testing should forward all Hi 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 Hi 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.[28] 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.[13, 29] A child who has recovered from invasive Hib disease should receive Hib conjugate vaccine because natural infection does not always result in the development of antibodies protective against the *H. influenzae* capsular polysaccharide. 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. In households with one or more infants younger than 12 months of age, with a child 1–3 years of age who is inadequately vaccinated, or with an immunocompromised child, all household contacts, including the index case-patient, should receive rifampin prophylaxis. The recommended dose is 20 mg/kg as a single daily dose (maximal daily dose 600 mg) for 4 days. Neonates (less than 1 month of age) should receive 10 mg/kg once daily for 4 days.[13] 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.[29]

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Chapter 3: Hepatitis A

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I. Disease Description

Hepatitis A is caused by infection with the hepatitis A virus (HAV), a nonenveloped RNA agent that is classified as a picornavirus.[1] HAV replicates in the liver and is shed in the feces. Peak concentrations in stool occur during the 2 weeks before onset of illness. Virus is also present in serum, although in concentrations several orders of magnitude less than in feces. The most common mode of HAV transmission is fecal-oral, with the virus transmitted from person to person between household contacts, between sex partners, or by contaminated food or water. Because virus is present in serum during acute infection, bloodborne HAV transmission can occur, but it has been reported infrequently.

The incubation period of hepatitis A is 15–50 days, with an average of 28 days. The illness caused by HAV infection typically has an abrupt onset of signs and symptoms that include fever, malaise, anorexia, nausea, and abdominal discomfort, followed several days later by dark urine and jaundice. Hepatitis A usually does not last longer than 2 months, although some persons may have prolonged or relapsing signs and symptoms for up to 6 months. The likelihood of having symptoms with HAV infection is directly related to age. Among children younger than 6 years of age, most infections are asymptomatic; among older children and adults, infection is usually symptomatic. HAV infection occasionally produces fulminant hepatitis A. The case-fatality rate among persons of all ages with reported cases is approximately 0.3%, but it tends to be higher among older persons (approximately 2% among persons over 40 years of age).

HAV infection does not result in chronic infection or chronic liver disease.

II. Background

Among cases of hepatitis A reported to CDC during 2002–2004, the most frequently reported risk factor was international travel.

Historically in the United States, large nationwide epidemics occurred approximately every 10 years, with the last increase in cases being in 1995.[2] Even between these epidemics, disease rates were relatively high, and many communities experienced periodic epidemics. During the 1980s and 1990s, hepatitis A was one of the most frequently reported infectious diseases in the United States, with approximately 20,000–30,000 cases reported to the National Notifiable Diseases Surveillance System (NNDSS) each year. However, in recent years, hepatitis A incidence has declined precipitously. In 2004, 5,683 hepatitis A cases were reported, for a rate of 1.9 cases per 100,000 population.[2] This is the lowest rate of disease ever reported in the United States, which after correcting for underreporting and asymptomatic infections, represents an estimated 56,000 infections. This remarkable decline in cases can be attributed, at least in part, to hepatitis A vaccination of children in states with consistently elevated rates, which has been recommended by the Advisory Committee on Immunization Practices (ACIP) since 1999.[3]

Based on testing from the Third National Health and Nutrition Examination Survey (NHANES III) conducted during 1988–1994, 31.3% of the general U.S. population has serologic evidence of prior HAV infection. Anti-HAV prevalence is directly related to age, ranging from 9.4% among children 6–12 years of age to 74.6% among persons 70 years of age or older.[4]

Among cases of hepatitis A reported to CDC during 2002–2004, the most frequently reported risk factor was international travel (13.2%), followed by household or sexual contact with a person with hepatitis A (12.8%) and injection drug use (9.4%). An additional 10% of reported cases occurred among children and employees of child care centers and members of their households. Cases occurring during suspected foodborne outbreaks and those among homosexual or bisexual men each accounted for approximately 5%–12% of cases. The proportion of cases associated with being a homosexual or bisexual male and injection drug use varies from year to year (5%–30% of cases) as a result of periodic outbreaks occurring in these subgroups in certain communities. Fifty-six percent of persons with hepatitis A do not identify risk factors; their source of infection may be infected persons who are asymptomatic or have unrecognized infection.[2]

Since 1996, the ACIP has recommended routine hepatitis A vaccination of children living in communities with the highest hepatitis A rates. These communities often are relatively well defined, either geographically or ethnically, and include American Indian, Alaska Native, and selected Hispanic, migrant and religious communities. Historically, epidemics typically occurred every 5–10 years, with peak disease rates severalfold higher than the national average. Coincident with implementation of hepatitis A vaccination of children in recent years, dramatic reductions in hepatitis A rates have been seen in these communities. For example, since 2000, national hepatitis A rates among American Indians and Alaska Natives have been below the national average.

In 1999, recommendations for routine vaccination of children were extended to include children living in the 11 states, as well as in counties and communities in other states, with rates that were at least twice the 1987–1997 national average (i.e., >20 cases per 100,000 population). Routine vaccination was to be considered for children living in the six states, as well as in counties and communities in other states, with rates exceeding the 1987–1997 national average (i.e., >10 but <20 cases per 100,000 population).[3] Coincident with implementation of these recommendations, national disease incidence has declined to historic lows, with the largest declines occurring in the age groups and parts of the country in which vaccination is recommended. The majority of disease and the highest rates currently are in areas in which hepatitis A vaccination of children is not recommended.[5]

In 2006, ACIP expanded their recommendations for hepatitis A vaccination with the intention of further reducing hepatitis A morbidity and mortality in the United States and making possible the consideration of eventual elimination of HAV transmission.[5] Hepatitis A vaccination is recommended routinely for children, for persons who are at increased risk for infection, and for any person wishing to obtain immunity.

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 aged 2–18 years can be considered. Such programs might especially be warranted in the context of rising incidence or ongoing outbreaks among children or adolescents.[5]

Vaccination of persons at increased risk for HAV infection

Persons traveling to or working in countries that have high or intermediate endemicity of infection, men who have sex with men, illegal drug users, persons working with nonhuman primates or with HAV in a research laboratory, persons with clotting-factor disorders, and persons who have chronic liver disease should be vaccinated against hepatitis A.[5]

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.

Pre- and postexposure prophylaxis

Immune globulin (IG) is a sterile preparation of concentrated antibodies (immunoglobulins) made from pooled human plasma. In the United States, only plasma that has tested negative for hepatitis B surface antigen (HBsAg), antibody to human immunodeficiency virus, and antibody to hepatitis C virus is used to produce IG. In addition, the Food and Drug Administration requires that the process used to produce IG include a viral inactivation step or that the final products test negative for HCV RNA.

IG provides protection against hepatitis A through passive transfer of antibody. When administered intramuscularly for preexposure prophylaxis, a dose of 0.02 mL/kg confers protection for more than 3 months, and a dose of 0.06 mL/kg confers protection for 3–5 months. When administered within 2 weeks following an exposure to HAV (0.02 mL/kg), IG is 80%–90% effective in preventing hepatitis A.[5] Efficacy is greatest when IG is administered early in the incubation period; when administered later in the incubation period, IG might only attenuate the clinical expression of HAV infection.

IG should be given to exposed persons as soon as possible, but not more than 2 weeks after the exposure. Recipients may include 1) persons with close contact (household, sexual, or needle sharing) with a person with hepatitis A; 2) staff and attendees at child care centers where a hepatitis A case is recognized; and 3) and persons in certain common-source exposure situations (e.g., patrons at a food establishment with an HAV-infected food handler, if the risk of transmission is determined to be high).[5]

IV. Importance of Surveillance

Disease surveillance should be used to 1) identify contacts of case-patients who require postexposure prophylaxis; 2) detect outbreaks; 3) determine the effectiveness of hepatitis A vaccination; 4) monitor disease incidence in all age groups; 5) determine the epidemiologic characteristics of infected persons, including the source of their infection; and 6) assess and reduce missed opportunities for vaccination. The interpretation of hepatitis A surveillance data depends upon an understanding of the local epidemiology.[6]

V. Disease Reduction Goals

The proposed disease reduction goal for hepatitis A calls for reducing the incidence of reported cases from a baseline of 11.3 cases per 100,000, reported in 1997, to no more than 5 cases per 100,000 by the year 2010.

An acute illness with a discrete onset of symptoms, and jaundice or elevated serum aminotransferase levels

VI. Case Definition

The following case definition for hepatitis A was adopted by the Council of State and Territorial Epidemiologists (CSTE), and was published in May 1997.[7]

Clinical case definition

An acute illness with

- A discrete onset of symptoms, and
- Jaundice or elevated serum aminotransferase levels

Laboratory criteria for diagnosis

- 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

IgM anti-HAV. Virtually all patients with acute hepatitis A have detectable IgM antibody to the capsid proteins of HAV (IgM anti-HAV). Therefore, the diagnosis of acute HAV infection is confirmed during the acute or early convalescent phase of infection by the presence of IgM anti-HAV in serum. IgM anti-HAV generally disappears within 6 months after the onset of symptoms. Persons who test positive for IgM anti-HAV more than 1 year after infection have been reported, as have likely false-positive tests for persons without evidence of recent HAV infection.

Total anti-HAV. IgG anti-HAV appears in the 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 detection of IgM and total (IgM and IgG) anti-HAV in serum.

Serologic testing is necessary to establish a diagnosis for a person with symptoms of acute hepatitis.

CDC laboratory special studies

Serologic testing is necessary to establish a diagnosis for a person with symptoms of acute hepatitis. Molecular virologic methods such as polymerase chain reaction (PCR)-based assays can be used to amplify and sequence viral genomes. These assays may be helpful in investigating 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. For additional information on laboratory support for surveillance of vaccine-preventable diseases, see Chapter 22.

VIII. Reporting

In the United States, case reports of acute viral hepatitis are classified as hepatitis A, acute hepatitis B, or acute hepatitis C, or 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 above). Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[8] These regulations/laws list the 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, schools, daycare facilities, and other institutions. Persons reporting these conditions should contact their state health department for state-specific reporting requirements.

Reporting to CDC

Case reports of hepatitis A and other reportable diseases are transmitted by the state health department weekly to NNDSS via the National Electronic Telecommunications System for Surveillance (NETSS). The NETSS core record includes basic demographic information (excluding personal identifiers)—age, race/ethnicity, sex, date of onset, date of report, and county of residence. The Division of Viral Hepatitis has developed an expanded Data Collection Worksheet to collect information about symptoms, risk factors 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.

IX. Vaccination Schedules

Immune globulin (for hepatitis A postexposure prophylaxis)

For persons with recent exposure (within 2 weeks) to HAV who have not previously received hepatitis A vaccine, a single intramuscular dose of IG (0.02 mL/kg) should be given as soon as possible, but not more than 2 weeks after the exposure. Persons who have received one dose of hepatitis A vaccine at least 1 month before exposure to HAV do not need IG.

Hepatitis A vaccine

Two single-antigen inactivated hepatitis A vaccines are commercially available, HAVRIX® (GlaxoSmithKline) and VAQTA® (Merck & Co., Inc.). Both vaccines are licensed for persons 12 months of age and older. A combined hepatitis A and B vaccine, Twinrix® (GlaxoSmithKline), is also available for use in persons aged 18 years and older. Twinrix is made of the antigenic components used in HAVRIX and Engerix-B® (hepatitis B vaccine). These vaccines should be administered by intramuscular injection in the deltoid muscle or lateral thigh, with a needle length appropriate for the person's age and size. Hepatitis A vaccine is recommended for all children at age 12–23 months, children aged 2–18 years in selected areas of the country, travelers to areas of high or intermediate hepatitis A endemicity, users of illicit drugs, men who have

sex with men, persons with clotting factor disorders who receive therapeutic blood products, and patients with chronic liver disease (see "Vaccination of Persons at increased risk for HAV infection" above.). Any person 18 years old or older who has an indication for both hepatitis A and B vaccination can receive Twinrix.

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).

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.*

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).

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.*

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. Primary vaccination consists of three doses, given on a 0, 1, and 6 month schedule, the same schedule as that used for single-antigen hepatitis B vaccine (Table 3).

Table 3. Recommended doses of TWINRIX® *

(combined hepatitis A and B vaccine for persons >18 years of age)

Group	Age	Dose (EL.U.† and µg)	Volume	No. doses	Schedule§
Adults	>18 years	20 µg (HBsAg protein) 750 EL.U. (Inactivated HAV)	1.0 mL	3	0, 1, 6

* *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

A number of activities can improve the detection and reporting of hepatitis A cases and improve the comprehensiveness and quality of reporting. Chapter 19 describes some general activities for enhancing surveillance; some specific recommendations for hepatitis A are listed below.

Appropriate serologic testing

Surveillance for acute hepatitis is challenging for several reasons. There are five different viruses (A–E) that account for nearly all human viral hepatitis. Because the clinical features of acute hepatitis caused by these viruses are similar, serologic testing is necessary to establish a diagnosis for a person with symptoms of acute hepatitis. Acute infection with several of the hepatitis viruses (HBV, HCV, and HDV) can progress to chronic infection, and review of serologic and clinical information of patients is necessary to make the differentiation between acute and chronic disease. A lack of understanding about the epidemiology of these diseases and underutilization of serologic testing may result in significant misclassification in reporting of acute viral hepatitis. For example, a provider may diagnose jaundice in a child as hepatitis A and not order serologic testing, when in fact the child may have another illness.

Aggressive case investigations of persons with acute disease provide the best opportunity to administer postexposure prophylaxis to contacts

To ensure accurate reporting of viral hepatitis and appropriate prophylaxis of household and sexual contacts, all case reports of viral hepatitis submitted to CDC should be investigated to obtain serologic testing information and risk factor data, and should be entered into the NEDSS base system and hepatitis extended record and reported by the state health department to CDC.

Provider education

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 postexposure prophylaxis to contacts of case-patients and have the potential to significantly reduce missed opportunities to prevent disease.

Case investigation

Aggressive case investigations of persons with acute disease provide the best opportunity to administer postexposure prophylaxis to contacts. Identifying risk factors among persons with acute disease can help better define the epidemiology of viral hepatitis at the state and local level. For example, recognition of hepatitis A outbreaks in child care centers, among men who have sex with men, or among injection-drug users can help target hepatitis A vaccination efforts. Analysis of risk factor data can identify populations where targeted interventions may be needed.

Monitoring surveillance indicators

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

- Cases of hepatitis A in vaccinated persons
- Cases of hepatitis A where death has occurred
- Cases of hepatitis A in children under 18 years of age

Laboratory reporting

Laboratories should be encouraged to report all persons with acute hepatitis. All IgM anti-HAV–positive results should be reported. To facilitate reporting, these IgM results could be included in the state's list of conditions reportable by laboratories.

Hospital-based reporting

Hospitals and infection control practitioners should be encouraged to report all persons with the ICD diagnosis codes of B15: hepatitis A. These patients may then be investigated to determine if they indeed have hepatitis A.

XI. Case Investigation

Guidelines for investigating a suspected case of 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.[6]

Information to collect

The following information is epidemiologically important to collect in a case investigation. Additional information may also be collected at the direction of the state health department.

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

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Chapter 4: Hepatitis B

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In infants, young children, and immunosuppressed persons, most newly acquired HBV infections result in chronic infection.[2]

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 serum-derived body fluids, such as semen and saliva, also have been demonstrated to be infectious. Thus, HBV is a bloodborne 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%.

During the past 10 years, an estimated 60,000–110,000 persons were infected with HBV annually, and 5,000 died from HBV-related disease in the United States.

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.[2] 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 associated with the disease occur in persons in whom chronic infection develops. 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 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 2004, approximately 6,200 cases of acute hepatitis B were reported,[3] which after correcting for underreporting and asymptomatic infections, represented an estimated 60,000 infections. Based on testing from the Third National Health and Nutrition Examination Survey (NHANES III) conducted during 1988–1994, 4.9% of the general U.S. population has serologic evidence of prior HBV infection. An estimated 1.25 million persons have chronic HBV infection.[4]

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 give 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 older adolescents and adults, the most frequently reported risk factor for acute hepatitis B is heterosexual contact with an infected partner or with multiple partners (40%), followed by injection-drug use (16%), male homosexual activity (15%), household contact with a person with hepatitis B (3%), and healthcare employment with frequent blood contact (1%).[3] 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.

In 2003, chronic HBV infection became nationally notifiable and is reportable by state health departments to the NNDSS.

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 factors 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. HBIG also has been shown to provide an estimated 75% protection from HBV infection when initiated within 1 week of percutaneous exposure to HBsAg-positive blood, or when initiated within 14 days of sexual exposure to an HBsAg-positive partner. 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 acute 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 do not need prophylaxis with HBIG but 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 2010 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 by 90% the estimated number of chronic HBV infections in infants and young children and the number of cases of acute hepatitis B reported among persons 2–18 years of age. *Healthy People 2010* objectives have been developed to increase hepatitis B vaccination coverage levels to at least 90% among children 19–35 months of age and adolescents 13–15 years of age.

Disease reduction goals for adults include reducing the rate of acute hepatitis B to 2.4/100,000 in persons aged 19–24 years, 5.1/100,000 in persons aged 25–39 years, and 3.8/100,000 in persons aged 40 years and older. Among adults in high-risk groups, disease reduction goals include reducing the number of cases of acute hepatitis B by 75% in injection-drug users and men who have sex with men, and by 90% in sexually active heterosexuals. Furthermore, efforts should be made to increase vaccination coverage among men who have sex with men to at least 60%.

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.[11]

Acute hepatitis B

Clinical case definition

An acute illness with

- A discrete onset of symptoms, and
- Jaundice or elevated serum aminotransferase levels

Laboratory criteria for diagnosis

1. IgM antibody to hepatitis B core antigen (anti-HBc) positive (if done) or hepatitis B surface antigen (HBsAg) positive.
2. 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

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 HBV infection

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 a 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. 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.

VII. Laboratory 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. One or more of these serologic markers are present during different phases of HBV infection (Table 1). Subtyping of HBsAg has occasionally been used to investigate outbreaks of hepatitis B, but this procedure is not routinely available in commercial laboratories.

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 and persists for variable periods. Anti-HBc develops in all 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. 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. 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.

Table 1. Interpretation of serologic test results for hepatitis B virus infection

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.*

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. Anti-HBs can also 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.

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

Special laboratory studies

Occasionally, molecular virologic methods such as polymerase chain reaction (PCR)-based assays are 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 Branch, Division of Viral Hepatitis, CDC, 404-718-8500.

VIII. Reporting

In the United States, case reports of acute viral hepatitis are classified as hepatitis A, acute hepatitis B, or 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 above). Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[12] These regulations/laws list the 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, schools, day care facilities, 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 hepatitis B virus 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 record includes basic demographic information (excluding personal identifiers)—age, race/ethnicity, sex, date of onset, date of report, county of residence. The Division of Viral Hepatitis has developed an extended Data Collection Worksheet to collect information about symptoms, risk factors 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.

IX. Vaccination Schedules

Hepatitis B immune globulin (HBIG; for hepatitis B postexposure prophylaxis) and the first dose of hepatitis B vaccine should be administered within 12 hours of birth to infants born to HBsAg-positive women. This combination also should be administered as soon as possible to unvaccinated infants whose primary caregivers have acute hepatitis B, to unvaccinated healthcare workers after occupational exposure (preferably within 24 hours but not longer than 1 week), and to sex partners of persons with acute hepatitis B (within 14 days). For infants, the dose of HBIG is 0.5 mL. For children and adults, the dose is 0.06 mL/kg.

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 2).

Table 2. 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 <20 years of age	5	(0.5)	10	(0.5)
Adolescents 11–15 years†	10	(1.0)		
Adults ≥20 years of age	10	(1.0)	20	(1.0)
Dialysis 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.*

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

A combined hepatitis A and B vaccine, Twinrix® (GlaxoSmithKline), is also available for use in persons aged 18 years and older. Twinrix is made 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 to *Neisseria meningitidis* outer membrane protein complex. Pediarix contains recombinant HBsAg, diphtheria and tetanus toxoids and acellular pertussis adsorbed (DTaP), and inactivated poliovirus (IPV). However, these vaccines may not be administered to infants younger than 6 weeks of age; 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 3).

Table 3. Recommended doses of currently licensed combination hepatitis B vaccines*

	Combination vaccine					
Group	COMVAX		PEDIARIX		TWINRIX†	
	Dose (µg)§, ¶	Volume (mL)	Dose (µg)§, **	Volume (mL)	Dose (µg)§, ††	Volume (mL)
Infants						
Mother HBsAg negative	5	0.5	10	0.5	NA	NA
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	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 7.5 µg Haemophilus influenzae type B polyribosylribitol phosphate (PRP) and 125 µg Neisseria meningitidis outer membrane protein complex (OMPC).*

** *Pediarix also contains 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.*

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

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

Any infant of 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 HepB 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.

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, and the minimum interval between doses 1 and 2 is 1 month, and between doses 2 and 3 is 2 months.[10] Dose 3 of hepatitis B vaccine should not be given before 24 weeks of age. Any infant of an HBsAg-negative woman who has not received the third dose of hepatitis B vaccine by the age of 19 months is not up-to-date (Table 4).

Table 4. 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	
	Dose	Age	Dose	Age
Positive	1†	Birth (≤12 hours)	1†	Birth (≤12 hours)
	HBIG§	Birth (≤12 hours)	HBIG§	Birth (≤12 hours)
	2	1-2 mos	2	2 mos
	3¶	6 mos	3	4 mos
			4¶	6 mos (Pediarix) or 12-15 mos (Comvax)
Unknown**	1†	Birth (<12 hours)	1†	Birth (<12 hours)
	2	1-2 mos	2	2 mos
	3¶	6 mos	3	4 mos
			4¶	6 mos (Pediarix) or 12-15 mos (Comvax)
Negative	1†, ††	Birth (before discharge)	1†, ††	Birth (<12 hours)
	2	1-2 mos	2	2 mos
	3¶	6 mos	3	4 mos
			4¶	6 mos (Pediarix) or 12-15 mos (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 preterm infants should be delayed until they weigh 2 kg or are 2 months old, 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 within 12 hours of birth regardless of birthweight.

Children and adolescents

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

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 (Table 2) 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.

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.

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 18 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.

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

The following information is epidemiologically important to collect in a case investigation for acute hepatitis B.[13] Additional information may also be collected at the direction of the state health department.

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

Information to collect for chronic HBV 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.

- Demographic information
- Laboratory results
- Risk factors
- Pregnancy status. All HBsAg-positive pregnant women should be reported to the perinatal hepatitis B program manager so that the women 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.[14] They should include the following:

- 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.

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.

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.[2] Types are classified by their association with cancer. Low-risk, or non-oncogenic types, such as HPV 6 or 11, can cause 1) benign or low-grade abnormalities of cervical cells, 2) anogenital warts, and 3) recurrent respiratory papillomatosis (RRP), a disease of the respiratory tract. High-risk, or oncogenic types, including types 16 and 18, can cause 1) low-grade cervical cell abnormalities, 2) high-grade cervical cell abnormalities that are precursors to cancer, and 3) anogenital cancers such as cervical, vulvar, vaginal and anal cancers as well as some oropharyngeal cancers.[3–5]

Among the cancer-related outcomes of HPV infection, cervical cancer causes the largest global burden of disease (over 300,000 deaths due to cervical cancer in 2002).[4] High-risk HPV (HR-HPV) types are detected in 99% of cervical cancers;[6] approximately 70% of cervical cancers worldwide are due to types 16 and 18.[7] 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.[8-11]

In addition to its association with cervical cancer, high-risk HPV infection is associated with cancer of the vulva, vagina, penis and anus (Table 1).[4] Each of these 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] Oncogenic types of HPV may play a role in the development of some oropharyngeal cancers.[17]

Table 1. Cancers attributable to high-risk human papillomavirus infection—United States, 2003

Anatomic site	Total cancers*	% estimated HPV attributable fraction†
Cervix	11,820	100
Anus	4,187	85
Vulva/vagina	4,577	40
Penis	1,059	40
Oral/pharyngeal	29,627	15

* *CDC. Quadrivalent human papillomavirus vaccine: recommendations of the Advisory Committee on Immunization Practices. MMWR 2007;56(No. RR-2):1–24.*

† *Parkin M. Presented at the International Papillomavirus Conference, Vancouver, Canada, 2005*

Genital HPV infection is primarily transmitted by genital contact, usually (but not necessarily) through sexual intercourse.[2, 18] Most HPV infections are transient and asymptomatic, causing no clinical manifestations. More than 90% of new HPV infections, including those with HR-HPV types, clear within 2 years, and clearance usually occurs in the first 6 months after infection.[8, 10, 11, 19] Persistent infection with high-risk HPV, typically over several decades, is the most important risk factor for cervical cancer precursors and invasive cervical cancer.[10, 19-22]

Non–cancer-related outcomes of HPV infection include anogenital warts and RRP. Anogenital warts are due to infection with low-risk (LR) HPV types. Approximately 90% of anogenital warts are associated with types 6 and 11.[23] The prevalence of genital warts has been examined using health-care claims data.[24] An estimated 1% of sexually active adolescents and adults in the United States have clinically apparent genital warts.[25] Rarely, infection with LR-HPV results in RRP, a disease 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 acquired perinatally from a mother with genital warts during delivery. Estimates of the incidence of JORRP are relatively imprecise

but in two cities in the United States have ranged from 0.12 to 2.1 cases per 100,000 children younger than 18 years.[26] Less is known about the adult form of RRP.

II. Disease Description

Most instances of HPV infection are asymptomatic (no clinical manifestations). However, even if asymptomatic, cervical infection can result in cervical changes which can be detected by Pap testing or cervical biopsy. Cervical cytology testing, or Pap testing, can detect changes in cervical epithelial cells (cells found on the surface of the cervix which can be either squamous or glandular). Most abnormal Pap tests results are categorized (by increasing grade of abnormality in squamous cells) as atypical squamous cells of unknown significance (ASC-US); atypical squamous cells—cannot rule out high-grade squamous intraepithelial lesion (ASC-H); low-grade intraepithelial lesions (LSIL); high-grade intraepithelial lesions (HSIL); and squamous cell carcinoma (SCC). Glandular cell abnormalities are either atypical cells of glandular origin (AGC) or adenocarcinoma in situ (AIS). 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 12.9% among women found to have ASC-US, 23.6% among those with LSIL, and 51.8% among those with HSIL Pap tests.[27] Each year, approximately 50 million women undergo Pap testing; approximately 3.5–5 million of these Pap tests will require some further evaluation including 2–3 million ASC-US, 1.25 million LSIL and 300,000 HSIL Pap tests.[28–30]

Abnormal Pap test results (typically LSIL, and HSIL) require further evaluation by colposcopic examination of the cervix. If a biopsy specimen is obtained during colposcopy, the cervical tissue is classified as normal, invasive cervical cancer (either squamous cell carcinoma or adenocarcinoma), or precancerous lesions. Precancerous lesions include cervical intraepithelial neoplasias (CIN) grades 1, 2, or 3; carcinoma in situ (CIS [based on increasing degree of abnormality in the cervical squamous epithelial cells]); or adenocarcinoma in situ (AIS). Cervical cancer incidence rates have decreased approximately 75%, and mortality rates approximately 70% since the 1950s, largely because of Pap testing.[28, 29] In 2003, cervical cancer incidence in the United States was 8.1 per 100,000 women, with approximately 11,820 new cases reported.[31] The median age of diagnosis for cervical cancer was 48 years.[32]

Anogenital warts 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 20%–30% regress spontaneously. Recurrence of anogenital warts is common (approximately 30%), whether clearance occurs spontaneously or following treatment.[33]

JORRP, believed to result from vertical transmission of HPV from mother to infant during delivery, is diagnosed at a median age of 4 years. A multicenter registry of JORRP in the United States, using data collected during 1999–2003, 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.[34]

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 cervical, vaginal and vulvar cancer precursor lesions (e.g., CIN) include topical agents (which can be patient-applied), cryotherapy, electrocautery, laser therapy, and surgical excision.

Cervical Cancer and Precancer

Persistent HPV infection can result in precancerous cervical lesions as well as invasive cervical cancer. Treatment decisions are based on cervical biopsy results (e.g., obtained with colposcopy) not on the Pap test result.

For mild precancerous cervical biopsy lesions (mild dysplasia, i.e., CIN 1), the recommended management is follow-up with further evaluation.[35] For severe precancerous cervical lesions such as CIN 2 or CIN 3, treatment options include removal of the area of abnormality (laser,

loop electrosurgical excisional procedure [LEEP], cold knife conization) or destruction of the area of abnormality (cryotherapy, laser vaporization). Each method has its indications, advantages and disadvantages, but cure rates are comparable.

For invasive cervical cancer, treatment options include surgery, radiation therapy and chemotherapy, alone or in combination, depending on stage of disease. Depending on the stage of disease at diagnosis, a woman may be able to keep her ovaries. The survival rate 5 years after diagnosis of cervical cancer varies depending upon the stage of cervical cancer. The risk increases with higher stages of disease.

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 single treatment is ideal for all patients. Most patients require a course of therapy rather than a single treatment.

Treatment regimens are classified into topical medications applied by the patient and provider-applied modalities, such as cryotherapy, podophyllin resin 10%–25%, trichloroacetic acid or bichloroacetic acid, or surgery. Other regimens include intralesional interferon or laser surgery.[36]

IV. Laboratory testing

HPV cannot be detected through culture methods; detection requires molecular testing. HPV testing has a clinical role in identifying individuals with an increased risk of an HPV-associated cervical precancer or cancer. The FDA-approved clinical test, (HPV Hybrid Capture®2 [HC2] High Risk Test, Digene, Gaithersburg, MD) uses exfoliated cervical cells (or cervical biopsy) and detects the presence of one or more of 13 high-risk types. It does not determine the specific type or types present, but indicates the presence of high-risk HPV. The HC2 High Risk test is approved 1) for use in women with equivocal cervical cytology results (i.e., ASC-US) to help determine if referral to colposcopy is needed, and 2) as an adjunct to cervical cancer screening with cytology in women older than 30 years.

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 polymerase chain reaction (PCR) testing; most PCR testing involves research procedures. 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.

Research tests such as serologic testing for HPV antibodies may be useful to monitor population exposure to HPV. Because 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. However, laboratory reagents are not standardized and serologic assays are currently available only in research settings.

V. HPV Vaccine

A quadrivalent HPV vaccine (GARDASIL™ produced by Merck and Co., Inc.) was licensed by the Food and Drug Administration in 2006.[37] The L1 protein found on the HPV capsid of HPV is the antigen used for HPV immunization. The vaccine protects against infection with HPV types 6, and 11, which are associated with anogenital warts, and types 16 and 18, associated with precancerous lesions and anogenital cancers. The vaccine is licensed for use in females only. Study of vaccine efficacy in males and need to vaccinate males is ongoing.

Clinical trials have demonstrated high levels of efficacy in preventing cervical precancers caused by the targeted HPV types, and vulvar and vaginal precancers and genital warts caused by the targeted HPV types among women who have not been infected with that HPV type. Among women in the clinical trials with no evidence of prior infection with HR-HPV, efficacy against these endpoints was almost 100%. In immunogenicity and safety studies conducted among females 9–15 years of age, over 99% of study participants developed antibodies after vaccination; titers were higher for young girls than for older females participating in the efficacy trials.

The vaccine is prophylactic has no therapeutic effect on HPV-related disease. If a girl or woman is already infected with one of the HPV types in the vaccine, the vaccine will not prevent disease associated with that type.

Quadrivalent HPV vaccine is administered intramuscularly as three separate 0.5-ml doses. The second dose should be administered 2 months after the first dose, and the third dose 6 months after the first dose. Table 2 summarizes The Advisory Committee on Immunization Practices recommended schedules for routine and catch-up HPV vaccination.[31]

Table 2. Recommended age groups, schedule, dosages and route of administration for Gardasil™ quadrivalent HPV vaccine

	Age group	Schedule	Dosage/route	Comment
Routine vaccination	Females 11–12 yrs	0, 2, 6 mos	0.5 ml/intramuscular injection	Provider may initiate series as early as age 9 yrs.
Catch-up vaccination	Females 13–26 yrs	0, 2, 6 mos	0.5 ml/intramuscular injection	

A second prophylactic bivalent vaccine against HPV types 16 and 18 is currently under development and has not been reviewed by FDA at this time. This vaccine may be licensed as early as 2008.

Ideally, vaccine should be administered before potential exposure to HPV through sexual contact. 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 and screening for HPV DNA or HPV antibody are not needed prior to vaccination at any age.

Cervical cancer screening among vaccinated females

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

VI. 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, 2) most infections will not have any associated clinical disease, and 3) the commercially available test for HPV infection requires laboratory testing of cervical specimens. However it is important to monitor rates of cervical cancer since this is the primary goal of HPV vaccination. Cervical cancer surveillance data (as well as data on other HPV-associated anogenital cancers) are measured by population-based cancer registries participating in CDC's National Program of Cancer Registries (NPCR) and/or the Surveillance Epidemiology and End Results (SEER) program of the National Cancer Institute, which cover over 96% of the U.S. population.

This surveillance activity is especially important because the vaccine protects against only four types of HPV, and over 40 types can infect the anogenital area. Data from cancer surveillance will be invaluable in measuring the success of HPV vaccination, but useful data are not expected until several decades after widespread adoption of the vaccine. The types of

data currently available through cancer registries will be limited in answering these and other important surveillance-related questions:

- How can surveillance systems be used to evaluate vaccine effectiveness and identify possible vaccine failures?
- What type of surveillance systems can be used to provide data on more proximal endpoints (e.g., genital warts, cervical precancers) of HPV infection?
- What is the impact of vaccination on the distribution of HPV type-specific infection? Specifically, does vaccination against types 16 and 18 result in increased prevalence of other oncogenic types ("replacement lesions")?
- How can type-specific data on HPV-associated anogenital cancers be collected (in order to compare vaccine type–associated cancers with non-vaccine type–associated cancers)?
- What is the impact of vaccination on medical costs related to procedures such as follow-up Pap tests (after an abnormal screening Pap test), colposcopy, cervical biopsy, and treatment of cervical lesions?
- What will be the impact of vaccination with the quadrivalent (against types 6, 11, 16, 18) versus the bivalent (types 16, 18 only) vaccine?
- How can surveillance systems measure disease rates among populations not adequately covered by vaccination and inform vaccination programs?
- How can surveillance systems inform cervical cancer screening programs in the HPV vaccine era?

CDC is currently exploring the feasibility and usefulness of surveillance activities to answer these questions. See section on Enhancing Surveillance.

VII. Disease Reduction Goals

Because the quadrivalent HPV vaccine was licensed in 2006, the *Healthy People 2010* Midcourse Review does not state a goal for vaccination coverage at this time.[38] However, it does include a goal to "Reduce the proportion of females with human papillomavirus (HPV) infection," although no target proportion is identified. It also states as a goal to "Reduce the death rate from cancer of the uterine cervix below a target of 2 deaths/100,000 females (from a baseline of 3 deaths/100,000 in 1998)." Another stated goal is to "increase the proportion of women receiving a Pap test," but no quantitative goal regarding the proportion has been suggested. No goals are currently stated for reduction of anogenital warts, recurrent respiratory papillomatosis or non-cervical anogenital cancers.

Another *Healthy People 2010* objective addresses surveillance to "increase the number of states that have a statewide population-based cancer registry that captures case information on at least 95 percent of the expected number of reportable cancers."

VIII. 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 any HPV-associated conditions, including HPV infection, anogenital warts, RRP, precancerous anogenital lesions, or anogenital cancers. The following descriptions of diagnosis and classification of HPV-associated conditions are included as aids to understanding possibilities for surveillance:

HPV infection: Tests for LR-HPV infection are not used for clinical purposes and are primarily research tools. Testing for HR-HPV infection status is important for its adjunctive role in cervical screening. Routine testing for HR-HPV infection is not recommended, but testing is clinically indicated in two specific clinical situations: 1) in order to triage women with ASCUS Pap tests for further evaluation, and 2) as an adjunct to Pap testing for women age 30 years and older.

Abnormal Pap tests and precancerous anogenital lesions: Abnormal Pap test categories are listed by increasing grade of severity: atypical squamous cells of unknown significance (ASCUS); atypical squamous cells—cannot rule out high-grade squamous intraepithelial lesion (ASC-H); low-grade intraepithelial lesions (LSIL); and high-grade intraepithelial lesions (HSIL). Precancerous lesions diagnosed by pathologists on specimens from cervical biopsy lesions provide a much more specific diagnosis of potential cancer than abnormal Pap tests. These precancerous lesions are grouped into cervical intraepthelial neoplasia (CIN) 1, CIN 2, and CIN 3; carcinoma in situ (CIS); or adenocarcinoma in situ (AIS). Precancerous lesions are also defined for vaginal intraepithelial neoplasias (VAIN), vulvar intraepithelial neoplasias (VIN), and anal intraepithelial neoplasia (AIN). These are defined and used for clinical diagnostics and management.

Anogenital cancers: The primary sites and pathologic diagnoses of the cancers are coded using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3). In the United States, disease burden from cervical, vaginal, vulvar and anal cancers is measured by population-based cancer registries participating in NPCR and/or SEER.

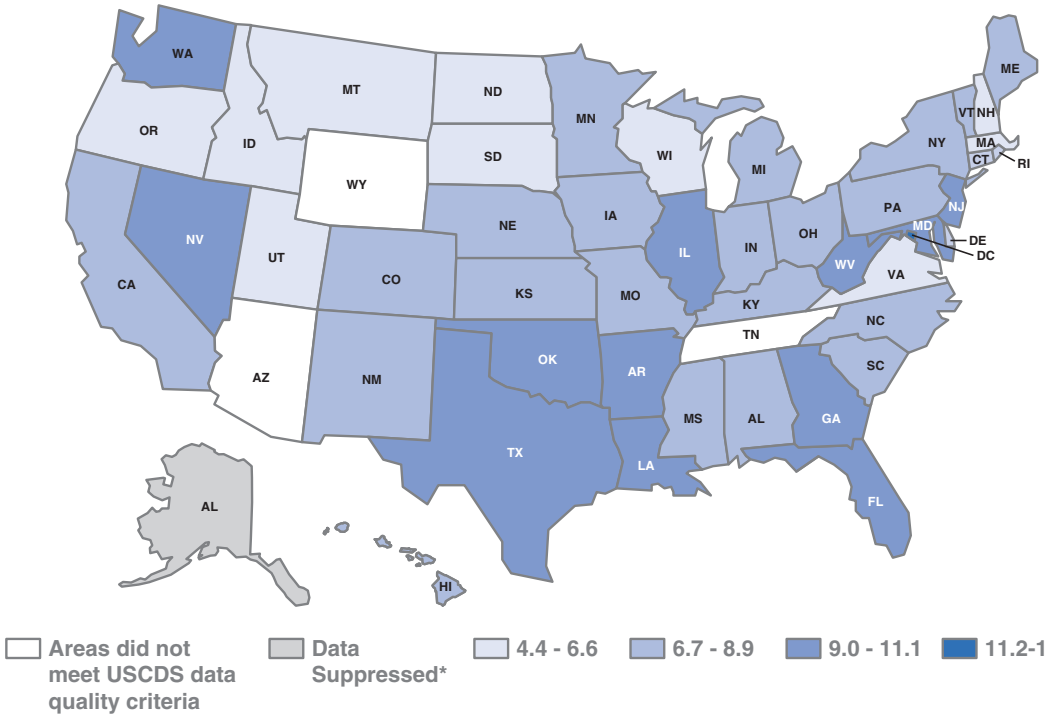
Anogenital warts: A diagnosis of anogenital warts is made based on visual inspection of the lesion(s). There are no case definitions for anogenital warts used for surveillance purposes.

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.

IX. Reporting

HPV infection and HPV-associated clinical conditions are not nationally reportable diseases and notification is currently not required by CDC. Persons reporting should contact the state health department for state-specific reporting requirements.

Figure 1. United States cervical cancer incidence rates*, by state, 2003†



* *Rates are per 100,000 and are age-adjusted to the 2000 U.S. standard population.*

† *Source: U.S. Cancer Statistics Working Group. United States Cancer Statistics: 2003 Incidence and Mortality (preliminary data). Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, and National Cancer Institute; 2006.*

Current established national systems that can monitor HPV and its associated conditions include the following:

- The National Health and Nutrition Examination Survey (NHANES) conducts annual surveys of HPV infection.
- CDC's National Program of Cancer Registries (NPCR) and the National Cancer Institute's (NCI) Surveillance Epidemiology and End Results (SEER) program continuously monitor incident anogenital cancer cases as well as anogenital cancer–related deaths. These data are collected at the state (central cancer registries) as well national (NPCR/SEER) levels (Figure 1).

Other less-established systems are discussed in the following section.

X. Enhancing Surveillance

The goal of HPV vaccination is to prevent clinical conditions associated with infection with vaccine HPV types (6, 11, 16, and 18), with the primary goal being prevention of cervical cancers. However, because infection with HPV is relatively commonplace and a high proportion of infections are asymptomatic and the consequences are not seen for many years, monitoring the impact of a vaccination program poses many challenges.

The proximal measures of vaccine impact include outcomes such as HPV infection cervical cancer precursors, and anogenital warts. Currently, the only national surveillance program in the United States for proximal measures is NHANES, which measures HPV infection. The distal measures of vaccine impact include anogenital cancers, which are monitored through an excellent system of state-based cancer registries that cover approximately 96% of the U.S. population. However, these distal measures may take as long as 20 or 30 years before any impact can be accurately detected.

CDC encourages state and local health programs to investigate the feasibility of making certain HPV-associated clinical conditions reportable.

A potentially important limitation to the collection of surveillance data on anogenital warts, Pap tests or cervical cancer precursors is the lack of any HPV-associated nationally notifiable conditions. Despite this limitation, CDC is currently considering surveillance approaches to answer other questions related to HPV vaccination impact. (See section on Importance of Surveillance.) Approaches recently initiated include 1) a pilot study exploring enhanced surveillance by select central cancer registries to include population-based statewide data on cervical intraepithelial neoplasia and cervical carcinoma in situ, 2) creating a network of investigator-led sentinel surveillance sites in catchment areas (typically, a county) within four states to establish an enhanced system for population-based assessment of CIN 2/3 and, importantly, linkage of cases with HPV vaccination status and HPV type, 3) monitoring HPV types and cervical precancers among patients in managed care organizations, and 4) monitoring volume of patient visits for anogenital warts through a sentinel network of sexually transmitted disease clinics. Other approaches being considered include using family planning clinic data to monitor abnormal Pap tests and referral patterns for colposcopy/treatment. CDC is also currently exploring the feasibility of using administrative datasets such as health insurer claims databases (Marketscan Medstat Dataset, Ingenix Dataset) and vaccine safety datasets (Vaccine Safety Datalink) to monitor HPV-associated outcomes. Specifically, administrative data consisting of ICD-9-CM codes in conjunction with Current Procedure Terminology (CPT) codes are being examined for usefulness in identifying specific Pap test diagnoses, cervical precancer diagnoses, and anogenital warts.

Currently, there are no recommendations for collection of routine surveillance data on HPV-associated conditions at the national level, other than the cancer-related data already being collected through cancer registries. However, several states have initiated various case reporting and other surveillance activities to measure HPV-related disease burden in their areas. To address the questions of usefulness of national reporting requirements, selection of appropriate disease endpoints for surveillance, and feasibility of data collection, CDC has initiated the activities described above. In preparation for future surveillance activities, CDC encourages state and local health programs to investigate the feasibility of making certain HPV-associated clinical conditions reportable, especially cervical precancers such as CIN 2/3

or CIS. CDC currently recommends that state and local health programs 1) educate providers and the public about the link between HPV vaccination and cervical cancer prevention, and 2) increase awareness of the availability of the newly licensed quadrivalent HPV vaccine and the importance of vaccinating 11- and 12-year-old girls, and 3) continue to emphasize the importance of ongoing cervical screening with the Pap test, even for vaccinated women.

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Chapter 6: Influenza

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I. Disease Description

Influenza is an acute respiratory disease caused by influenza type A or B 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. Influenza epidemics, particularly epidemics caused by influenza A (H3N2) viruses, are associated with increased mortality. From the 1990–91 through the 1998–99 influenza seasons, an average of 36,000 influenza-associated excess deaths occurred each year.[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 or outbreaks 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, dogs, and whales. While only a few influenza A subtypes have been isolated from mammals, all the known subtypes have been isolated from avian species. The two influenza A 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) viruses during the 2001–02 and 2002–03 influenza seasons.

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 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 begin circulating. 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. This can result in a worldwide epidemic called a pandemic. During the 20th century, pandemics occurred in 1918 (type A [H1N1]), 1957 (A [H2N2]), and 1968 (A [H3N2]). The recent emergence of avian influenza A (H5N1) as a cause of widespread illnesses in wild birds and poultry and sporadic illnesses in humans has increased concerns about the likelihood of an influenza pandemic.

III. Vaccination

Annual influenza vaccination is recommended for persons 6 months of age and older who are at increased risk for influenza-associated complications and persons such as health-care providers and household contacts who have close contact with high-risk persons.[8]

Persons at high risk for severe influenza related complications include the following:

- Persons 65 years of age and older
- Residents of nursing homes and other long-term care facilities that house persons of any age with chronic medical conditions
- Adults and children with chronic pulmonary or cardiovascular disorders, including children with asthma
- Adults and children who required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications)
- Adults and children who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration
- 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
- Women who will be pregnant during the influenza season
- Children aged 6–23 months

Annual vaccination also is recommended for the following persons because of an increased risk for influenza-associated clinic, emergency department or hospital visits, particularly if they have a high-risk medical condition:

- Children aged 24–59 months[9–12]
- Persons aged 50–64 years

To prevent transmission of influenza to persons at increased risk for influenza-related complications, vaccination is also recommended for the following persons:

- Household contacts and out-of-home caretakers of persons at high risk for severe complications from influenza, and contacts and caretakers of children younger than 5 years old, particularly infants 0–5 months old. (The pediatric group at greatest risk of complications is children younger than 6 months old. However, influenza vaccines are not approved by the Food and Drug Administration [FDA] for use among children younger than 6 months.[8])
- Healthcare workers

In the United States, both inactivated and live attenuated influenza vaccines are available. The live attenuated vaccine is approved for use in healthy persons age 5 through 49 years. Inactivated vaccine is approved for use in all persons 6 months of age and older. Both are trivalent vaccines containing influenza A (H3N2), influenza A (H1N1), and influenza B strains 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 efficacy of the vaccine depends on the match between the vaccine strains and the circulating strains as well as the recipient's age, immunocompetence, and previous exposure to influenza. In a randomized, double-blind, placebo-controlled challenge study among 92 healthy adults aged 18–41 years, the efficacy of inactivated and live attenuated influenza vaccines in preventing laboratory-documented influenza was 71% and 85%, respectively. The difference in efficacy between the two types of vaccine was not statistically significant.[13] In healthy persons younger than 65 years of age, inactivated influenza vaccine is approximately 70%–90% effective in preventing illness when the match between the vaccine strains and

circulating viruses is good.[14] The effectiveness of inactivated influenza vaccine in preventing hospitalization for pneumonia and influenza among persons 65 years of age and older living in settings other than nursing homes or similar long-term care facilities ranges from 30% to 70%.[15, 16] Among elderly persons residing in nursing homes, influenza vaccine is most effective in preventing severe illness, secondary complications, and death. Studies among this population have indicated that the inactivated vaccine can be 50%–60% effective in preventing hospitalization and pneumonia and 80% effective in preventing death, even though efficacy in preventing influenza illness may often be in the range of 30%–40%.[17, 18] Achieving a high rate of vaccination among nursing home residents can reduce the spread of infection in a facility through herd immunity, thus preventing disease.[19] Further, vaccination of nursing home staff has been associated with decreased mortality among residents, presumably by further lessening transmission from healthcare workers to patients.[20]

IV. Antiviral Drugs

Four antiviral medications in two classes are currently approved for use in the United States: the adamantanes—amantadine and rimantadine—and the neuraminidase inhibitors—zanamivir and oseltamivir. However, resistance of influenza A viruses to adamantanes can occur spontaneously or emerge rapidly during treatment.[21] During the 2005–06 influenza season, surveillance showed that more than 90% of influenza A(H3N2) viruses isolated in the United States were resistant to amantadine and rimatadine. Because of this, CDC recommended that the adamantanes not be used for treatment or chemoprophylaxis of influenza A infections.[22, 23] Testing of influenza virus isolates for antiviral resistance continues and these recommendations will be updated as needed.

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. When administered prophylactically to healthy adults or children, oseltamivir and zanamivir are approximately 70%–90% effective in preventing illness from influenza A or B infection.[24–28] Resistance of influenza viruses to oseltamivir and zanamivir is also being monitored.

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.

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 for antigenic analysis) and disease surveillance are necessary to identify influenza virus variants, to monitor their health impact in populations, and to inform selection of influenza vaccine components each year. Knowledge of the prevalent circulating virus type 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 for the identification of drug-resistant strains of influenza viruses. Finally, disease surveillance allows for identification of high-risk persons and for determining the effectiveness of current prevention strategies, and is used for refining vaccine and antiviral recommendations each year.

VII. Importance of Vaccination

Annual vaccination of persons at high risk for influenza

Vaccination against influenza remains the most important method of prevention. Annual vaccination against influenza is recommended for persons or groups at increased risk for influenza-associated complications and their close contacts. Previous vaccination may offer little or no protection against strains 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, chemoprophylaxis is not a substitute for vaccination.

Disease reduction goals

The U.S. Department of Health and Human Services has established a *Healthy People 2010* goal of increasing rates of pneumococcal and influenza vaccination among institutionalized adults and all persons age 65 and older to at least 90%, and to at least 60% among noninstitutionalized, high-risk persons age 18–64 years.[29]

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

VIII. Case Definitions

Definitive diagnosis of influenza requires laboratory confirmation in addition to signs and symptoms. Case definitions for influenza-like illness vary depending on the purpose for which they are used. A case definition of fever 100°F or greater and cough or sore throat is used by CDC in its sentinel provider surveillance system, 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 infection cannot be diagnosed accurately based on signs and symptoms alone. Laboratory testing is necessary to confirm the diagnosis.

Although influenza infection generally leads to more severe illness among adults than other respiratory viruses, individual cases of influenza infection cannot be distinguished from other respiratory virus infections based on clinical information alone. Laboratory testing is necessary to confirm the diagnosis. 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] testing), commercially available rapid diagnostic kits, and less frequently, electron microscopy, and serologic testing.[30, 31] 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 of vaccine preventable diseases, see Chapter 22, "Laboratory Support for Surveillance of Vaccine-Preventable Diseases."

Virus isolation and rapid culture assays

Virus isolation is the gold standard for influenza diagnosis. Appropriate clinical specimens include nasal washes, nasopharyngeal aspirates, nasal and throat swabs, transtracheal aspirates, and bronchoalveolar lavage. Specimens should be taken within 72 hours of onset of illness. Influenza viruses can be isolated in fertilized chicken eggs or in tissue culture. The Madin Darby canine kidney 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. 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 culture.[31]

Molecular testing methods

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. 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. 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 specimen can be stained using an immunofluorescent antibody that reveals 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 test for the presence of viral antigens. Currently available test kits 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. Another less frequently used antigen detection method is immunostaining and visualization of viral antigens by electron microscopy. This method may be used for detection of influenza antigens in postmortem 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 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 influenza is not accepted for the purposes of national surveillance because of a lack of standardized methods for testing and interpretation. Paired serum specimens are required for serologic diagnosis of influenza 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 the preferred method of 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, 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 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 10 data sources:

- Viral surveillance
  - U.S. WHO collaborating laboratories
  - National Respiratory and Enteric Virus Surveillance System (NREVSS)
  - Novel influenza A reporting
- Outpatient illness surveillance
  - Influenza Sentinel Provider Surveillance Network
  - BioSense Department of Veterans Affairs and Department of Defense Outpatient Surveillance
- Mortality surveillance
  - 122 Cities Mortality Reporting System
  - Influenza-associated pediatric mortality reporting
- Hospitalization surveillance
  - Emerging Infections Program (EIP)
  - New Vaccine Surveillance Network (NVSN)
- 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

Each week approximately 130 US WHO and NREVSS collaborating laboratories report the total number of specimens received for respiratory virus testing and the number of positive isolations of influenza A (H1N1), A (H3N2), A (not subtyped), or B. WHO collaborating laboratories report these data by age group (in years, less than 1, 1–4, 5–24, 25–44, 45–64, 65 and older, or unknown). The laboratories participating are in state or local health departments, universities, and hospitals. The information gathered through this system is either recorded on facsimile forms (CDC form CDC 55.31) and faxed to CDC, or transmitted to CDC via the Internet or the Public Health Laboratory Information System (PHLIS). A subset of the isolates obtained in these laboratories is submitted to the WHO Collaborating Center for Surveillance, Epidemiology, and Control of Influenza at CDC for complete antigenic characterization and antiviral resistance testing.

Novel influenza A reporting

Human infection with a novel influenza A virus became a nationally notifiable condition in 2007. Cases can be reported through NNDSS

Influenza Sentinel Provider Surveillance Network

Each week from October through May, approximately 1,300 healthcare providers report the number of patient visits for the week and the number of those patients examined for influenza-like illness by age group in years (0–4, 5–24, 25–64, 65 and older). A subset of the providers continue to report year-round. The participating healthcare provider may collect nasal and throat swabs for virus isolation. Data are reported electronically to CDC either by Internet or fax (CDC form CDC 55.20) each week.

BioSense Department of Veterans Affairs (VA) and Department of Defense (DoD) Outpatient Surveillance

Approximately 350 DoD and 800 VA treatment facilities transmit information on outpatient visits by active military personnel and their dependents and veterans daily in the form of ICD-9 codes. The percentage of patient visits with any ICD-9 code for an acute respiratory infection is calculated by age group each week.

Emerging Infections Program

The EIP Influenza Project conducts surveillance for laboratory-confirmed influenza related hospitalizations in persons less than 18 years of age in 60 counties covering 12 metropolitan areas of 10 states (San Francisco CA, Denver CO, New Haven CT, Atlanta GA, Baltimore MD, Minneapolis/St. Paul MN, Albuquerque NM, Las Cruces NM, Albany NY, Rochester NY, Portland OR, and Nashville TN). Cases are identified by reviewing hospital laboratory and admission databases and infection control logs for children with a documented positive influenza test conducted as a part of routine patient care.

New Vaccine Surveillance Network (NVSN)

The New Vaccine Surveillance Network (NVSN) provides population-based estimates of laboratory-confirmed influenza hospitalization rates for children less than 5 years old residing in three counties: Hamilton County OH, Davidson County TN, and Monroe County NY. Children admitted to NVSN hospitals with fever or respiratory symptoms are prospectively enrolled and respiratory samples are collected and tested by viral culture and RT–PCR. NVSN estimated rates are reported every 2 weeks during the influenza season.

122 Cities mortality reporting system

Each week throughout the year the vital statistics offices of 122 cities report the total number of death certificates filed due to all causes for that week and the number of deaths for which pneumonia or influenza was mentioned in any position on the certificate. This information is reported to CDC each week by fax form or voice mail. A seasonal baseline is calculated, and if the proportion of deaths due to pneumonia and influenza (P&I) for a given week exceeds the baseline value for that week by a statistically significant amount, influenza related deaths are said to be above the epidemic threshold.

Influenza-associated pediatric mortality reporting

Influenza-associated pediatric mortality was added as a nationally notifiable condition in 2004. Laboratory-confirmed influenza-associated deaths in children less than 18 years old are reported through NNDSS.

State and territorial epidemiologists' reports

Each week from October through May, epidemiologists from each state and territory report the estimated level of influenza activity in their area as "no activity," "sporadic," "local," "regional," or "widespread." Sporadic activity is defined as small numbers of laboratory-confirmed influenza cases or a single influenza outbreak, but no increase in cases of influenza-like illness (ILI). Local activity is outbreaks of influenza or increases in ILI cases and recent laboratory-confirmed influenza in a single region of the state. Regional activity is 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. Widespread activity is outbreaks of influenza or increases in ILI cases and recent laboratory-confirmed influenza in at least half the regions of the state. These reports come to National Center for Public Health Informatics (NCPHI), CDC, via the National Electronic Telecommunications System for Surveillance (NETSS).

The information sources used to make this determination vary from state to state. Reports of laboratory-diagnosed influenza and ILI reports from the sentinel provider network are used by most states. Some states may also include reports of increased visits for respiratory illness to hospital emergency departments, school or worksite absenteeism reporting, or nursing home surveillance. 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 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 ease with which influenza infection can be confirmed by laboratory tests 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/fluactivity.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 increase the number of sentinel physicians 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 virus isolation.

XII. Case Investigation

Any influenza A virus that cannot be subtyped 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 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 and H1N1 antisera included in the influenza reagent kit distributed by CDC or by 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. Finally, guidelines for testing of suspect human cases of avian influenza A (H5N1), published by CDC in June 2006, are available at http://www2a.cdc.gov/han/ArchiveSys/ViewMsgV.asp?AlertNum=00246.

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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 Paramyxoviridae, genus *Morbillivirus*. Measles is characterized by a prodrome of fever and malaise, cough, coryza, and conjunctivitis, followed by a maculopapular rash. The illness is usually mild or moderately severe; however, measles can result in complications such as pneumonia, encephalitis and death. During 1987–2000, in the United States, nearly one-third (29%) of measles cases had some complication, with 6% complicated by pneumonia and 19% requiring hospitalization. During that period, measles resulted in encephalitis in 1 of 1,000 reported cases, and death was reported in 0.3% of 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 United States 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 before 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. Fewer than 150 cases were reported each year during 1997–2004,[7–9] and measles incidence decreased to a record low of 37 reported cases in 2004.[9] In recent years, outbreaks of measles have been small, with fewer than 35 cases reported.[8–10] Recent outbreaks do not have one predominant transmission setting but mostly involve persons who are exposed to imported measles cases and who are unvaccinated or have received only one 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 and healthcare workers, groups who routinely refuse vaccination.[11, 12]

Globally, more than 30 million people are affected each year by measles.

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, an estimated 454,000 measles deaths occurred globally; this translates to more than 1,200 deaths every day or 50 people dying every hour from measles. The overwhelming majority (more than 95%) of measles deaths occur in countries with per capita gross national income of less than US $1,000. In countries where measles has been largely eliminated, cases imported from other countries remain an important source of infection.[13]

In May 2003, the 56th World Health Assembly unanimously adopted a resolution[14] to reduce measles deaths by 50% by the end of 2005, compared with 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% (compared with 2000 estimates) by 2010. 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 in the Western Pacific region for 2012. The African and Southeast 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:[13]

- 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 provided to all children, 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.

The highly contagious measles virus is frequently imported into the United States by persons from other countries.

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 Centers for Disease Control and Prevention (CDC), United Nation's 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.[15]

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 undervaccinated 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.[16] Current surveillance data indicate this goal has been achieved, and endemic measles was declared eliminated in the United States in 2000.[17] 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 measles has been approved by the Council of State and Territorial Epidemiologists (CSTE) and was published in 2007.[18] The following case classifications for importation status were approved by the CSTE in 2006.[19]

Clinical case definition

An illness characterized by all of the following:

- A generalized rash lasting ≥3 days
- A temperature ≥101°F (≥38.3°C)
- Cough, coryza, or conjunctivitis

Laboratory criteria for diagnosis

- Positive serologic test for measles immunoglobulin M (IgM) antibody, or
- Significant (generally a fourfold) rise in measles antibody (lgG) level by any standard serologic assay, or
- Isolation of measles virus from a clinical specimen*

** Identification of measles genotype by RT-PCR and sequencing by WHO reference laboratory (CDC) from clinical samples confirms infection.*

Case classification

Case classification requires a consideration of the clinical presentation.

Suspected: Any febrile illness accompanied by rash.

Probable: A case that meets the clinical case definition, has noncontributory or no serologic or virologic testing, and is not epidemiologically linked to a confirmed case.

Confirmed: A case that is laboratory confirmed or that meets the clinical case definition and is epidemiologically linked to a confirmed case. A laboratory-confirmed case does not need to meet the clinical case definition.

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:

Internationally imported case: 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 United States during that time. All other cases are considered U.S.-acquired.

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

Many clinicians have never seen a case of measles, and most patients who present with measles-like illness today do not have measles.

VII. Laboratory Testing

Because measles is an extremely rare disease in the United States, clinical evidence is not sufficient to confirm a case. 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 highly contagious 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, laboratory diagnosis is crucial to confirm the few actual measles cases among the thousands of patients with suspected measles.

Even with the excellent laboratory tests available, some false-positive results will occur. (The positive predictive value [PPV] of a test is the proportion of persons 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, case investigation and laboratory tests should be restricted to patients most likely to have measles, i.e., 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 at http://www.cdc.gov/ncidod/dvrd/revb/measles

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 obtained approximately 2 weeks apart.

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

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 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-phase) may be tested for increase 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 multiple methods are available for testing for IgM antibody, EIA is the most consistently accurate test and is therefore recommended. 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. Failure to remove IgG antibodies can sometimes lead to false-positive[20] 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 in its use. Although the IgM capture format is the preferred reference test for measles, several commercially available indirect measles IgM tests 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 with a second serum obtained 72 hours or longer after rash onset (Table 1). IgM is detectable for at least 30 days after rash onset and frequently longer.[21]

When a laboratory IgM result is suspected of being 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 and have also been documented when a patient has 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 of 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 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 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, including 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 the plaque reduction neutralization test (PRNT). This is a quantitative assay for anti-measles IgG, and a fourfold rise in titer between acute- and convalescent-phase paired sera is indicative of recent measles infection. EIA values are not titers and increases in EIA values between paired sera 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. Among persons with a recent MMR vaccination, determination of the measles genotype is necessary to distunguish between wild-type virus infection and a rash caused from measles vaccination.[22] A negative culture or negative 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.

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 United States. 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.

Aggressive case investigations of persons with acute disease provide the best opportunity to administer postexposure prophylaxis to contacts

Specimens (urine, nasopharyngeal aspirates, heparinized blood, or throat swabs) for virus culture obtained from persons with clinically suspected cases of measles 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 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.[23] 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

Reporting to CDC

Provisional reports of suspected measles should be promptly reported to CDC by the state health department or directly to CDC by telephone at 404-639-8230 or by e-mail (sbrl@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) within 14 days of the initial report to the state or local health department. 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.

Note: *The Division of Viral Diseases, National Center for Immunization and Respiratory Diseases (NCIRD), CDC, publishes periodically a measles update that is distributed by mail, fax, or e-mail to all states. The update describes details of recent measles activity (sporadic cases and epidemics) by state. To receive the update, call your state health department or send an e-mail request to CDC (sbrl@cdc.gov).*

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**
  - Serologic 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
- **Epidemiologic**
  - Transmission setting
  - Source of infection (e.g., age, vaccination status, relationship to case-patient)
  - 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 importation)
  - Residency (Did the patient reside in the United States?)
  - 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). 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.[3]

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, 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 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 to confirm or rule out the case. If a case is confirmed, a case investigation should be conducted. Measles specimens should also 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, child care, 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 healthcare 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.[24]

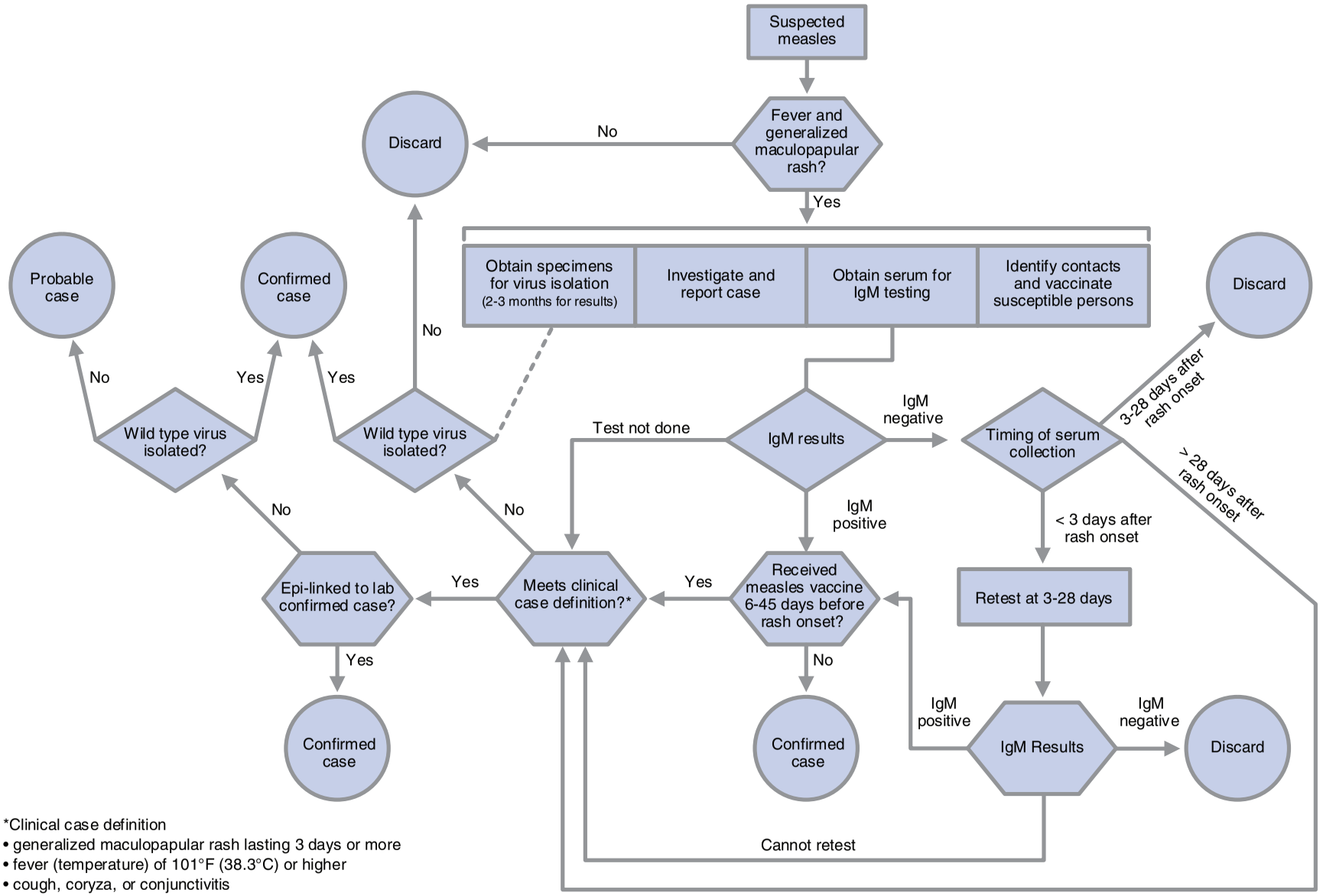
Monitering surveillance indicators

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 that 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."

Figure 1. Measles Case Investigation



*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

Virus isolation or positive RT–PCR. *Among persons with a recent MMR vaccination, determination of the measles genotype is necessary to distinguish between wild-type virus infection and a rash caused from measles vaccination.*[22]

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 persons with 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.

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[f]	Yes or No	Yes	Yes	No	Confirmed
-	No[f]	Yes or No	Yes	No	No	Probable
-	No[f]	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 at 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.

Efforts should be made to identify the source of infection for every confirmed case of measles.

Case-patients or their caregivers may have personal copies of immunization records that include dates of administration; these are acceptable for reporting purposes. Usually immunization records must be sought from review of child care or school records (generally available for children attending licensed child care 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, healthcare settings and other institutions (e.g., colleges, prisons). 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. This information is available at http://www.cdc.gov/ncidod/dq/quarantine_stations.htm. If unable to contact the Quarantine Station, call the DGMQ 24-hour number at 866-694-4867 for assistance.

Because susceptible contacts are at risk for infection and further transmission to others, 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 case-patients 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.[1, 7] By comparing isolates from new case-patients with 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 duties, or even 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 (or large chalkboard) or an electronic database 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 (e.g., "draw blood," "call pediatrician for vaccination history," "notify contacts").
- Keep the logbook in one well-defined location, preferably with folders from 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 laboratory results, and a separate stack of discarded cases.
- Establish protocols for control measures necessary for all likely situations (e.g., exposure in a child care center, school, doctor's office, workplace) 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, which allows ready identification of known and unknown data and ensures complete case investigation. A line listing can be maintained on a computer by using database management or spreadsheet software, but it 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 (e.g., unvaccinated preschool-age children, high school students who have only received one dose of measles vaccine, persons who visited the emergency department of Hospital A on a certain day), determine where transmission is occurring (child care centers, high schools, healthcare settings), and identify persons who are at potential risk of infection (other unvaccinated preschool-age children, students attending other schools) In general, the most effective outbreak control efforts are those that are targeted on the basis of 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 department logs or laboratory records. As part of outbreak response, active surveillance for measles should be established to ensure timely reporting of suspected cases in the population known to be affected by the outbreak, as well as in 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 departments and physicians serving affected communities are usually recruited to participate in active surveillance. Active surveillance should be maintained for at least two 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 (i.e., two doses of measles vaccine) in the population affected by the outbreak. In practice, the population affected is usually more 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, daycare). 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. Recent experience in measles outbreaks shows that almost all persons who are excluded from an outbreak area because they lack documentation of immunity quickly comply with vaccination requirements.

If many cases are occurring among infants younger than 12 months of age, measles vaccination of infants as young as 6 months of age may be undertaken as an outbreak control measure. Monovalent measles vaccine is preferred, but MMR may be administered to children before

the first birthday if monovalent measles vaccine is not readily available. In practice, this recommendation may take several months to implement, and several months to halt once the outbreak has ended. 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, postexposure 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 persons, 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 schools, colleges and other institutions of higher education, and other institutions where young adults may have close contact (such as prisons), a program of vaccination with two 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 persons who are not immune to measles should be vaccinated; this includes all students and their siblings and all school personnel born during 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). Persons who cannot readily provide documentation of measles immunity should be vaccinated or excluded from the school or other institution. Persons receiving second doses, as well as previously unvaccinated persons receiving their first dose as part of the outbreak control program may be immediately readmitted to school. Persons who continue to be exempted from or who refuse measles vaccination should be excluded from the school, child care, 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 healthcare 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 be immune to measles to prevent any potential outbreak. If an outbreak occurs within or in the areas served by a hospital, clinic, or other medical or nursing facility, all personnel born during or after 1957 should receive two doses of MMR vaccine, unless they have documentation of measles immunity. Personnel born before 1957 without documentation of measles immunity should receive one dose of MMR. Serologic screening of healthcare workers during an outbreak to determine measles immunity is not generally recommended, because stopping measles transmission requires the rapid vaccination of susceptible healthcare workers, which can be impeded by the need to screen, wait for results, and then contact and vaccinate susceptible persons.

Susceptible personnel who have been exposed to measles should be relieved from patient contact and excluded from the facility from the third to the 21st day after exposure, regardless of whether they received vaccine or immune globulin after the exposure. Personnel who become ill should be relieved from all patient contact and excluded from the facility for 7 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 epidemiologic 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 1,400–2,800 cases of meningococcal disease occur annually in the United States, a rate of 0.5–1.1/100,000 population.[1] *N. meningitidis* became one of the leading causes of bacterial meningitis in the United States after the introduction of conjugate vaccines for *Streptococcus pneumoniae* and *Haemophilus influenzae* type b resulted in declines in meningitis due to these pathogens.[2, 3]

The epidemiology of meningococcal disease in the United States has changed dramatically over the past 100 years.

N. meningitidis can be classified into 13 serogroups based on the immunologic reactivity of their capsular polysaccharides.[4] 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.[1] 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.[4]

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%.[5] 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.[1]

More than 98% of meningococcal disease cases in the United States are sporadic, while the other 2% are associated with outbreaks. Compared with the 1980s, the frequency of meningococcal outbreaks has increased. The majority of outbreaks have been caused by serogroup C, although the incidence of serogroup Y outbreaks has increased as well.[1]

Meningococcal disease occurs year-round but has a seasonal pattern with peak incidence occurring in later winter and early spring.[4] There is a natural cyclical pattern of meningococcal disease with peaks of disease occurring every 7–10 years (CDC, unpublished data).

Risk factors

Risk factors for meningococcal disease include organism, host, and environmental factors. Persons with terminal complement deficiency are at risk for meningococcal disease. Other immune deficiencies which predispose to invasive meningococcal disease include anatomic or functional asplenia and properdin deficiency.[6]

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.[7] Active or passive smoking and recent upper respiratory tract infections also increase risk of disease.[5] In the United States, 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.[8] Race and socioeconomic status are likely markers for differences in risk factors such as household crowding, exposure to tobacco smoke, and urban residence.

Infants in the first month of life are protected by maternal antibodies, but as this protection wanes, risk of meningococcal disease increases. Meningococcal disease rates in children younger than 1 year peak at 3–4 months.[9] 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.[10]

Those who have close contact with case-patients, such as household members, are at a substantially increased risk for acquiring carriage and disease.[11] Rates of secondary disease are also elevated among daycare workers and attendees[12] as well as among schoolchildren.[13]

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 and is characterized by abrupt onset of fever, headache, and stiff neck (CDC, Active Bacterial Core Surveillance [ABCs], unpublished data). 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 (CDC, ABCs, unpublished data). A portion of these cases will present as meningococcemia, the most severe manifestation of meningococcal bacteremia.[8] 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.[8] 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.[14]

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.[15]

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.[4] 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*.[4] 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.[1] 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).

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. 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. Not recommended for pregnant women.

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.

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.

Over time, the tetravalent meningococcal conjugate vaccine is expected to reduce the incidence of meningococcal disease among those for whom it is recommended for routine use.

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.[16]

Meningococcal serogroup surveillance data are important to monitor the impact of the new tetravalent meningococcal conjugate vaccine (MCV4, Menactra® [sanofi pasteur, Swiftwater, PA]), which was licensed for use in January 2005. Meningococcal serogroup data also help to determine the epidemiologic link between cases in cluster or outbreak situations.[16]

V. Disease Reduction Goals

The *Healthy People 2010* goal is to reduce incidence of meningococcal disease to 1.0 cases/100,000 population.[17] Over time, the tetravalent meningococcal conjugate vaccine is expected to reduce the incidence of meningococcal disease among those for whom it is recommended for routine use, including 11–12-year-olds, adolescents at high school entry, and college freshmen living in dormitories. In addition, the conjugate vaccine is expected to confer long-lasting immunity and reduce nasopharyngeal carriage. The goal of the Advisory Committee on Immunization Practices (ACIP) recommendation is routine vaccination with the conjugate vaccine of all adolescents beginning at age 11 years by 2008.[1]

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.[18]

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).[1]

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.[19] Serogroup A, C, Y and W135 polysaccharides all elicit a serogroup-specific immune response, which allows for a successful tetravalent 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.[5]

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.[20] Gram staining is commonly used for identification of *N. meningitidis* 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.

The case definition for confirmed meningococcal disease requires isolation of N. meningitidis from a normally sterile site.

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.[4]

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.[19] 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. *N. meningitidis* strains with decreased susceptibility to penicillin G have been identified sporadically from several regions of the United States, Europe and Africa.[21] Most of these isolates remain moderately susceptible (penicillin minimum inhibitory concentration of 0.12 µg/mL–1.0 µg/mL). High-dose penicillin G remains an effective treatment strategy against moderately susceptible meningococci. Surveillance of susceptibility patterns in populations should be conducted in order to monitor trends in *N. meningitidis* susceptibility.

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.[1] 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.[22, 23] 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

A tetravalent meningococcal conjugate vaccine, MCV4 (Menactra®, manufactured by sanofi pasteur) was licensed in January 2005 for persons aged 11–55 years. The Advisory Committee on Immunization Practices (ACIP) recommends MCV4 at age 11–12 years. For those who have not previously received MCV4, ACIP recommends vaccination before high school entry (at approximately 15 years).[1] Routine vaccination is also recommended for college freshman living in dormitories and for other populations at increased risk, including

- microbiologists who are routinely exposed to isolates of *N. meningitidis*
- military recruits
- 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
- persons who have terminal complement component deficiencies
- persons who have anatomic or functional asplenia

Polysaccharide vaccine

The tetravalent meningococcal polysaccharide vaccine, MPSV4 (Menomune-A/C/Y/W135®, manufactured by 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.[1] 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.[1]

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[3] and in the dramatic reduction in invasive disease caused by *Streptococcus pneumoniae*.[2]

Bacterial polysaccharides are T-cell–independent antigens and do not stimulate a memory response. Polysaccharides alone do not confer long-lasting immunity or cause a substantial reduction in nasopharyngeal carriage of *N. meningitidis*, limiting the ability of polysaccharide vaccine to elicit herd immunity. 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.[1]

MCV4 was demonstrated to be non-inferior to MPSV4 and was licensed based on safety and immunogenicity data. A randomized controlled trial compared the immunogenicity of MCV4 with that of MPSV4 among 11–18-year-olds, and an additional randomized, controlled trial compared immunogenicity between MCV4 and MPSV4 among 18–55-year-olds.[1] Persistence of antibodies after 3 years and response to revaccination were evaluated for MCV4.[1] Studies to evaluate the effectiveness of the vaccine, including its effect on carriage, are currently under way.

In October 2005, reports indicating a possible association between Guillain-Barré syndrome (GBS) and receipt of MCV4 were made to the Vaccine Adverse Event Reporting System (VAERS). As of October 2006, a total of 17 cases have been reported in persons receiving Menactra. Preliminary analysis of the data suggests a small association between GBS and MCV4 vaccination, but the inherent limitations of VAERS and the uncertainty of background rates for GBS require that these findings be viewed with caution. Because of the risk of meningococcal disease and the associated morbidity and mortality, CDC continues to recommend routine vaccination with MCV4 for adolescents, college freshman living in dormitories, and other populations at increased risk. Persons with a history of GBS may be at increased risk for GBS and should discuss their risk of meningococcal disease with their healthcare provider when deciding whether to be vaccinated.[24]

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.[1] 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/ncidod/dbmd/abcs

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.[1] Rifampin, ciprofloxacin, and ceftriaxone are all effective as chemoprophylaxis against meningococcal disease.[1]

XII. Outbreaks

Compared with the 1980s, outbreaks of meningococcal disease have been detected more frequently in the United States. From July 1994 to June 2002, 69 outbreaks were identified. These outbreaks occurred in 30 states and involved 229 cases, accounting for less than 2% of total meningococcal disease cases in the United States during this period. Twenty-five of the 69 outbreaks were community based and 44 were organization based. Of the organization-based outbreaks, 19 occurred in primary and secondary schools, 12 in colleges and universities and 8 in nursing homes. Vaccination campaigns were conducted in 31 outbreaks. Forty-three of the outbreaks were caused by serogroup C, 17 by serogroup B, and 9 by serogroup Y.[25]

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.[1] 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.[1] In some instances the attack rate will be greater than 10 cases per 100,000 population with only two or three cases.[1] 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.[1]

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.[13]

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.[1]

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.[1] 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.[1]

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Chapter 9: *Mumps*

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I. Disease Description

The classic symptom of mumps is parotitis, most commonly bilateral, which develops an average of 16 to 18 days after exposure.

Mumps is a viral illness caused by a paramyxovirus of the genus *Rubulavirus*. The classic symptom of mumps is parotitis, most commonly bilateral, which develops an average of 16 to 18 days after exposure.[1] Nonspecific symptoms, including myalgia, anorexia, malaise, headache, and low-grade fever, may precede parotitis by several days. As many as 20% of infections are asymptomatic and nearly 50% are associated with nonspecific or primarily respiratory symptoms,[2] particularly among children less than 5 years.[3, 4] Hence, the diagnosis is easily missed.

Not all cases of parotitis—especially sporadic ones—are due to mumps infection. Parotitis can also 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 other noninfectious causes such as drugs, tumors, immunologic diseases, and obstruction of the salivary duct. However, these agents do not produce parotitis on an epidemic scale.

The average incubation period for mumps is 16–18 days, with a range of 12–25 days.[5] Fever may persist for 3–4 days, and parotitis, when present, usually lasts 7–10 days. Persons with mumps are considered most infectious from 1–2 days before until 5 days after onset of parotitis.[6] However, mumps virus has been isolated from saliva from 7 days before symptom onset until 9 days after onset of symptoms.[2, 6]

Severe complications of mumps are rare. However, mumps can cause acquired sensorineural hearing loss in children; incidence is estimated at 5 per 100,000 cases. Mumps-associated encephalitis occurs in fewer than 2 per 100,000 cases, and approximately 1% of encephalitis cases are fatal.

Some complications of mumps are known to occur more frequently among adults than among children. Adults have a higher risk for mumps meningoencephalitis than children. In addition, orchitis occurs in up to 40% of cases in postpubertal males; although it is frequently bilateral, it rarely causes sterility. Oophoritis and mastitis have also been reported in approximately 5% and 30% of cases, respectively, in postpubertal female patients. Pancreatitis has also been reported as a rare complication of mumps.

Permanent sequelae such as paralysis, seizures, cranial nerve palsies, aqueductal stenosis, and hydrocephalus are rare, as are deaths due to mumps. Although some data suggest that mumps infection in the first trimester of pregnancy may result in fetal loss, there is no evidence that mumps during pregnancy causes congenital malformations.

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 in 1977. In 1989, children effectively 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).

Following mumps vaccine licensure, reported mumps decreased steadily from 152,209 cases in 1968 to 2,982 in 1985. During 1986–1987, a resurgence occurred with more than 20,000 mumps cases reported. The resurgence occurred mainly as a result of low vaccination levels among adolescents and young adults.[7] In the late 1980s and early 1990s, outbreaks were reported among highly vaccinated populations.[8, 9] In 1991, a mumps outbreak was sustained in a population where 98% of individuals had been vaccinated.[8] Between December 1997 and May 1998, a mumps outbreak occurred in New York City. Among the 111 case-patients with known vaccination history, 92% had received at least one dose of mumps-containing vaccine, and 62%

had received two or more doses.[10] In 2004, only 258 mumps cases were reported, the lowest annual number since reporting began. In 2006, however, another resurgence occurred, with approximately 6,500 cases reported. The incidence was highest among persons aged 18–24 years, many of whom were college students. Approximately 50% of the case-patients with known vaccination status had received two doses of MMR vaccine.[11]

Mumps continues to be endemic globally. Mumps vaccine is routinely used in 57% of countries or areas in the world.[12] Importation of mumps into the United States is now increasingly recognized.

III. Importance of Rapid 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 susceptible persons.

IV. Importance of Surveillance

Surveillance and prompt investigation of cases and contacts help to halt the spread of disease. 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.

V. Disease Reduction Goals

The 338 reported cases of mumps in 2000 met the *Healthy People 2000* reduction goal of fewer than 500 cases. With this achievement, a goal of elimination of indigenous mumps by the year 2010 has been established.[13]

VI. Case Definition

The following case definition for mumps was approved by the Council of State and Territorial Epidemiologists (CSTE) in 2007.[14]

Clinical case definition:

- An illness with acute onset of unilateral or bilateral tender, self-limited swelling of the parotid and or other salivary gland(s), lasting at least 2 days, and without other apparent cause.

Clinically compatible illness:

Infection with mumps virus may present as aseptic meningitis, encephalitis, hearing loss, orchitis, oophoritis, parotitis or other salivary gland swelling, mastitis or pancreatitis.,

Laboratory criteria

- Isolation of mumps virus from clinical specimen, or
- Detection of mumps nucleic acid (e.g., standard or real time RT-PCR assays), or
- Detection of mumps IgM antibody, or
- Demonstration of specific mumps antibody response in absence of recent vaccination, either a fourfold increase in IgG titer as measured by quantitative assays, or a seroconversion from negative to positive using a standard serologic assay of paired acute and convalescent serum specimens.

Case classification

Suspected: A case with clinically compatible illness or meets the clinical case definition without laboratory testing, or a case with laboratory tests suggestive of mumps without clinical information.

Probable: A case that meets the clinical case definition without laboratory confirmation and is epidemiologically linked to a clinically compatible case.

Confirmed: A case that 1) meets the clinical case definition or has clinically compatible illness, and 2) is either laboratory confirmed or is epidemiologically linked to a confirmed case.

Comment: With previous contact with mumps virus either through vaccination (particularly with 2 doses) or natural infection, serum mumps IgM test results may be negative; IgG test results may be positive at initial blood draw and viral detection in RT-PCR or culture may have low yield.

Therefore, mumps cases should not be ruled out by negative laboratory results. Serologic tests should be interpreted with caution, as false-positive and false-negative results are possible with IgM tests.

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 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 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.*

Comment: *Currently, there is insufficient information to determine whether any mumps strains are endemic to the United States or to distinguish endemic from non-endemic strains...*

Note: *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

Acute mumps infection can be laboratory 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 reverse transcriptase polymerase chain reaction (RT-PCR).

In 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.[16, 17] The timing of the IgM response to mumps infection in vaccinated persons is highly variable,[18] and it may be delayed.

In unvaccinated persons, IgG antibody increases rapidly after onset of symptoms and is long-lasting. Among vaccinated persons, the IgG may already be quite elevated in the acute-phase blood sample, which may obviate the fourfold rise in IgG titer in the convalescent serum specimen.

Virus may be isolated from the buccal mucosa from 6 days before until 10 days after salivary enlargement. Maximal viral shedding, however, seems to occur during the first 5 days after onset of symptoms. Among vaccinated persons who become infected, isolation of virus from the buccal mucosa seems to be more likely within the first few days after the onset of symptoms.

Serologic testing

The serologic tests available for laboratory confirmation of mumps acute infection and immunity vary among laboratories. The state health department can provide guidance regarding available laboratory services.

- 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. If the acute-phase IgM result is negative, a second (convalescent) serum specimen should be collected 2–3 weeks after the onset of symptoms. This second specimen should be tested for IgM, to be able to detect a delayed response.
- The paired serum specimens may also be used to demonstrate a fourfold increase in IgG titer or a seroconversion from negative to positive from acute to convalescent, which is considered a positive diagnostic result for mumps. Prior immunologic experience with mumps, either from childhood disease or from vaccination, may be documented by the presence of serum IgG mumps-specific antibodies.

Tests for IgM antibody

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 suspected mumps cases to the CDC Measles, Mumps, Rubella, and Herpes Laboratory Branch for IgM detection by EIA.

Immunofluorescence assay (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 not currently FDA-approved. Therefore, each laboratory must validate these tests independently.*

Tests for IgG antibody

IgG tests can be performed in the state laboratory or at CDC. 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.

IgG testing for laboratory confirmation of mumps requires the demonstration of seroconversion from negative to positive by EIA or a fourfold 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.

Virus detection (RT-PCR and culture)

Mumps virus can be detected from fluid collected from the parotid duct, other affected salivary gland ducts, throat, urine, and 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 3 days of parotitis and should not be collected more than 10 days after parotitis onset.

Successful isolation should always be confirmed by immunofluorescence with a mumps-specific monoclonal antibody or by molecular techniques. Molecular techniques such as 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 provides important epidemiologic information and is now recommended.

Molecular typing provides important epidemiologic information and is now recommended. Molecular epidemiologic surveillance, (i.e., genotyping of virus) 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.

Specific instructions for specimen collection and shipping may be obtained from the CDC mumps website [http://www.cdc.gov/nip/diseases/mumps/faqs-lab-spec-collect.htm#5034] 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."

VIII. Reporting

Each state and U.S. territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[19] 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 probable and confirmed 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.

Information to collect

Basic demographic information (age, race, ethnicity, sex, county, and country of birth), date of onset of symptoms, and mumps vaccination history allow cases to be characterized and also allow identification of groups at increased risk of disease. In most states, resource limitations have prevented routinely conducting detailed case investigations or obtaining laboratory

confirmation of reported mumps cases. However, laboratory confirmation is important, particularly for sporadic cases, since not all cases with parotitis are due to mumps infection.[20] In cases for which laboratory testing is done, final laboratory results may not be available for the initial report but should be submitted via NNDSS when available.

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
  - Country of birth
  - Length of time in United States
- Reporting source
  - County
  - Earliest date reported
- Clinical
  - Date of illness onset, especially parotitis
  - Duration of parotitis
  - Symptoms
  - Parotitis or other salivary gland involvement (pain, tenderness, 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
    - Meningitis
    - Deafness (transient or permanent)
    - Encephalitis
    - Orchitis
    - Oophoritis
    - Mastitis
    - 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

- Laboratory
  - Serology (IgM, IgG)
  - Virus detection (PCR, culture)
  - Specimen collection date
- Vaccine information
  - Dates of mumps vaccination
  - Number of doses of vaccine given
  - Manufacturer of vaccine
  - Vaccine lot number
  - If not vaccinated, reason
- Epidemiologic
  - Epidemiologic linkages
  - Transmission setting (e.g., college, daycare, doctor's office)
  - Import status*
  - Source of exposure (country, if international import; state, if out-of-state import)
  - Travel history

** 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 symptoms) occurring outside the United States and symptom onset occurring within 25 days of entering the United States and there is no known exposure to mumps in the United States during that time.*

IX. Vaccination

Live attenuated mumps virus vaccine is incorporated with measles and rubella vaccine as a combined vaccine (MMR). With the use of MMR for measles vaccination under the currently recommended two-dose schedule, most children and adolescents receive two doses of mumps vaccine. The current ACIP recommendations for routine vaccination for children indicate a first dose of MMR at 12–15 months of age with a second dose at school entry (4–6 years).[21] Studies have shown a trend toward a lower attack rate among children who have received two doses of mumps-containing vaccine as opposed to those who have received one dose.[9, 22]

Two doses of MMR vaccine are also recommended for adults at high risk, such as international travelers, college students, or healthcare workers born during or after 1957.[21, 23] For healthcare workers born before 1957 without other evidence of immunity, one dose of a live mumps virus vaccine should be considered.[23] Vaccination recommendations for an outbreak setting are discussed in Section XIII, Outbreak Control.

Mumps vaccine is also now available incorporated with measles, rubella and varicella vaccines as a combined vaccine (MMRV). 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.[24]

X. Enhancing Surveillance

Rapid detection, investigation, and implementation of control measures may reduce the occurrence and magnitude of outbreaks.[25] The activities listed below can improve reporting of mumps 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

Mumps case investigations should include complete immunization histories that document all doses of mumps-containing vaccines. Vaccination histories may be obtained from schools, medical providers, or immunization records provided by the case-patient. Verbal history of receipt of mumps vaccine is not considered adequate proof of vaccination.

Laboratory testing

Experience suggests that careful case investigation, combined with routine use of laboratory testing for confirmation of sporadic mumps cases, will result in many suspected cases being discarded.[26, 27] Therefore, if mumps is suspected, laboratory testing should be performed to confirm or rule out sporadic cases. If a case is confirmed, a case investigation should be conducted. Mumps specimens may also 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, child care, and other close contacts), and following up with susceptible persons may reveal previously undiagnosed and unreported cases.

Promoting awareness

Healthcare personnel should be aware that mumps outbreaks have occurred in highly vaccinated populations (e.g., college students). Therefore, mumps should not be ruled out on the assumption that individuals are already immune because of vaccination.

Active surveillance

Active surveillance for mumps should be conducted for every confirmed mumps case, if possible. In the case of an outbreak, 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. 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.

A number of other activities can improve the detection and reporting of cases as well as the comprehensiveness and quality of reporting. For general information on improving surveillance of vaccine-preventable diseases, see Chapter 19, "Enhancing Surveillance."

Active surveillance for mumps should be conducted for every confirmed mumps case, if possible.

Monitoring surveillance indicators

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

- The proportion of confirmed cases reported to NNDSS with complete information (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 confirmed cases that are laboratory confirmed
- The proportion of cases that have an imported source

XI. Case investigation

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

Establishing a diagnosis of mumps

Because clinical diagnosis of mumps may be unreliable, cases of suspected mumps should be laboratory confirmed. Not all cases of parotitis, especially sporadic ones, are due to mumps infection; however, mumps is the only known cause of epidemic parotitis. Experience indicates that case investigations combined with laboratory testing will result in many sporadic, suspected mumps cases being discarded. Because laboratory confirmation may be difficult, especially for vaccinated case-patients, negative laboratory results do not necessarily rule out the diagnosis of mumps, particularly in the event of epidemic parotitis.

Obtaining accurate, complete immunization histories

Mumps case investigations should include complete immunization histories that document all doses of mumps-containing vaccine. Recent outbreaks of mumps have occurred among older children and adults, many of whom had already received at least one dose of a mumps-containing vaccine. In a large U.S. outbreak in 2006, approximately 50% of the case-patients had received two doses of a mumps-containing vaccine (CDC, unpublished data). All vaccination histories should be 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. Usually immunization histories can be obtained from child care, school (generally available for children attending licensed childcare centers or kindergarten through high school), or healthcare provider records. Immunization registries, if available, can also readily provide vaccination histories.

Identifying the source of infection

Efforts should be made to identify the source of infection for every confirmed case of mumps. Case-patients should be asked about contact with other known patients. When no history of contact with a known case can be documented, opportunities for exposure to unknown cases should be sought. After determining when and where transmission likely occurred, investigative efforts should be directed to these locations.

Assessing potential transmission and identifying contacts

As part of the case investigation, the potential for further transmission should be assessed. Contacts of the case-patient during the infectious period should be identified, assessed for immunity, and educated about signs and symptoms.

Obtaining specimens for virus detection

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.

XII. Outbreak Investigation

Case investigation and control activities at the household level should not be delayed pending the return of laboratory results. Initial preparation for major control activities also may need to be started before 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).

The following are general guidelines for outbreak investigation:

Tracking information 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. Such a line listing provides a current summary of the outbreak and of ongoing case investigations.

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 mumps and how many case-patients

have had none, one dose, or two doses of mumps-containing vaccine), 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 preschool-age children, high school students who have only received one dose of mumps vaccine, persons who visited the emergency department of Hospital A on a certain day), determine where transmission is occurring (e.g., child care centers, high schools, healthcare settings), and identify individuals who are at potential risk of infection (e.g., other unvaccinated preschool-age children, students attending other schools)

Enhancing surveillance for mumps

Many of the activities outlined in Section X, "Enhancing surveillance," are applicable in the outbreak setting. Previously unreported cases may be identified by reviewing emergency department logs or laboratory records. As part of outbreak response, active surveillance for mumps should be established to ensure timely reporting of suspected cases in the population known to be affected by the outbreak. Hospital emergency departments and physicians serving affected communities are usually recruited to participate in active surveillance. Active surveillance should be maintained for two incubation periods after the last confirmed case is reported.

XIII. Outbreak Control

Mumps is the only known cause of epidemic parotitis. The main strategy for controlling a mumps outbreak is to define the at-risk population(s) and transmission setting(s), and to rapidly identify and vaccinate susceptible persons or, if a contraindication exists, to exclude susceptible persons from the setting to prevent exposure and transmission. According to ACIP recommendations published in 2006, acceptable presumptive evidence of mumps immunity includes 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 (healthcare workers, 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.[23]

Mumps vaccine, preferably as MMR, should be administered to susceptible persons. Although mumps 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 infected. If susceptible persons can be vaccinated early in the course of an outbreak, they can be protected. However, because of the long incubation period for mumps, cases are expected to continue to occur for at least 3 weeks among newly vaccinated persons who were already infected before vaccination.[28] As with all vaccines, some individuals will not gain 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.[23]

If susceptible persons can be vaccinated early in the course of an outbreak, they can be protected.

Exclusion of susceptible students from schools/colleges affected by a mumps outbreak (and other, unaffected schools judged by local public health authorities to be at risk for transmission of disease) should be considered among the means to control mumps outbreaks.[21] Once vaccinated, students can be readmitted to school. Students who have been exempted from mumps vaccination for medical, religious, or other reasons should be excluded until at least 26 days after the onset of parotitis in the last person with mumps in the affected school.[21]

Patients should be isolated for 9 days following onset of symptoms. However, an isolation period of 5 days, which is the maximum period of communicability after onset of parotitis, is being considered.

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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 a primary vaccination series, 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] Pertussis can be either the cause (primary) or contributing (secondary) cause of death.

Three other *Bordetella* species 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.

When pertussis is strongly suspected, attempts to identify and provide prophylaxis to close contacts should proceed without waiting for laboratory confirmation.

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, and in 2005, the incidence of reported pertussis was 8.6 per 100,000 persons (CDC, unpublished data). Reasons for this increase are not fully understood, but likely contributing factors include increased awareness of the disease and the increased use of diagnostic tests for adolescents and adults.

From 2001 through 2003, persons older than10 years of age accounted for 56% of reported cases,[3] more than double the 24% they accounted for from 1990 to 1993.[3, 4]

Despite this increase in reported pertussis among adolescents and adults, incidence remained highest among young infants.[3] In 2005, most (38 of 39) 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).

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 investigation are used to assess burden of disease and 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.

Laboratory tests can be negative even when the patient has pertussis.

V. Disease Reduction Goals

A disease reduction goal of 2,000 indigenous pertussis cases per year in children younger than 7 years of age was proposed as a part of the *Healthy People 2010* project.[8] In 2005, 7,347 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*
- A case that meets the clinical case definition and is confirmed by PCR
- 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]

Collection of epidemiologic and clinical data is essential for reporting cases that meet the clinical case definition. Investigators should collect information on paroxysms of cough, whoop, and posttussive vomiting; when that is not possible, information on duration of cough should be collected for each suspected case. 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.

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.

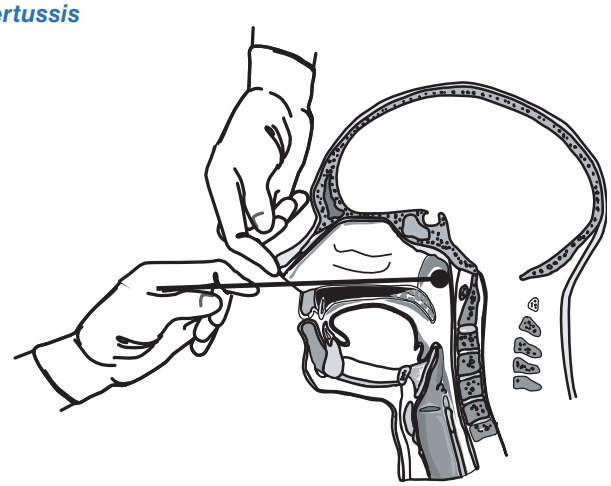
All persons with suspected cases of pertussis should have a nasopharyngeal aspirate or swab obtained from the posterior nasopharynx for culture. For *B. pertussis*, nasopharyngeal aspirates will yield similar or higher rates of recovery than nasopharyngeal swabs;[11–14] throat and anterior nasal swabs 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 Dacron® or rayon 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 can be used as the transport medium.

Polymerase chain reaction for B. pertussis *DNA*

PCR testing of nasopharyngeal swabs or aspirates can be a rapid and sensitive method of diagnosing pertussis.[16, 17] Since its inclusion in the case definition in 1997, the proportion of cases confirmed by PCR has increased, and many laboratories now use only PCR to confirm pertussis. As of February 2007, there are no standardized PCR assays for pertussis; assay procedures, as well as sensitivity and specificity can vary greatly between laboratories. CDC recommends that PCR be used alongside culture, rather than as an alternative test. Direct comparison with culture is necessary for validation of PCR tests performed in different laboratories. Even when a laboratory has validated its PCR method, culturing for *B. pertussis* should continue; this is especially important when an outbreak is suspected, because isolation of the bacterium confirms pertussis (see above). 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

Although serologic testing of persons aged 11 years or older who were vaccinated 3 or more years prior to disease has been used to diagnose pertussis in clinical studies, standardized tests are not available. Some practitioners use commercial tests to diagnose pertussis, but the results of these tests are difficult to interpret. At this time, 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.[18] A serologic test performed at CDC or at the Massachusetts state laboratory might be used to help investigate large outbreaks. Few other validated diagnostic serologic tests are available in the United States. 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), and PFGE results might show diversity within larger geographic areas such as cities, counties, and states. It is not done for routine surveillance.[19, 20]

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.[21] 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.

CDC recommends investigation of deaths associated with *B. pertussis*, regardless of whether they meet the CSTE pertussis case definition. Investigators are requested to complete the Pertussis Death Report Worksheet (Appendix 12) and forward the worksheet and copies of the documents listed therein to CDC at the direction of the state health department.

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 three doses, 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.[21] 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, 22] who have not previously received Tdap.

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

Table 1. Persussis-containing vaccines

Pertussis-Containing Vaccines for Children		
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		
Tdap	ADACEL® BOOSTRIX®	First available in 2005
Other Vaccines		
Pertussis Only		Not available in the U.S.
DT/Td	DECAVAC™ TENIVAC™	Do not contain pertussis; DT used for primary series when pertussis vaccination was not desired; 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) submitted by a jurisdiction.

Unlike many other vaccine-preventable diseases of childhood, pertussis remains endemic in the United States.

Monitoring surveillance indicators

Regular monitoring of surveillance indicators might identify specific areas of the surveillance and reporting system that need improvement. Some indicators are markers of the thoroughness of investigation and the timeliness of reporting:

- 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, and clinic records, 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.[23] 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.[24] 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.[25]

Three macrolides are recommended by CDC for treatment of pertussis. Azithromycin is most popular because it is given in a short, simple regime 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 regime 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 regime and completion of the course are generally lower than for the other macrolides. 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 regime of two doses a day for 14 days. TMP-SMZ should not be used to treat infants younger than 2 months of age.[25]

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.[25]

Prophylaxis of infant contacts of persons with *B. parapertussis* infection should be considered, and infants with *B. parapertussis* infection should be treated. The same antibiotics that are used for treatment and prophylaxis of pertussis are effective for the treatment of parapertussis.[25]

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. Adult and adolescent 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*.[22, 26]

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. In order 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 suspicious 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 always be encouraged to 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 middle and high schools can occur as protection from childhood vaccines wanes.[22] In school outbreaks, prophylaxis is recommended for close classroom and team contacts. Pertussis outbreaks in hospitals and other clinical settings can put infants and other patients at risk. Healthcare personnel with pertussis and exposed healthcare personnel who are symptomatic should be relieved from direct patient contact during the infectious period or until they have completed 5 days of treatment.[26] The efficacy of Tdap vaccination in controlling school or institutional outbreaks has not been evaluated; adolescents and adults 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.[22, 26]

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Chapter 11: Pneumococcal Disease

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I. Disease Description

Streptococcus pneumoniae is a leading cause worldwide of illness and death for young children, persons with underlying medical conditions, and the elderly. The pneumococcus is the most commonly identified cause of bacterial pneumonia; since the widespread use of vaccines against *Haemophilus influenzae* type b, it has become the most common cause of bacterial meningitis in the United States.[1] CDC's Active Bacterial Core Surveillance (ABCs) system has tracked invasive pneumococcal disease (IPD) in selected regions of the United States since 1994. ABCs data suggest that rates of invasive disease are highest among persons younger than 2 years of age and those 65 years of age or older.[2, 3]

Pneumococci can be found in the upper respiratory tract of 15% of well adults; in child care settings, up to 65% of children are colonized.

Cross-sectional studies suggest that pneumococci can be found in the upper respiratory tract of 15% of well adults; in child care settings, up to 65% of children are colonized. Although pneumococcal carriage can lead to invasive disease (e.g., meningitis or bacteremia), 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.[4]

Each year in the United States, pneumococcal disease accounts for a substantial number of cases of meningitis, bacteremia, pneumonia, and AOM (Table 1).[2, 5–11] Approximately 12% 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.[2, 6–8]

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

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 or older who have any of several underlying medical conditions, and to all persons 65 years of age or older.[5] Despite its availability and payment provided under Medicare, current vaccination rates remain below the *Healthy People 2010* national objectives of 90% coverage among persons 65 years of age or older, and 60% coverage among persons 18–64 years of age with underlying medical conditions.[13] In 2003, the median proportion of persons aged 65 years or older who reported ever having received PPV was 64%; the PPV vaccination rate was only 37% among persons 18–64 year of age with diabetes, a group at increased risk for pneumococcal disease.[14, 15] Methods such as the use of standing orders in clinics and hospitals, physician reminder systems, and simultaneous administration of pneumococcal vaccine with influenza vaccine have been shown to improve vaccine utilization.[5]

In February 2000, a 7-valent pneumococcal polysaccharide–protein conjugate vaccine (PCV7) (Prevnar®, manufactured by Wyeth Pharmaceuticals) was licensed for use in infants and young children. PCV7 offers protection against the seven serotypes (PCV7-types) that most commonly cause IPD in children in the United States.[4] In a study conducted among Northern California Kaiser Permanente members, the efficacy of PCV7 was 97% for IPD caused by PCV7 types and 89% for all serotypes.[16] Among Navajo children younger than 2 years of age, efficacy was 76.8% in the per protocol analysis, and 82.6% in the intent-to-treat analysis.[17] Although the efficacy of PCV7 against all AOM episodes is 6%–7%, the efficacy against AOM caused by serotypes included in PCV7 is 57%.[16, 18] In a large clinical trial, radiograph-positive pneumonia episodes were reduced 24.3% in the first year of life, 22.7% in the first 2 years, and 9.0% among children aged 2 years and older.[19]

Since 2000, PCV7 has been recommended for all children younger than 2 years and children 2–4 years of age with certain high-risk conditions.[4] Beginning in August 2001, delays in delivery of PCV7 to some health departments and healthcare providers occurred, with intermittent shortages continuing through September 2004. The ACIP issued updated recommendations to healthcare providers during the shortage, advising them to fully vaccinate high-risk children younger than 5 years and decrease the number of doses administered to healthy infants in lieu of leaving some infants unvaccinated.[20] PCV7 coverage with three or more doses among all U.S. children 19–35 months of age was estimated to be 11% in 2002, and increased to 73% in 2004.[21]

Trends in invasive pneumococcal disease

Despite the vaccine shortages following PCV7 introduction, dramatic declines in invasive pneumococcal disease were reported as early as 2001. Among children younger than 2 years of age, the overall incidence of invasive disease declined by 69%, and the incidence of PCV7-type disease declined by 78% compared with prevaccine rates in 1998–1999.[22] As of 2004, the rate of vaccine-type invasive disease has continued to decline among children in the target age group to 2.5 cases per 100,000, a 93% reduction compared with 1998–1999.[23] The use of PCV7 has also reduced the burden of invasive pneumococcal disease among older children and adults through reduced transmission of vaccine-serotype pneumococci (i.e., herd effect). Declines in the incidence of PCV7-type invasive disease among adults were observed first in 2001 and have continued through 2004, reducing the incidence to 64%–77% below the 1998–1999 baseline, depending on age.[24, 25] 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.[26, 27]

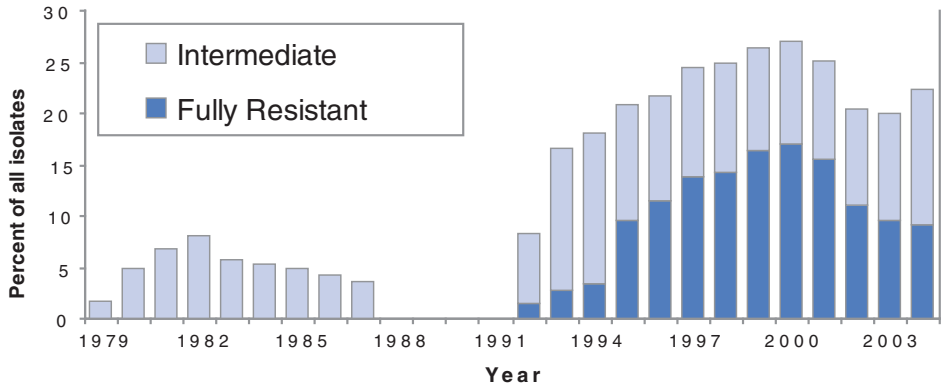
Antimicrobial resistance trends

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 1990s, 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 three or more drug classes.[28–31] In 1998, 24% of invasive pneumococcal isolates were nonsusceptible to penicillin, and 78% of these strains belonged to five of the seven serotypes included in PCV7 (types 6B, 9V, 14, 19F, and 23F).[28] Outbreaks due to both susceptible *S. pneumoniae* and drug-resistant *S. pneumoniae* (DRSP) have been reported in child care centers and among residents of long-term care facilities in which pneumococcal vaccine coverage was low.[32–34]

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.[22, 35–38] In 2004, the rate of penicillin-nonsusceptible invasive disease caused by serotypes included in PCV7 had declined by 98% among children younger than 2 years of age and by 79% among adults 65 years or older. In contrast, an increase in penicillin-nonsusceptible disease caused by serotypes not included in PCV7 was identified in 2004, although the magnitude of this effect remains small.[35] Before the introduction of PCV7, the proportion of pneumococcal illnesses caused by DRSP among children was higher than that among adults.[28] In 2004, children younger than 2 years of age and adults 65 years of age

and older had similar rates of antibiotic-nonsusceptible invasive disease.[35] The prevalence of resistance varied by geographic area both before and after PCV7 was introduced, with higher prevalence noted for the southeastern United States.[28]

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]

Inappropriate antimicrobial use contributes to the development of DRSP.

The emergence of 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. The increasing prevalence of DRSP has prompted groups of experts to provide national guidance for treating infections commonly caused by pneumococcus, such as otitis media and pneumonia.[39–41] Few communities remain in which resistance is 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.

Because of 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.[9, 42–45]

III. Importance of Surveillance

Goals of surveillance

Surveillance for invasive pneumococcal disease has several goals: to observe national and local trends, to detect geographic and temporal changes in the prevalence of DRSP, to monitor the impact of PPV and PCV7 vaccines on disease, and to inform future vaccine development.

With the recent introduction of PCV7, surveillance for invasive pneumococcal disease among children younger than 5 years of age 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 of invasive disease in persons 5 years of age and older is useful for monitoring the impact of PPV vaccination, the indirect effects of PCV7, and replacement disease.

Serotyping of pneumococcal isolates is useful for understanding 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 state public health and academic research centers in the near future.[46, 47]

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.

Reportable conditions

In 1994, the Council of State and Territorial Epidemiologists (CSTE) recommended that states adopt mandatory reporting of invasive infections caused by DRSP.[48] In 2000, the CSTE recommended national reporting of all invasive pneumococcal disease in children younger than 5 years of age.[49] It also suggested surveillance of disease in all age groups, especially by making laboratory reporting mandatory. Surveillance including all age groups would enable more complete analysis of the impact of the new PCV7 vaccine and of campaigns to increase the use of the 23-valent pneumococcal polysaccharide vaccine. In addition, surveillance in all age groups is desirable to calculate the prevalence of DRSP among all pneumococci causing invasive disease.

Between September 2001 and March 2005, the Respiratory Diseases Branch of CDC tracked reports from state health departments of cases of invasive pneumococcal disease among infants and young children who had received at least one dose of PCV7. Data from this surveillance project suggest that children who develop invasive pneumococcal disease following PCV7 vaccination tend to have been incompletely vaccinated or vaccinated late (CDC, unpublished data). Data from ABCs suggest that most cases of invasive pneumococcal disease among vaccinated children are caused by serotypes not covered by the vaccine.[26] True PCV7 failures—defined as PCV7-type invasive disease among fully vaccinated children—occur but are uncommon; therefore, collection of isolates from vaccinated children is no longer routinely recommended.

IV. Disease Reduction Goals

Since the introduction of PCV7 into the childhood immunization schedule in 2000, a significant decrease in invasive pneumococcal disease among infants and young children in the age groups targeted for vaccination has been observed.[22, 23] The *Healthy People 2010* goals for children under 5 years are to reduce the annual rate of invasive pneumococcal disease to 46 cases per 100,000 population from a baseline of 76 cases per 100,000 population in 1997, and to reduce the annual rate of penicillin-resistant invasive pneumococcal disease to 6 cases per 100,000 population from a baseline of 16 cases per 100,000 population in 1997.[13] The overall incidence of invasive disease among children younger than 5 years of age declined to 24 cases per 100,000 population in 2003, exceeding the *Healthy People 2010* objective for this age group.[26] Rates of penicillin-nonsusceptible invasive disease in children younger than 5 years ranged from 25.9 to 33.8 per 100,000 between 1996 and 1999, before the introduction of conjugate vaccine, and declined to 7.5 per 100,000 in 2004, thereby exceeding this *Healthy People 2010* objective as well.[35]

The *Healthy People 2010* goal for overall disease reduction for adults 65 years of age or older is 42 cases per 100,000 population compared with a baseline of 62 cases per 100,000 in 1997.[13] In 2003, the overall incidence of invasive disease declined to 42 cases per 100,000 population, meeting the *Healthy People 2010* objective for this age group.[26] The *Healthy People 2010* target for reduction of invasive pneumococcal disease due to penicillin-nonsusceptible strains is 7 cases per 100,000 persons 65 years and older. In this group, the rate of penicillin-nonsusceptible disease decreased from 16.4 per 100,000 in 1999 to 8.4 per 100,000 in 2004, a 49% reduction.[35] Continuous surveillance is important to evaluate whether reductions in invasive pneumococcal disease incidence will be sustained and whether increases in disease caused by pneumococcal serotypes not included in PCV7 (i.e., replacement disease) will reduce the overall benefit of PCV7.

Disease reduction goals also focus on minimizing complications of DRSP infections through prevention and control measures. In 1995, CDC launched a national campaign to reduce antimicrobial resistance through promotion of appropriate antibiotic use. The control efforts initially targeted the pediatric population and later expanded to include adults.[42, 44]

V. Case Definition

The following case definitions are used for national surveillance of pneumococcal disease in the United States. They were approved by the Council of State and Territorial Epidemiologists (CSTE) for drug-resistant *S. pneumoniae* (DRSP) invasive disease in 1994, and for invasive pneumococcal disease in children younger than 5 years of age in 2000.[48, 49] They were modified in 2006 to prevent duplicate reporting of individual cases.[50]

Drug-resistant *S. pneumoniae* (DRSP) invasive disease

Clinical description

Pneumococci may cause a wide variety of clinical syndromes depending on the site of infection (e.g., otitis media, pneumonia, bacteremia, meningitis). For purposes of national surveillance, "invasive" pneumococcal disease shall refer only to bacteremia and/or meningitis. Although *S. pneumoniae* infections involving other normally sterile sites such as joint, pleural, or peritoneal fluid are sometimes considered invasive, these infections are not intended for inclusion under this surveillance system.

Laboratory criteria for diagnosis

1. Isolation of *S. pneumoniae* from blood or cerebrospinal fluid.

2. Intermediate and high-level resistance* (defined by NCCLS-approved methods and interpretive MIC breakpoints) of the *S. pneumoniae* isolate to at least one antimicrobial agent currently approved for use in treating pneumococcal.

**Resistance defined by Clinical and Laboratory Standards Institute (CLSI [formerly National Committee for Clinical Laboratory Standards, NCCLS])–approved methods and CLSI-approved interpretive minimum inhibitory concentration (MIC) standards (µg/ml) for* S. pneumoniae *(NCCLS Guidelines, 1994). CLSI recommends that all* S. pneumoniae *isolates from patients with life-threatening infections undergo susceptibility testing by using a quantitative MIC method acceptable for penicillin, extended-spectrum cephalosporins, and other drugs as clinically indicated.*[51]

Case classification

Probable: A clinically compatible case due to laboratory-confirmed culture of *S. pneumoniae* identified as "nonsusceptible" (i.e., oxacillin zone size <20 mm) when oxacillin screening is the only method of antimicrobial susceptibility testing performed.

Confirmed: A clinically compatible case due to laboratory-confirmed *S. pneumoniae* identified as "nonsusceptible" according to MIC interpretive breakpoints as outlined in CLSI guidelines for susceptibility testing to any antimicrobial agent currently approved for use in treating pneumococcal infections.

Comment: A variety of methods are available for determining the antimicrobial susceptibility of *S. pneumoniae*; these commonly include disk diffusion, testing by agar dilution or broth microdilution, and testing by antimicrobial gradient agar diffusion (E-test® method). When oxacillin disk screening is the only antimicrobial susceptibility method used, the antimicrobial susceptibility profile cannot be definitively determined. Oxacillin screening is highly sensitive and somewhat specific for detecting beta-lactam–resistant *S. pneumoniae*; however, resistance to non–beta-lactam antibiotics is not detected with this screening method (see Section VI, "Laboratory testing").

Invasive *S. pneumoniae* (Children younger than 5 years)

Case definition

For purposes of this surveillance recommendation, invasive pneumococcal disease is defined as isolation of *S. pneumoniae* from a normally sterile site (e.g., CSF, blood, joint fluid, pleural fluid, pericardial fluid, other).[52]

Modification of case classifications for DRSP and IPD

Case classifications for DRSP and IPD have been modified as follows:

- Isolates causing IPD from children younger than 5 years of age and which antimicrobial susceptibility testing has determined to be DRSP should be reported ONLY as DRSP (event code 11720).
- Isolates causing IPD from children younger than 5 years of age that are susceptible, or for which susceptibility results are not available, should be reported ONLY as IPD (11717).
- All other components of the case definitions remain as referenced.[48, 49]

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 strain may be helpful in interpreting cultures of expectorated sputum; finding a predominance of gram-positive diplococci and more than 25 leukocytes with fewer than 10 epithelial cells per high power field on microscopic examination supports the diagnosis of pneumococcal pneumonia.

Recommendations from CLSI state that clinical laboratories should test all isolates of *S. pneumoniae* from CSF for resistance to penicillin, cefotaxime or ceftriaxone, meropenem, and vancomycin.[51] Recently, susceptibility breakpoints have been changed for isolates from sites other than CSF, resulting in somewhat lower proportions of nonmeningeal isolates characterized as nonsusceptible to third-generation cephalosporins.[53] For organisms from other sources, laboratories should consider testing for resistance to erythromycin, penicillin, trimethoprim–sulfamethoxazole, clindamycin, cefotaxime or ceftriaxone, meropenem, tetracycline, vancomycin, and a fluoroquinolone such as levofloxacin. 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, reported to the state health department. Because pneumococci are fastidious organisms, some susceptibility testing methods used for other organisms are not appropriate for pneumococci; CLSI's Performance Standards for Antimicrobial Susceptibility Testing should be consulted 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 CDC. CDC's Streptococcal Reference Laboratory will serotype pneumococcal isolates from blood, CSF or other sterile sites in outbreak settings. The recent development of a PCR-based technique for determining capsular serotypes could broaden the capacity for state health departments and other countries to perform pneumococcal serotyping.[46, 47]

VII. Reporting

Each state and territory has regulations and laws governing the reporting of diseases and conditions of public health importance.[54] These regulations and laws list the diseases that are to be reported, and describe those persons or institutions responsible for reporting, such as healthcare providers, hospitals, laboratories, schools, daycare and child care facilities, and other institutions. Persons reporting should contact the state health department for state-specific reporting requirements.[52]

Reporting to CDC

Reporting invasive pneumococcal disease in children younger than 5 years of age. Healthcare providers or laboratories should report to their local or state health department all cases of invasive *S. pneumoniae* occurring in children younger than 5 years of age. Some states also require reporting cases among those 5 years and older. The following data are recommended for case investigation and reporting:

- Patient's date of birth or age
- The anatomic site of specimen collection
- Type of infection

Other epidemiologic information that is useful includes patient's sex, race and ethnicity, specimen collection date, whether the patient was hospitalized for the episode, 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. If the isolate causing IPD from a child younger than 5 years of age is known to be antibiotic susceptible, or if susceptibility results are not available, the case should be reported only as IPD in a child younger than 5 years of age (event code 11717 in the National Electronic Telecommunications System for Surveillance [NETSS]).[50]

Reporting drug-resistant invasive pneumococcal disease. Participating healthcare providers or laboratories should report to their local or state health department all cases of DRSP. The following data are recommended for case investigation and reporting:

- Patient's date of birth or age
- The anatomic site of specimen collection
- Type of infection

Other epidemiologic information that is useful includes patient's sex, race and ethnicity, specimen collection date, whether the patient was hospitalized for the episode, 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. Accurate reporting of all cases of IPD—not only those occurring among children younger than 5 years of age—along with the antibiogram of the *S. pneumoniae* isolate will allow calculation of the prevalence of DRSP. Such a change in the case reporting requirements has been adopted or is under consideration in several states. An additional benefit of conducting surveillance for all invasive pneumococcal disease is the ability to track the progress of vaccine efforts to reduce the incidence of *S. pneumoniae* infections. See Appendix 13 for the *S. pneumoniae* Surveillance Worksheet. If a state is reporting through NETSS, use code 11720. If the DRSP case is in a child younger than 5 years of age, please note the modifications of case classifications for DRSP and IPD (Section V, above) and follow the reporting recommendations from CSTE:[50]

- Isolates causing IPD from children <5 years of age and which antimicrobial susceptibility testing has determined to be DRSP should be reported ONLY as DRSP (event code 11720).
- Isolates causing IPD from children <5 years of age which are susceptible, or for which susceptibility results are not available, should be reported ONLY as IPD in children <5 years of age (11717).
- All other components of the case definitions remain as referenced.[48, 49]

VIII. Vaccination

The Advisory Committee on Immunization Practices (ACIP) recommends that the pneumococcal conjugate vaccine (PCV7) be used for all children 23 months of age or younger and for children ages 24–59 months who are at increased risk for pneumococcal disease (e.g., children with sickle cell disease, CSF leak, human immunodeficiency virus infection, and other immunocompromising or chronic medical conditions).[4] ACIP also recommends that the vaccine be considered for all other children ages 24–59 months, with priority given to the following groups:

- Children ages 24–35 months
- Children who are of Alaska Native, American Indian, and African-American descent
- Children who attend group daycare centers

The conjugate vaccine has not been studied sufficiently with older children or adults to make recommendations for its use for persons 5 years old or older who are at increased risk for serious pneumococcal disease. These persons should continue to receive 23-valent polysaccharide vaccine in accordance with previous ACIP recommendations.

The 23-valent pneumococcal polysaccharide vaccine (PPV) is approximately 56%–75% efficacious for the prevention of invasive pneumococcal infection caused by vaccine serotypes.[55, 56] Children 2–4 years of age with high-risk medical conditions should receive PPV at least 2 months after receiving recommended PCV7 doses. A dose of vaccine should be administered to all persons 5–64 years of age who are at increased risk of serious pneumococcal infection because of underlying medical conditions and to all persons 65 years of age and older.[5] A single revaccination after at least 3–5 years (3 years for persons younger than 10 years of age, 5 years for persons 10 or years of age or older) should be considered for persons ages 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 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

It is important to educate providers about which events should be reported and about how accurate reporting is critical to control of communicable diseases.

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 children younger than 5 years

CSTE has recommended reporting of all invasive pneumococcal disease in children younger than 5 years of age to monitor the impact of the pneumococcal conjugate vaccine for this age group; to track progress toward *Healthy People 2010* objectives; and, in conjunction with reporting of drug-resistant strains, to determine the burden of DRSP.

Enhancing reporting of DRSP

Concern over increasing resistance to antimicrobial agents has prompted many state health departments to institute reporting of resistant *S. pneumoniae* strains. Health departments are tracking DRSP using a variety of methods, including electronic laboratory-based reporting. CDC is working with state health departments to evaluate different surveillance methods to determine which methods would improve the reliability of surveillance data, given certain goals and resource limitations.[57] 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,[58] 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 provide an accurate view of resistance if designed well.[59]

Encouraging provider reporting

Most states' infectious disease surveillance systems depend upon receipt of case reports from healthcare providers and laboratories. These data are usually 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.[54] 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 DRSP and local reporting requirements could improve 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.[51] In addition, many laboratories are not monitoring resistance to some agents that are widely used for suspected pneumococcal infections, such as fluoroquinolone agents.[29] Universal adoption of optimal testing methods and testing for resistance to recommended antibiotics would improve the ability to detect and monitor resistant pathogens.

Streamlining reporting using electronic methods

Most surveillance systems still rely on paper and pencil for data collection; use of electronic data transferred directly from clinical laboratories would significantly improve reporting speed and data quality as well as reduce workload. Efforts are under way to implement electronic reporting.[60]

X. Case Investigations

As with most respiratory pathogens, rapid, sensitive, and specific diagnostic tests for *S. pneumoniae* infection are not available; thus, early in the course of illness, diagnosis 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: Polio

Special Notice

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Chapter 13: Rotavirus

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I. Disease Description

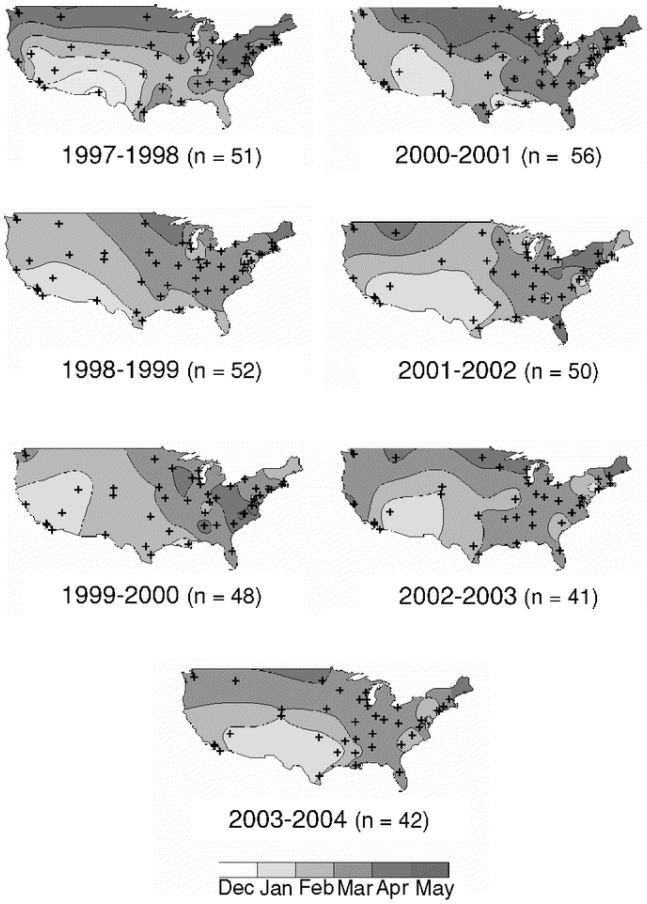
Rotavirus is the most common cause of severe gastroenteritis in infants and young children worldwide. Nearly every child in the United States is infected with rotavirus by age 5 years, and the majority will have symptomatic gastroenteritis. The clinical spectrum of rotavirus illness ranges from mild, 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. As many as one-third of patients have a temperature of greater than 102°F (39°C). Severe, dehydrating rotavirus infection occurs primarily among children aged 3–35 months.[1–6]

The risk for rotavirus gastroenteritis and its outcomes does not appear to vary by geographic region.

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 fewer than 100 virus particles.[9]

In the United States, rotavirus causes marked winter seasonal peaks of gastroenteritis. Of note, peak activity usually begins in the Southwest during November–December and spreads to the Northeast by April–May (Figure 1).[10–12] The risk for rotavirus gastroenteritis and its outcomes does not appear to vary by geographic region. Some studies suggest that premature infants and children from disadvantaged socioeconomic backgrounds have an increased risk for hospitalization from gastroenteritis, including rotavirus.[13, 14] At least one study has observed that breastfeeding might have a protective effect against hospitalization for rotavirus patients under 6 months of age.[14] Children who are immunocompromised sometimes experience severe, prolonged, and even fatal rotavirus gastroenteritis.[15–18] Repeated infections occur from birth to old age, but natural immunity renders the majority of infections asymptomatic after the first years of life.[19] Rotavirus also is an important cause of nosocomial gastroenteritis.[3, 20–25]

Figure 1. Maps reflecting the peak month of rotavirus activity reported by National Respiratory and Enteric Virus Surveillance System laboratories.[12]



Crosses indicate the location of reporting laboratories whose data were included for analysis each season. The total number of laboratories included for analysis is noted in parentheses.

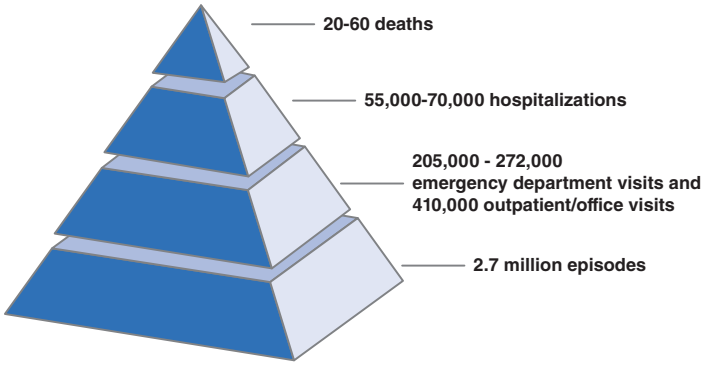
Among U.S. adults, rotavirus infection can cause gastroenteritis, primarily in travelers returning from developing countries, persons caring for children with rotavirus gastroenteritis, immunocompromised persons, and older adults.[26]

II. Background

Burden of disease

In the first 5 years of life, four of five children in the United States will have symptomatic rotavirus gastroenteritis,[4, 27, 28] one in seven will require a clinic or emergency department (ED) visit, one in 70 will be hospitalized, and one in 200,000 will die from this disease.[5, 29] The direct and indirect costs of these 410,000 physician visits, 205,000–272,000 ED visits, and 55,000–70,000 hospitalizations is approximately $1 billion (Figure 2). Relatively few childhood deaths are attributed to rotavirus in the United States (approximately 20–60 deaths per year among children younger than 5 years of age).[30] However, in developing countries, rotavirus gastroenteritis is a major cause of severe childhood morbidity and is responsible for approximately half a million deaths per year among children aged younger than 5 years.[31]

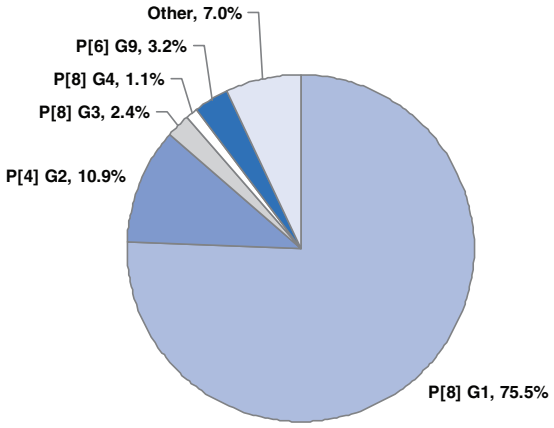
Figure 2. Estimated number of annual deaths, hospitalizations, emergency department visits, and episodes of rotavirus gastroenteritis among United States children aged <5 years. [1]



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. In the United States, 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 (Figure 3), although more than 40 rare or regional strains have been identified in the United States and globally.[32] 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 to have been formed by reassortment of one or more animal rotavirus genes into a human rotavirus during a mixed infection in vivo.

Figure 3. Prevalent strains of rotavirus among children aged <5 years in the United States, 1996–1999[33]



III. Vaccination

In 2006, a live, oral, human–bovine reassortant rotavirus vaccine (RotaTeq®, produced by Merck and Company, Whitehouse Station, New Jersey) was licensed in the United States. The Advisory Committee on Immunization Practices has recommended routine vaccination of U.S. infants with three doses of this vaccine 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 three phase III trials, including a large-scale clinical trial of more than 70,000 infants. The efficacy of three doses of RotaTeq against rotavirus gastroenteritis of any severity was 74% (95% confidence interval [CI] = 67%–79%) and against severe rotavirus gastroenteritis was 98% (CI = 90%–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 cause was 59% (CI = 56%–65%).[1]

Surveillance efforts should focus on monitoring trends of severe rotavirus disease.

IV. Importance of Surveillance

With the introduction of a new rotavirus vaccine into the U.S. childhood immunization schedule, surveillance is important to 1) monitor the impact of vaccination in reducing 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; and 4) identify population groups that might not be adequately covered by vaccination. Since nearly every child experiences 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 ED visits, at the national level and through more intensive efforts at some sentinel sites. In addition to surveillance of severe and medically attended disease, viral strain surveillance is also essential.

V. Disease Reduction Goals

Because the current rotavirus vaccine was licensed in 2006, *Healthy People 2010* does not state a goal for overall rotavirus disease reduction or target for vaccination coverage at this time.

VI. Case Definition

Definitive diagnosis of rotavirus gastroenteritis requires laboratory confirmation of infection. Currently, no case definition for rotavirus gastroenteritis has been approved by the Council of State and Territorial Epidemiologists. Active surveillance being conducted at sentinel sites by CDC defines a confirmed case of rotavirus gastroenteritis as diarrhea (3 or more loose stools in 24 hrs) OR vomiting (1 or more episodes in 24 hrs) in a child, with detection of rotavirus in a fecal specimen by a standard assay (e.g., commercially available enzyme immunoassay).

VII. Laboratory Testing

Rotavirus infection cannot be diagnosed 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.[34] Polyacrylamide gel electrophoresis and silver staining is about as sensitive as EIA but is very labor intensive.[35] Latex agglutination is less sensitive than EIA but is still used in some settings.[1] Other techniques, including electron microscopy, reverse transcription polymerase chain reaction (RT-PCR), nucleic acid hybridization, sequence analysis, and culture are used primarily in research settings.

Rotavirus serotypes can be determined directly from rotavirus-positive stool specimens by using both EIA and RT-PCR methods. Monoclonal antibody–based EIA techniques have been invaluable in defining four globally common serotypes (G1–G4) that represent more than 90% of the circulating strains and make up four of the five serotypes in the Rotateq vaccine.[36, 37] 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.[38–41] 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. Persons reporting should contact the state health department for state-specific reporting requirements.

National rotavirus surveillance is currently being done by the following methods:

New Vaccine Surveillance Network (NVSN)

The NVSN consists of three participating medical centers in Tennessee, New York, and Ohio that conduct active, population-based surveillance for rotavirus-associated hospitalizations, ED visits, and outpatient visits among children younger than 3 years of age. Rotavirus surveillance activities through NVSN began in the 2005–2006 rotavirus season. Acute gastroenteritis cases are identified during the rotavirus season, and additional epidemiologic 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. Future efforts will include observational studies to assess rotavirus vaccine effectiveness in field use.

National Respiratory and Enteric Virus Surveillance System (NREVSS) and 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 participate in NREVSS. Participating laboratories submit weekly reports to CDC on 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.

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 Edition, 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 less than 50%.

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 that warrant medical attention.

X. Control

Routine immunization of infants is anticipated to be the most effective public health intervention for population-wide rotavirus infection control.

Routine immunization of infants is anticipated to be the most effective public health intervention for population-wide rotavirus infection control. Postexposure vaccine prophylaxis is not a recommended strategy in response to an outbreak of rotavirus gastroenteritis.

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Chapter 14: Rubella

Susan Reef, MD; Susan Redd; Emily Abernathy, MS; Joseph Icenogle, PhD

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] The average incubation period is 14 days with a range of 12–23 days. Persons with rubella are most infectious when rash is erupting, but they can shed virus from 7 days before to 5–7 days after rash onset (i.e., the infectious period).

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.[1] See Chapter 15, "Congenital Rubella Syndrome," for more details.

II. Background

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.[1]

In 2004, an independent panel of internationally recognized experts in public health,.... unanimously agreed that rubella is no longer endemic in the United States.

In 1969, live attenuated rubella vaccines were licensed in the United States. The goal of the rubella vaccination program was to prevent congenital infections, including CRS.[2] Following vaccine licensure, the number of reported cases of rubella in the United States has declined more than 99%, from 57,686 cases in 1969 to 10 cases in 2005 (CDC, unpublished data). Since 2001, the largest number of annual reported cases was 23 in 2001, and since 2003, 10 or fewer cases have been reported annually.[3] During the 1990s, the incidence of rubella among children younger than 15 years decreased (0.63 versus 0.06 per 100,000 population in 1990 versus 1999), whereas the incidence among adults aged 15 to 44 years increased (0.13 versus 0.24 per 100,000 in 1990 versus 1999).[4] However, since 2001, the incidence both among persons younger than 15 years and those age 15 to 44 years has been less than 10/1,000,000 population.[3]

Between mid-1990 and 2000, most of the reported cases occurred among persons of Hispanic ethnicity; most of these persons were born outside the United States. In 1992, incidence among Hispanics was 0.06, and rose to a high in 1998 of 0.97 per 100,000 population. Since 2001, fewer than 50% of cases were among persons of Hispanic ethnicity. 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.[3, 4] Since 2001, two 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 is no longer endemic in the United States.[2]

Despite this, rubella continues to be endemic in many parts of the world. It is estimated more than 100,000 cases of CRS occur annually globally. According to a survey of the member countries in the World Health Organization, the number of countries that have incorporated rubella-containing vaccines into their routine national immunization programs increased from 65 (12% of the birth cohort) in 1996 to 117 countries (26% of the birth cohort) in 2005. As of September 2006, two WHO regions (European, The Americas) have established rubella elimination goals for the year 2010.

III. Importance of Rapid Case Identification

Prompt identification 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.

IV. Importance of Surveillance

Surveillance data are used to identify groups of persons or areas in which additional disease control efforts (such as immunization) are required to reduce disease incidence and to evaluate the effectiveness of disease prevention programs and policies.

V. Disease Reduction Goals

The proposed *Healthy People 2010* objectives include a goal to eliminate indigenous rubella and CRS in the United States by the year 2010.[5]

VI. Case Definition

The following case definition for rubella has been approved by the Council of State and Territorial Epidemiologists (CSTE) and was published in 1997.[6] The following case classifications for importation status were approved by CSTE in 2006.[7]

Clinical case definition

Rubella is an illness that has all of the following characteristics:

- Acute onset of generalized maculopapular rash
- Temperature >99°F (37.2°C), if measured
- Arthralgia or arthritis, lymphadenopathy, or conjunctivitis

Laboratory criteria for diagnosis

Laboratory criteria for diagnosis consist of the following:

- Isolation of rubella virus, 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
- PCR positive for rubella virus

Case classification

Suspected: Any generalized rash illness of acute onset

Probable: A case that meets the clinical case definition, has no or noncontributory serologic or virologic testing, and is not epidemiologically linked to a laboratory-confirmed case

Confirmed: A case that is laboratory confirmed or that meets the clinical case definition and is epidemiologically linked to a laboratory-confirmed case

Comment: Serum rubella IgM test results that are false positives have been reported in persons with other viral infections (e.g., acute infection with Epstein-Barr virus [infectious mononucleosis], recent cytomegalovirus infection, and parvovirus infection) or in the presence of rheumatoid factor. Patients who have laboratory evidence of recent measles infection are excluded.

Importation status

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.

Because many rash illnesses may mimic rubella infection and 20%–50% of rubella infections may be subclinical, laboratory testing is the only way to confirm the diagnosis.

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 epidemiologic or virologic 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 epidemiologic or virologic 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

Diagnostic tests used to confirm acute or recent rubella infection or CRS include serologic testing and virus cultures. Because many rash illnesses may mimic rubella infection and 20%–50% of rubella infections may be subclinical, laboratory testing is the only way to confirm the diagnosis. Acute rubella infection can be confirmed by the presence of serum rubella IgM, a significant rise in IgG antibody titer in acute- and convalescent-phase serum specimens, positive rubella virus culture, or detection of the rubella virus by RT-PCR. Detection of wild-type virus is considered the gold standard.

Sera should be collected as early as possible (within 7–10 days) after onset of illness. IgM antibodies may not be detectable before day 5 after rash onset. In case of a negative rubella IgM in specimens taken before day 5, serologic testing should be repeated. If testing is for documentation of seroconversion (IgG), a second serum sample should be collected about 14–21 days after the first specimen. In most rubella cases, rubella IgG is detectable by 8 days after rash onset.[8] 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.

As rubella incidence decreases, the predicative positive value of rubella IgM results decreases. False-positive serum rubella IgM tests have occurred in persons with parvovirus B19 infections or infectious mononucleosis or with a positive rheumatoid factor (indicating rheumatologic disease).[9, 10] When a false-positive rubella IgM is suspected, a rheumatoid factor, parvovirus IgM, and heterophile test may be used to rule out a false-positive rubella IgM test result. Avidity testing is another method of ruling out false-positive IgM results. Properly done identification of wild-type rubella virus also can resolve uncertainties in the serologic evaluation of suspected cases.

Immunity to rubella may be documented by determining the presence of serum IgG rubella-specific antibodies by enzyme immunoassay, hemagglutination inhibition, latex agglutination, and immunofluorescent antibody assays. (See below.)

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

Serologic testing

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 to screen for rubella immunity and laboratory confirmation of disease. The state health department can provide guidance on available laboratory services and preferred tests.

Enzyme immunoassay (EIA): Most diagnostic testing done for rubella IgG and IgM antibodies uses 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 was once the standard and most commonly used technique and allows for either screening or diagnosis (if paired acute- and convalescent-phase sera are tested). A fourfold or greater rise in HI antibody titer in paired sera is diagnostic of recent infection. The test may be modified to detect rubella-specific IgM antibody.

Latex agglutination (LA) test: LA appears to be sensitive and specific for screening when performed by experienced laboratory personnel.

Immunofluorescent antibody (IFA) assay: IFA is an option for detection of IgG and IgM antibodies to rubella virus. Commercial assays are available in the United States. Typically, cells expressing rubella virus proteins and control cells are reacted with test serum, and any rubella virus-specific antibodies are then detected with fluorescent dye-labeled goat anti-human IgG (or IgM) and fluorescent microscopy. Negative human sera are useful for monitoring nonspecific signal. Fluorescence should be cell associated. Staining restricted to the periphery of the cell monolayer is not indicative of a true-positive result.[8]

Avidity test: The avidity assay is not a routine test and should be performed in reference laboratories. A number of avidity assays have been described.[11, 12] The purpose is 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.

Virus detection/isolation

Rubella virus can be isolated from nasal, blood, throat, urine and cerebrospinal fluid specimens from persons with rubella and CRS (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 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.[13] Molecular epidemiologic surveillance provides important information on

- Origin of the virus,
- Virus strains circulating in the United States, and
- Whether these strains have become endemic in the United States.

For molecular typing, throat swabs should be collected within 4 days of rash onset and sent to CDC as directed by the state health department.

Reverse transcription polymerase chain reaction (RT-PCR)

RT-PCR has been extensively evaluated for its usefulness in detecting rubella virus in clinical specimens.[14] Clinical specimens obtained for virus isolation and sent to CDC are routinely screened by RT-PCR

VIII. Reporting

Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[15] 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.

Reporting to CDC

Provisional reports of rubella and CRS cases should be sent to CDC by the state health department via 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 NEDSS 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 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
  - Duration of rash
  - Symptoms
    - Fever
    - Arthralgia or arthritis
    - Lymphadenopathy
    - Conjunctivitis
  - Complications
    - Encephalitis
    - Arthralgia or arthritis
    - Thrombocytopenia
  - 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
    - Date and specific titer result of prior serum rubella IgG titer
    - 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
- Vaccine Information
  - Number of doses of rubella-containing vaccine received
  - Dates of vaccination
  - If not vaccinated, reason
- Epidemiologic
  - Transmission setting (infection acquired in daycare, school, workplace)
  - Relationship to outbreak (Is case part of an outbreak or is it sporadic?)
  - Source of exposure and travel history (indigenous case or imported; if imported, international out-of-state import; include state name, country name, and dates of travel)

IX. Vaccination

Live attenuated rubella virus vaccine is recommended for persons 12 months of age and older unless one of these conditions applies: a medical contraindication such as severe immunodeficiency or pregnancy; documented evidence of rubella immunity as defined by serologic evidence (e.g., a positive serum rubella IgG); documented immunization with at least one dose of rubella vaccine on or after first birthday; or birth before 1957 (except women who could become pregnant). Clinical diagnosis of rubella is unreliable and should not be considered in assessing immune status.

Because two doses of combined measles-mumps-rubella (MMR) vaccine are recommended in the current schedule for measles vaccination, most children and adolescents now receive two doses of rubella vaccine. Rubella vaccine, as MMR, is recommended at 12–15 months of age. A second dose of MMR is recommended at 4–6 years of age.[16]

Healthcare providers who treat women of childbearing age should routinely determine rubella immunity and vaccinate those who are susceptible and not pregnant. Women found to be susceptible during pregnancy should be vaccinated immediately postpartum.[16]

In 2001, the Advisory Committee on Immunization Practices (ACIP) reviewed data from several sources indicating that no cases of CRS had been identified among infants born to women who were vaccinated against rubella within 3 months prior to conception or early in pregnancy. However, a small theoretical risk of 0.5% cannot be ruled out. On the basis of these data, ACIP recommended that pregnancy be avoided for 28 days after receipt of a rubella-containing vaccine instead of 3 months, as previously recommended.[17]

X. Enhancing Surveillance

The following activities may be undertaken to improve the comprehensiveness and quality of surveillance for rubella. Additional guidelines for enhancing surveillance are presented in Chapter 19, "Enhancing Surveillance."

Promoting awareness of rubella and CRS in the United States

Although only 68 cases of rubella and 5 cases of CRS were reported between 2001 and 2005, it is likely that not all cases were identified. Efforts should continue to promote physicians' awareness of the possibility of rubella and CRS, especially when evaluating patients with suspected measles who have negative serologic tests for acute measles infection, (i.e., negative serum measles IgM).

Many persons who received childhood immunizations in other countries may never have had the opportunity to receive rubella vaccine.

Promoting awareness of high-risk groups for rubella infection and CRS birth

Rubella vaccine is not administered routinely in many countries, and in others rubella vaccine was only recently added to the childhood immunization schedule. Thus, many persons who received childhood immunizations in other countries may never have had the opportunity to receive 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 recently implemented programs.

Expanding laboratory testing

Serologic tests for measles and rubella may be done sequentially or simultaneously. All persons with suspected cases of measles who have a negative serum measles IgM test should be tested for rubella IgM and IgG. All persons with suspected cases of rubella should be tested for serum rubella IgM and, if negative and measles is suspected, tested for measles IgM.

Searching laboratory records

Audits of laboratory records may provide reliable evidence of previously unreported, serologically confirmed or culture-confirmed cases of rubella. This activity is particularly important during outbreaks as an aid to defining the scope of disease transmission in an area.

Conducting active surveillance

In outbreak settings, 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. Surveillance for CRS should be implemented when confirmed or probable rubella cases are documented in a setting where pregnant women might have been exposed.

Monitoring surveillance indicators

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

- The median interval between rash onset and notification of a public health authority, for confirmed cases
- The proportion of confirmed cases reported to the NNDSS with complete information
- The proportion of confirmed cases that are laboratory confirmed
- The proportion of confirmed cases among women of child-bearing age with known pregnancy status

XI. Case Investigation

The goal of rubella case investigation is to prevent exposure of susceptible pregnant women, and thereby prevent cases of CRS. It is essential that potentially susceptible, exposed pregnant women be identified, evaluated, and counseled. The Rubella Surveillance Worksheet (see Appendix 16) may be used as a guideline in conducting a case investigation, as well as the *MMWR* Recommendations and Reports issue entitled "Control and Prevention of Rubella:

Evaluation and Management of Suspected Outbreaks, Rubella in Pregnant Women, and Surveillance for Congenital Rubella Syndrome."[18]

Establishing a diagnosis of rubella

Because clinical diagnosis of rubella is unreliable, cases must be laboratory confirmed, especially if the reported cases are not epidemiologically linked to a laboratory-confirmed case.

The occurrence of a rubella-like illness in recently vaccinated persons can pose particular difficulties in the outbreak setting. Five percent of recipients of rubella-containing vaccine may develop rash approximately 1 week after vaccination, and vaccination of susceptible persons results in production of IgM antibody that cannot be distinguished from that resulting from natural infection. 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. Molecular typing techniques can distinguish between vaccine and wild-virus rash for those vaccinated 7–10 days before rash onset. Specimens for molecular typing should be obtained within 4 days of rash.

Obtaining accurate pregnancy status for adult women

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 is susceptible to rubella, 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.[17]

Obtain accurate and complete immunization histories

Rubella case investigations should include complete immunization histories that document any doses of rubella-containing vaccine.

Identifying 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 (20%–50%) 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 high-risk populations (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. Such exposures may occur in colleges or universities, workplaces, and communities where unvaccinated persons congregate.

Assessing potential for transmission and identifying contacts

In recent outbreaks, transmission has occurred in households, communities, workplaces, and prisons. As part of the case investigation, the potential for further transmission should be assessed, and contacts (particularly susceptible pregnant women) of the case-patient during the infectious period (7 days before to 7 days after the onset of rash) should be identified.

Obtaining specimens for virus isolation

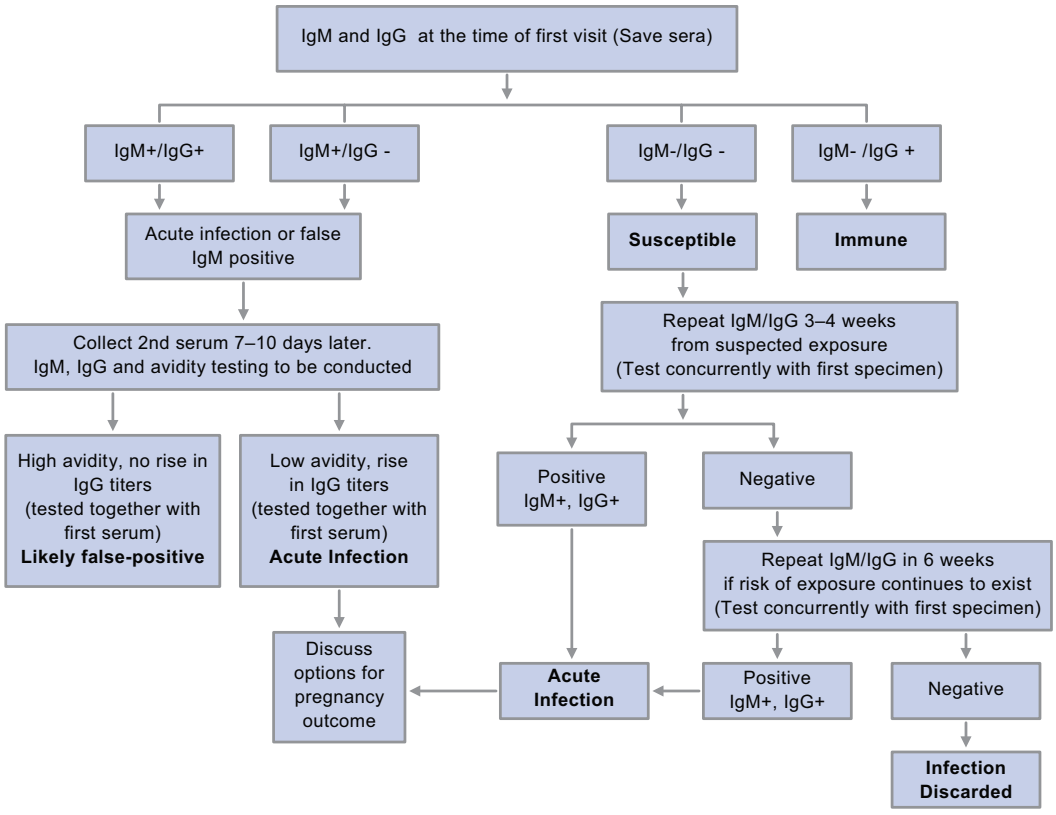
Efforts should be made to obtain clinical specimens (throat swabs and urine) for virus isolation from all case-patients (or from at least some patients in each outbreak) at the time of the initial investigation. These specimens for isolation of rubella virus should be obtained within 4 days after rash onset. Isolates are essential for tracking the epidemiology of rubella in the United States, now that rubella virus may no longer continuously circulate in this country. By comparing isolates from new case-patients with other virus samples, the origin of particular virus types in this country can be tracked.[13] Furthermore, this information may help in documenting the interruption of indigenous transmission. See Appendix 15 for the procedure to follow in collection of specimens.

Conducting laboratory evaluation of exposed pregnant women

The algorthim in Figure 1 shows a stepwise process for laboratory evaluation of pregnant women exposed to rubella. A blood specimen should be taken as soon as possible and tested for rubella IgG and IgM antibody. The specimen should be 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 to repeat the test in 7–10 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. With the low incidence of rubella in the United States, false-positive tests are common. Reinfection with rubella occurs more frequently with vaccine-induced immunity than with natural disease; however, the risk of fetal infection is extremely rare. If the IgM is negative and the IgG is positive at the time of exposure (the first specimen), this mostly likely indicates immunity. If the IgM and IgG are negative in the first specimen, a second specimen should be taken 3 to 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.

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 IgM test results are 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. The difference is that the timing of exposure to rubella is unknown.

Figure 1. Algorithm for serologic evaluation of pregnant women exposed to rubella



Establishing a pregnancy outcome registry 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.

XII. Outbreak Control

Aggressive response to rubella outbreaks may interrupt disease transmission and will increase vaccination coverage among persons who might otherwise not be protected. The main strategies are to define at-risk populations, to ensure that susceptible persons 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.

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. All persons at risk who cannot readily provide laboratory evidence of immunity or a documented history of vaccination on or after their first birthday should be considered susceptible and should be vaccinated if no contraindications exist.

In schools and other educational institutions, exclusion of persons without valid evidence of 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 3 weeks after the onset of rash of the last reported case-patient in the outbreak setting.

Mandatory exclusion and vaccination of adults should be practiced during rubella outbreaks occurring in medical settings because pregnant women may be exposed.

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Chapter 15: Congenital Rubella Syndrome

Susan Reef, MD; Susan Redd

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% to 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. Arthralgia or arthritis may occur in up to 70% of adult women with rubella. When rubella infection occurs during pregnancy, especially during the first trimester, serious consequences—such as miscarriages, stillbirths, and a constellation of severe birth defects known as congenital rubella syndrome (CRS)—can result. Of the mothers infected during the first 11 weeks of gestation, 90% will deliver an infant born with CRS; the rate of CRS for infants born to women infected during the first 20 weeks of pregnancy is 20%. The most common congenital defects of CRS are cataracts, heart defects and hearing impairment.

II. Background

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.[1]

In 1969, live attenuated rubella vaccines were licensed in the United States. The goal of the rubella vaccination program was to prevent congenital rubella infections, including CRS. Following vaccine licensure, the number of reported cases of CRS in the United States has declined 99%, from 77 cases in 1970 to one imported case in 2004.[2, 3] During 1998–2004, 28 cases of CRS were reported to the National Congenital Rubella Syndrome Registry (NCRSR); five of these were in infants born during 2001–2004. In 26 (93%) of the 28 cases occurring during 1998–2004 in which the mother's country of birth was known, the mother was born outside the United States. Of the 24 CRS cases with known import status occurring during this time, 12 (50%) were imported.[3]

The goal of rubella vaccination is to prevent congenital rubella infection.

In 2004, an independent panel of internationally recognized experts in public health, infectious diseases and immunizations reviewed the available data on rubella occurrence and epidemiology and unanimously agreed that rubella is no longer endemic in the United States.[4]

Although rubella is no longer endemic in the United States, it continues to be endemic in many parts of the world. It is estimated that more than 100,000 cases of CRS occur annually worldwide.[5] According to a survey of the member countries in the World Health Organization, the number of countries that have incorporated rubella-containing vaccine into their routine national immunization programs increased from 65 (12% of the birth cohort) in 1996 to 116 countries (26% of the birth cohort) in 2004. As of February 2006, two WHO regions (European, The Americas) have established rubella elimination goals for the year 2010.[3]

III. Importance of Rapid Identification

Infants with CRS may shed virus for up to 1 year. Therefore, it is essential that infected infants be identified as early in life as possible in order to prevent further spread of the virus. Infected infants should be considered infectious until they are at least 1 year old or until two cultures of clinical specimens obtained 1 month apart after the infants is older than 3 months of age are negative for rubella virus.[6]

Early diagnosis of CRS facilitates early intervention for specific disabilities. Results of recently published reports demonstrate significant enhancement of speech and language development, and eventual success in school for children with hearing impairment if they are identified early and intervention begins immediately.[7, 8]

IV. Importance of Surveillance

The goal of rubella vaccination is to prevent congenital rubella infection. Surveillance data are used to identify groups of persons or areas in which disease control efforts such as immunization can reduce or eliminate endemic disease and to evaluate the effectiveness of disease prevention programs and policies.

V. Disease Reduction Goals

As part of the proposed *Healthy People 2010* objectives, a goal was established to eliminate U.S.-acquired rubella and CRS in the United States by the year 2010.[9]

As part of the proposed Healthy People 2010 objectives, a goal was established to eliminate U.S.-acquired rubella and CRS in the United States by the year 2010.

VI. Case Definition

The following case definition for congenital rubella syndrome was approved by the Council of State and Territorial Epidemiologists (CSTE) in June 1999.[10] The case classification for importation status was approved by the CSTE in June 2006.[11]

Clinical case definition

An illness, usually manifesting in infancy, resulting from rubella infection in utero and characterized by signs or symptoms from the following categories:

- Cataracts and congenital glaucoma, congenital heart disease (most commonly patent ductus arteriosus or peripheral pulmonary artery stenosis), hearing impairment, pigmentary retinopathy
- Purpura, hepatosplenomegaly, jaundice, microcephaly, developmental delay, meningoencephalitis, radiolucent bone disease

Clinical description

Presence of any defect(s) or laboratory data consistent with congenital rubella infection. 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.

Laboratory criteria for diagnosis

- Isolation of rubella virus, or
- Demonstration of rubella-specific immunoglobulin M (IgM) antibody, or
- Infant rubella antibody level that persists at a higher level and for a longer period than expected from passive transfer of maternal antibody (i.e., rubella titer that does not drop at the expected rate of a twofold dilution per month)
- PCR positive for rubella virus

Case classification

Suspected: A case with some compatible clinical findings but not meeting the criteria for a probable case.

Probable: A case that is not laboratory confirmed and that has any two complications listed in first paragraph of the clinical case definition or one complication from the first paragraph and one from the second paragraph, and lacks evidence of any other etiology.

Confirmed: A clinically consistent case that is laboratory confirmed.

Infection only: A case that demonstrates laboratory evidence of infection, but without any clinical symptoms or signs.

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 loss) are identified later, the case is reclassified as confirmed.

Importation Status

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 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.

VII. Laboratory Testing

Diagnostic tests used to confirm CRS include serologic assays and isolation of the virus. Laboratory confirmation can be obtained by any of the following:

- 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.[6]
- Documentation of persistence of serum rubella IgG titer beyond the time expected from passive transfer of maternal IgG antibody (i.e., rubella titer that does not decline at the expected rate of a twofold dilution per month).
- Isolation of rubella virus, which may be shed from the throat and urine for a year or longer.
- Detection of rubella virus by reverse transcription polymerase chain reaction (RT-PCR).

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."

Serologic testing

The serologic tests available for laboratory confirmation of CRS infections vary among laboratories. The following tests are widely available and may be used for screening for laboratory confirmation of disease. The state health department can provide guidance on available laboratory services and preferred tests. For additional information on laboratory testing for rubella virus, see Chapter 14, "Rubella."

Enzyme immunoassay (EIA). Most diagnostic testing done for rubella antibodies uses some variation of the EIA, which is sensitive, widely available, and relatively easy to perform. EIA, using the capture technique, is the preferred testing method for IgM. Indirect assays are also acceptable.

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; complexes due to rheumatoid antibody or IgG antibodies can lead to a false-positive result.

Virus isolates are extremely important for molecular epidemiologic surveillance to help determine the origin of the virus, the virus strains circulating in the U.S., and whether these strains are no longer endemic in the U.S.

Virus isolation

Rubella virus can be isolated from nasal, blood, throat, urine, and cerebrospinal fluid specimens from rubella and CRS patients (best results come from throat swabs). 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 for a prolonged period, specimens obtained later may also yield rubella virus. Infants with CRS should be considered infectious until two cultures of clinical specimens obtained 1 month apart after the infant is older than 3 months of age are negative for rubella virus.

Molecular typing

Virus isolates are extremely important for molecular epidemiologic surveillance to help determine 1) the origin of the virus, 2) virus strains circulating in the United States, and 3) whether these strains are no longer endemic in the United States.[12] Specimens for molecular typing should be obtained from patients with CRS as soon as possible after diagnosis. Appropriate specimens include throat swabs, cerebrospinal fluid, 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

Extensive evaluations have documented the usefulness of PCR for detection of rubella virus in clinical specimens.[13–15] Clinical specimens obtained for virus isolation and sent to CDC are routinely screened by RT-PCR

VIII. Reporting

Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[16] 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 facilities, and other institutions. Persons reporting should contact the state health department for reporting requirements specific to that state.

Reporting to CDC

Within 14 days of the initial report to the state or local health department , provisional reports of rubella and CRS cases should be sent by the state health department to CDC via the National Electronic Telecommunications System for Surveillance (NETSS) or the National Electronic Disease Surveillance System (NEDSS). Reporting should not be delayed because of incomplete information or lack of confirmation.

In addition, each possible and confirmed case of CRS should be reported to the National Congenital Rubella Syndrome Registry (NCRSR), National Center for Immunization and Respiratory Diseases (NCIRD) at (404) 639-8253. The Congenital Rubella Sydrome 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. NCRSR cases are classified by year of patient's birth. Although case report forms should be as complete as possible, lack of complete information should not delay the reporting.

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
  - 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
- Outcome (infant survived or died)
  - Date of death
  - Postmortem examination results
  - Death certificate diagnoses
- Laboratory (performed on both mother and infant)
  - Virus isolation
  - Dates and results of previous serologic tests for rubella immunity
  - Serology
- Maternal history
  - Dates of rubella vaccinations
  - Number of doses of vaccine given
  - If not vaccinated, reason
  - History of documentation of rubella infection during pregnancy
  - History of pregnancies within and outside the United States (including country and years of pregnancies)
- Epidemiologic
  - Transmission setting
  - Source of transmission (e.g., age, vaccination status, relationship to decedent)
  - Source of exposure
  - Travel history

IX. Vaccination

Because birth defects are noted in 3%–5% of all births, confusion about the etiology of birth defects may result if vaccine is administered during pregnancy. In 2001, the Advisory Committee on Immunization Practices (ACIP) reviewed data from several sources indicating that no cases of CRS had been identified among infants born to women who were vaccinated against rubella within 3 months of or early in pregnancy. On the basis of these data, ACIP changed its recommendation regarding the time period for avoiding pregnancy after receipt of a rubella-containing vaccine from 3 months to 28 days.[17]

Data were available on 680 live births to susceptible women who were inadvertently vaccinated within 3 months prior to conception or early in pregnancy. No infant was born with CRS. However, a small theoretical risk of CRS of not greater than 0.5% cannot be ruled out. Limiting the analysis to the 293 infants born to susceptible mothers vaccinated 1–2 weeks before to 4–6 weeks after conception, the maximal theoretical risk is 1.3%.[17]

X. Enhancing Surveillance

Guidelines for enhancing surveillance are contained in Chapter 18, "Enhancing Surveillance," as well as in the MMWR report entitled "Control and Prevention of Rubella: Evaluation and Management of Suspected Outbreaks. Rubella in Pregnant Women, and Surveillance for Congenital Rubella Syndrome."[6] In addition, the following activities may be undertaken to improve the detection and reporting of cases and to improve the comprehensiveness and quality of surveillance for rubella and CRS.

Promote awareness that rubella and CRS still occur in the United States.

Although only 10 rubella cases and one imported CRS case were reported in 2004, it is likely that not all cases were identified. Efforts should continue to promote physicians' awareness of the possibility of rubella and CRS, especially when evaluating patients with suspected measles who have negative serologic tests for acute measles infection (negative serum measles IgM).

Promote awareness of groups at high risk for rubella infection and CRS births.

Rubella vaccine is not administered routinely in many countries, and in others rubella vaccine was only recently added to the childhood immunization schedule.[3, 5] 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 among persons from countries without a history of routine rubella vaccination programs.

Conduct 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.[6] Women who contract rubella while pregnant should be monitored for birth outcome, and a rubella-specific IgM antibody test should be performed on the infant after birth. Healthcare providers should be advised to evaluate infants born with conditions consistent with CRS and to perform a rubella-specific IgM antibody test on infants suspected of having CRS.

Search laboratory records.

Audits of laboratory records may provide reliable evidence of previously unreported serologically confirmed or culture-confirmed cases of congenital rubella syndrome. Infants with CRS have been identified by including the serologic results for toxoplasmosis, rubella, cytomegalovirus, and herpes (TORCH) agents in audits of laboratory records. This may be particularly useful in hospitals serving high-risk populations.

Compare other data sets and identify speciality schools and clinics.

After a rubella outbreak has occurred, surveillance for CRS can be enhanced in several ways. Birth defects registries may reveal unreported CRS cases.[2] In addition, children with CRS whose cases were never reported may be enrolled in schools for the deaf or blind. Pediatric specialty clinics caring for children with mental retardation, congenital heart defects, congenital deafness and hearing impairment, congenital cataracts, or growth retardation may be a source of unreported CRS patients.

Review hospital discharge data and linkages with newborn hearing screening programs.

Reviewing hospital discharge data in high-risk areas has proved useful in identifying undiagnosed cases of CRS.[18] Infants with discharge codes consistent with CRS may then be categorized according to the CRS case definition, allowing for greater insight into the rates

of CRS in high-risk populations. Furthermore, if newborn hearing screening is performed routinely, infants identified with hearing deficiencies or progressive hearing loss may also be tested for CRS, since hearing impairment is the most common single defect associated with CRS.

XI. Case Investigation

The diagnosis of a single case of CRS in a community should trigger intensified rubella and CRS surveillance.

Cases of U.S.-acquired CRS are sentinel events indicating the presence of rubella infections in the 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. The classic presentation for CRS is cataracts, hearing impairment, and congenital heart disease (especially patent ductus arteriosus or peripheral pulmonic stenosis). Infants born to women infected with rubella 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, cord blood or serum to be tested for rubella IgM and urine and throat specimens for viral isolation should be obtained. In the event of a negative IgM result from a specimen taken within 1 month of birth, a second specimen should be obtained and tested once the infant is at least 1 month of age. A CRS case report form (see Appendix 17) should be completed.

Efforts should be made to obtain clinical specimens (throat swabs and urine) for virus isolation from all case-patients. These isolates are essential for tracking the epidemiology of rubella in the United States now that it is believed rubella virus no longer continuously circulates in this country. By comparing isolates from new case-patients with other rubella virus samples, the origin of particular virus types in this country can be tracked.[12] See Appendix 15 for the procedure for collection of specimens.

XII. Preventing Transmission From Infants With CRS

Cases of U.S.-acquired rubella have occurred among susceptible persons providing care for infants with CRS.[19] Infants with CRS can shed the virus for prolonged periods, up to 1 year of age or longer in some cases. Persons having contact with infants with CRS should be immune to rubella. Infants with CRS should be placed in contact isolation. These precautions should be enforced during any admission before the first birthday, unless two cultures of throat and urine specimens obtained 1 month apart after the infant is older than 3 months are negative for virus.[6]

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Chapter 16: Tetanus

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I. Disease Description

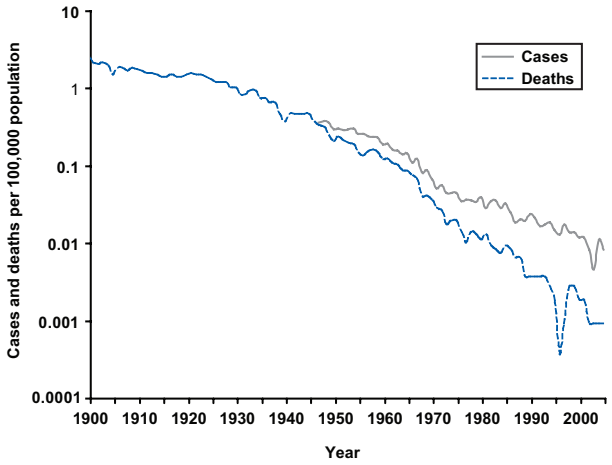
Tetanus is an acute, often fatal disease that is characterized by generalized increased rigidity and convulsive spasms of skeletal muscles. Tetanus is caused by the spore-forming bacterium *Clostridium tetani*. *C. tetani* spores (the dormant form of the organism) are found in soil and in animal and 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 vegetative organisms excrete the potent toxin tetanospasmin 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 2005, a total of 27 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]

Tetanus is almost entirely preventable through immunization.

Figure 1. Mortality and incidence rates of tetanus reported in the United States, 1900 to 2005.

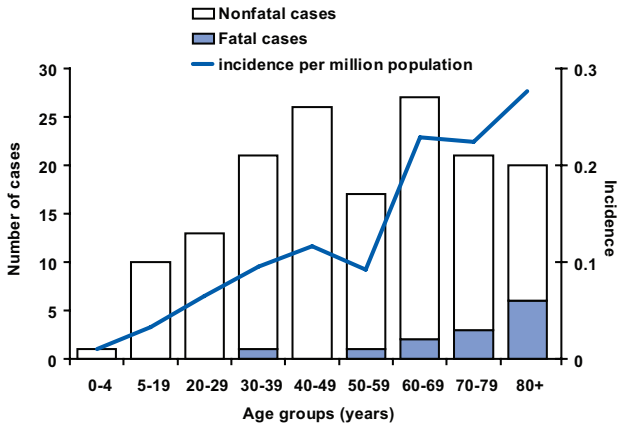


Not all states reported deaths from tetanus until after 1932. The estimated rates shown here are based on the population of the reporting states. National reporting of cases began in 1947. Source: Centers for Disease Control and Prevention.

Tetanus is almost entirely preventable through immunization. Vaccination status was known for 993 (61%) of 1,805 tetanus cases reported from 1972 to 2001.[2] In only 113 (11%) was receipt of three or more doses of tetanus toxoid reported, and 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 2001–2005, a total of 142 cases were reported in the United States: 57 (40%) were in persons aged 60 years or older, 74 (52%) were in persons aged 20–59 years, and 11 (8%) were in persons younger than 20 years, including one case of neonatal tetanus (Figure 2).[3–7] 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.[8] 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.[9]

Figure 2. Number of reported cases of tetanus, survival status of patients, and average annual incidence rates by age group—United States, 2001–2005.



Source: Centers for Disease Control and Prevention

Rates of coverage with booster doses of tetanus toxoid–containing vaccine decrease with increasing age. In a 1999 survey, 66% of adults aged 18–49 years reported receiving a dose of tetanus toxoid–containing vaccine within the preceding 10 years, compared with only 42% of adults 65 years of age or older.[10] 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.[11]

Diabetes and intravenous drug use may be risk factors for tetanus. From 1987 to 2001, persons with diabetes accounted for 13% of all reported tetanus cases and 29% of all tetanus deaths.[2] 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 1998 to 2000,[12] and a cluster of cases was noted in California earlier in the 1990s.[13]

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.[14] 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.[15] 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.[13]

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

The *Healthy People 2010* goal for tetanus is to eliminate all tetanus cases among persons under age 35 years in the United States.[16] 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.

VI. Case Definition

The following case definition for tetanus has been approved by the Council of State and Territorial Epidemiologists (CSTE), and was published in 1997.[17]

Tetanus clinical case definition

Tetanus is defined by the acute onset of hypertonia or by painful muscular contractions (usually of the muscles of the jaw and neck) and generalized muscle spasms without other apparent medical cause.

Case classification

Confirmed: A clinically compatible case, as reported by a healthcare professional.

Note: *Probable cases of tetanus are not included in the notifiable disease case count.*

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.

VII. Laboratory Testing

There are no laboratory findings characteristic of 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 can never 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.[18] 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

- Sex
- 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 TT 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 Td and TIG
  - Date started
- Vaccine Information
  - Dates of vaccination (prior tetanus toxoid history)
  - Time since last dose of tetanus toxoid
  - 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. A tetanus and diphtheria toxoids and acellular pertussis formulation for adolescents and adults (Tdap) was 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.[19] 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.[20, 21]

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.[20] A single dose of Tdap is also recommended for adults through age 64 years 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 is also important for the prevention of tetanus (Table 1).[20–22]

A single dose of Tdap is recommended for adolescents at age 11–18 years if they have not previously received Tdap.

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 or 65 years or older, Td is recommended. For persons 10–64 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.[23] 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%.[23]

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, at 404-639-3679

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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 patients with either varicella or herpes zoster 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 15%–30% of infected persons during their lifetime, resulting in herpes zoster (shingles).[21, 22] 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, and 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.[23–25] 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 now licensed and provisionally recommended for adults 60 years of age and older in the United States.

Before the availability of varicella vaccine in the United States, almost everyone had varicella.

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, 26–29] 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.[30–31]

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.[32–34] One-dose varicella vaccination coverage among children 19–35 months of age was 88% nationally in 2005, with state and city estimates ranging from 69% to 96%.[35] In active surveillance areas, varicella vaccination coverage among children age 19–35 months has risen to 92%, and varicella disease incidence has declined approximately 85% from 1995 to 2004.[36] 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 53% to 88% decline in cases has been reported as of 2004. 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%.[37] By 2002, national varicella hospitalizations declined by 88% compared with rates in 1994–1995.[28]

With vaccine coverage increasing and the disease burden declining, varicella disease surveillance is especially important to monitor changes in varicella epidemiology.

Although increased vaccination of children has lowered the overall burden of disease, a higher proportion of the cases will 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 rash lesions and fewer vesicles compared with 300 or more lesions and many vesicles 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 is likely to be more difficult to recognize clinically by practitioners and parents.

III. Importance of Rapid Case Identification

Although rapid identification of all suspected cases of varicella may not be feasible at this stage of the vaccination program, reporting of varicella cases in child care centers, schools, institutions, and barracks will facilitate public health action and outbreak control. In addition, in certain high-risk settings (e.g., hospitals and other healthcare settings, schools with students with acute lymphoblastic leukemia), 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.[32]

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 2010 disease reduction goals, and determine whether any improvements to the vaccination policy are needed. *Healthy People 2010* goals for varicella include a greater than 90% reduction in the estimated number of varicella cases in 1998, greater than 90% vaccine coverage among children 19–35 months, and greater than 90% 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[40] and varicella deaths in 1998.[41]

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 almost always 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/nip/diseases/varicella/surv/default.htm]. These tests are also useful for diagnosing breakthrough disease (Table 1).
- Positive serologic test for varicella-zoster IgM antibody
- 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 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. A negative IgM result should not be used to rule out the 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 is laboratory confirmed or that meets the clinical case definition and 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. [42] 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 attributed to the vaccine.[42] Rash occurring less than 7 or more than 42 days after vaccination should be considered wild-type virus, and rash occurring 7–42 days postvaccination may be due to either wild- or vaccine-type virus.[43] Attribution of disease to a vaccine strain 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.[44]

Secondary transmission of vaccine virus: A varicella-like rash occurring 10–21 days after exposure to a person recently vaccinated. It is extremely rare. No transmission of vaccine virus has ever been documented from a vaccinated person in the absence of vaccine rash. Since 1995, only six secondary cases of transmission of vaccine virus from five immunocompetent source patients have been documented with the varicella (Oka/Merck) vaccine. Transmission of vaccine-strain virus can only be confirmed by strain differential real-time PCR or by PCR combined with RFLP.

The need for laboratory confirmation has grown because with the decline in varicella disease since the introduction of vaccine, fewer physicians have direct experience with breakthrough infections.

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 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

The need for laboratory confirmation has grown because with the decline in varicella disease since the introduction of vaccine, fewer physicians have direct experience with breakthrough infections, which are often atypical in appearance 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 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. 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 virus isolation and 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 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. 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/vaccines/vpd-vac/varicella/surv-collect-virus-spec.htm. Additional information about collecting and submitting specimens for testing can be found on this site or by calling the National VZV laboratory at 404-639-0066 or 404-639-3667, or emailing vzvlab@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 conventional and real-time PCR methods.

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. 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. 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. The National VZV Laboratory at CDC has developed a reliable IgM capture assay.

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. Commercial ELISAs are recommended for the purpose of screening.[45] Routine testing for varicella immunity following vaccination is not recommended. Recent evidence suggests 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. Commercially available serologic IgG tests are not sufficiently sensitive to detect low levels of antibody following vaccination.

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)	Identify VZV. Cost. Limited availability. Requires up to a week for result.
PCR	Vesicular swabs or scrapings; scabs from crusted lesions; biopsy tissue	Very sensitive method. Specific for VZV. Real-time methods (not widely available) have been designed that distinguish vaccine strain from wild-type. Rapid (within 3 hours). Requires special equipment.
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)	Observe multinucleated giant cells with inclusions. Specific for VZV. Diagnostic of alpha herpes viruses (VZV, herpes simplex viruses). Less sensitive than DFA.
Capture IgM	Acute or convalescent serum specimens for IgM	Specific for VZV. IgM inconsistently detected. Not reliable method for routine confirmation, especially in vaccinated persons, but positive result indicates current/recent VZV immune response. Requires special equipment.
EIA	Acute and convalescent serum specimens for IgG	Specific for VZV. Requires special equipment. May not be sensitive enough to identify vaccine-induced immunity.
LA	Acute and convalescent serum specimens for IgG	Specific for VZV. 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 IgG	Specific for VZV. Requires special equipment. Good sensitivity, specificity.
gpELISA	Acute and convalescent serum specimens for IgG	Specific for VZV. Highly specific and sensitive but not widely available. Suitable for evaluation of vaccine seroconversion.
FAMA	Acute and convalescent serum specimens for IgG	Specific for VZV. Highly specific and sensitive but not widely available. Suitable for evaluation of vaccine seroconversion.
CF	Acute and convalescent serum specimens for IgG	Specific for VZV. Poor sensitivity. Cumbersome to perform.

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; CF, complement fixation.*

VII. Reporting

Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[46] 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,[41] 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 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.[47] States are encouraged to report varicella cases to NNDSS via NETSS or NEDSS. As of 2006, 31 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.
- 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)
  - 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.

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 document reported second infections)
  - Medications
  - Dates of rash onset
  - Duration of rash
  - Symptoms and date of onset
  - Hospitalizations
  - Complications
- Vaccination status
  - Number of doses of varicella vaccine
  - 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).

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.[32, 48]

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, 49, 50] 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.[51–57]

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 ($p<0.001$).[58] A second dose of vaccine reduced varicella attack rates by 3.3-fold.[58] Although the field effectiveness of two doses is not yet known, the protection is expected to be greater compared with one dose of varicella vaccine. 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[32, 34]

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 born during or after 1980 and without evidence of immunity to varicella 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, and other post–high school educational institutions.
- 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:[32, 34, 48]

- 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.[59]
- 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.[60]

Additional precautions:

- Severe illness. Vaccination of persons with severe illness should be postponed until recovery.
- Varicella virus vaccine should not be administered for at least 5 months after administration of blood (except washed red blood cells), plasma, IG, or VZIG. IG and VZIG should not be administered for 3 weeks after vaccination unless the benefits exceed those of vaccination.
- Salicylates (i.e., aspirin and related medications) should not be used for 6 weeks after receiving varicella virus 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

Elementary schools are now the most common sites for varicella outbreaks, although some are occurring in middle and high schools.

Although investigation of all cases of varicella may not be feasible in all areas, 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.[32, 61] 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. For varicella postexposure prophylaxis of contacts, see the section, "Post-exposure use of varicella vaccine and VZIG."

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 some are occurring 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). Investigations of outbreaks of vaccine-preventable diseases help determine whether outbreaks are occurring from the 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. As the two-dose varicella vaccine policy is implemented, it will be important to study the effectiveness of two doses of varicella vaccine. In the course of an investigation, health authorities may use information on susceptibility and reliability of history of disease to develop an appropriate screening and vaccination policy for the affected population (e.g., correctional facilities, residential institutions, military).

An outbreak of varicella is defined as the occurrence of five or more cases in a specific setting (e.g., school) that are epidimiologically linked.

A systematic approach to investigation and control of outbreaks includes 1) laboratory confirmation of the outbreak, 2) identification of new cases, 3) implementation of varicella control measures, 4) establishment of active surveillance for additional cases, 5) analysis of data, and 6) development of a plan for preventing future varicella outbreaks. These steps are outlined in Table 2. A worksheet to be used for reporting varicella outbreaks is in Appendix 20.

Table 2. Steps for investigation and control of varicella outbreaks

Step	Description and details
1	Confirm the diagnosis • Every effort should be made to establish epidemiologic links for cases and obtain clinical specimens for laboratory confirmation of the outbreak
2	Case finding and assessment of evidence of immunity • Survey the affected population to identify all cases and to collect key information on persons with and without varicella. • Conduct case investigations to help characterize the illness and the outbreak
3	Implement varicella control measures • Send letter of notification of outbreak to persons potentially exposed to varicella • Notify healthcare providers in community of outbreak and ask them to report cases seen in their practice • Exclude persons with varicella from school or child care • Offer VZIG to exposed persons at high risk of severe disease and with contraindications to vaccination • Exclude persons without evidence of immunity from school or child care • Refer persons with active cases to primary care provider for assessment of need for treatment
4	Establish surveillance for additional varicella cases and continue for 21 days after last case
5	Analyze collected data • Describe cases and transmission (e.g., date of rash onset, age, sex, country of birth, severity) • Evaluate outbreak control efforts • Calculate vaccine effectiveness, if warranted
6	Develop plan for preventing future varicella outbreaks • Ensure high levels of varicella immunity • Establish and maintain varicella surveillance • Develop outbreak guidelines to provide guidance for future outbreaks

Controlling outbreaks

Varicella vaccine is recommended by the ACIP for outbreak control.[33, 34] Varicella vaccine may prevent or significantly modify disease if administered within 3 days, and possibly up to 5 days following varicella exposure.[4, 62, 63] In an outbreak setting, however, exposure may not yet have occurred, and ongoing exposures are likely and may continue for weeks to months. Therefore, ACIP recommends that vaccination be offered to all persons without evidence of immunity even more than 5 days after the first exposure, to limit transmission and to provide protection against subsequent exposures. If exposure to varicella does not cause infection, postexposure vaccination with varicella vaccine should induce protection against subsequent infection. If the exposure results in infection, the vaccine may reduce the severity of the disease. There is no evidence that administration of varicella vaccine during the incubation period of illness increases the risk for vaccine-associated adverse events.

Outbreak control measures should be implemented as soon as an outbreak is identified. Vaccination during school outbreaks will shorten the duration of the outbreak.[64] State and local health departments should use a two-dose vaccination policy for outbreak control. Persons without evidence of varicella immunity or who have received one dose of vaccine can be referred to their healthcare provider for vaccination. Alternatively, vaccination can be offered through the health department or school vaccination clinic, resources permitting. Two-dose vaccination is recommended for optimal protection during outbreaks involving preschool-aged children. Persons vaccinated with a first or second dose as part of the outbreak control program, may be immediately readmitted to school.

Isolation (exclusion) or cohorting of individuals with varicella until all of their lesions have crusted, faded away, or no new lesions appear within a 24-hour period, is routinely recommended for outbreak control. Exclusion is also recommended for exposed persons without evidence of immunity to varicella. Exclusion is required for the duration of the period of communicability (i.e., from 10 days after the first case until 21 days after the last case in outbreaks).[32, 61] In outbreaks involving children covered by child care or school requirements, unvaccinated children with no history of varicella should be instructed to be vaccinated immediately or excluded from school until 21 days after the last case. Children vaccinated during the outbreak can return to school immediately after being vaccinated.

For outbreaks in child care centers and schools, the minimum public health response must include 1) exclusion of case-patients; 2) notification to parents and caregivers of the occurrence of the outbreak; and 3) provision of information on a) varicella and its potential to cause severe complications, b) availability of the vaccine, c) recommendations for vaccination, and d) recommendations for excluding those without evidence of immunity to varicella covered by school requirements.

In institutional outbreaks or outbreaks involving adolescents and adults, vaccination of persons without evidence of immunity to varicella with a first or second dose of vaccine is recommended because it is likely to limit or control the outbreak by interrupting transmission. Health department personnel and officials in other institutions (e.g., healthcare settings, correctional facilities) should recommend vaccination of persons without evidence of immunity to varicella for outbreak control. Outbreak control is recommended at any stage of an outbreak if there are remaining persons without evidence of immunity to varicella.

In healthcare settings, following an exposure, healthcare workers with two doses of varicella vaccine should be monitored daily from day 10 to day 21 to determine their clinical status (i.e., screen for fever, skin lesions, systemic symptoms) and instructed to immediately report any symptoms. If symptoms occur, the healthcare worker should be placed on sick leave. Healthcare workers who received one dose should be vaccinated with a second dose immediately and within 3–5 days after exposure to a person with rash (if 4 weeks have elapsed since their first dose). Management after vaccination is similar to that of two-dose vaccinees. Unvaccinated healthcare workers with no other evidence of immunity are potentially infective from 10 to 21 days after exposure and should be furloughed during this period. Postexposure vaccination should occur as soon as possible, preferably within 5 days of exposure to rash (more effective within 3 days). It can be given after 5 days to provide protection against subsequent exposures if the current exposure does not result in infection. Although postexposure use of varicella vaccine in healthcare workers can prevent spread of varicella in the hospital setting, vaccination is routinely recommended for all susceptible healthcare workers when they begin employment and is the preferred method for preventing varicella in healthcare settings.[32, 61]

Assessing vaccine effectiveness

The majority of postlicensure estimates of effectiveness of one dose of varicella vaccine have been in the range of prelicensure estimates of 70%–90%, with higher estimates for protection against severe disease. Calculations of vaccine effectiveness from outbreak investigations should be interpreted carefully because of the small number of persons involved in outbreaks and the potential for non-uniform exposure. With the new recommendation for two doses of varicella vaccine, calculation of the effectiveness of two doses versus one dose will be more

important than those of the effectiveness of one dose. Vaccine effectiveness may be estimated by using the proportion of case-patients who were vaccinated and vaccination coverage (i.e., screening method).[65]

A more precise measure of the vaccine effectiveness of two versus one dose can be obtained by comparing rates of disease among two-dose and one-dose vaccinees (with no previous history of varicella disease) in outbreak settings such as schools and child care centers.[66] To calculate vaccine effectiveness, varicella case-patients, as well as non–case-patients, should be interviewed for history of receipt of vaccine and history of varicella disease.

Postexposure use of varicella vaccine and VZIG

The ACIP recommends the use of varicella vaccine for persons without evidence of immunity to varicella following exposure to varicella.[33] Studies on postexposure effectiveness of varicella vaccination have been conducted exclusively among children; data are not available for adults. If administered within 3–5 days following varicella exposure, varicella vaccine may prevent or significantly modify disease.[4, 62, 63] Postexposure vaccine use should be considered following exposures in healthcare settings and in households. If exposure to varicella does not cause infection, postexposure vaccination with varicella vaccine should induce protection against subsequent infection. If exposure results in infection, the vaccine may reduce the severity of the disease. There is no evidence that administration of varicella vaccine during the incubation period of illness increases the risk for vaccine-associated adverse events.

Varicella zoster immune globulin (VZIG) is recommended for postexposure prophylaxis of susceptible persons who are at high risk for developing severe disease and those for whom varicella vaccine is contraindicated.[32, 67] VZIG is most effective in preventing varicella infection when given within 96 hours (i.e., 4 days) of varicella exposure. The decision to administer VZIG to a person exposed to varicella should be based on 1) whether the patient has evidence of immunity, 2) whether the exposure is likely to result in infection, and 3) whether the patient is at greater risk for complications than the general population. Such groups include newborn infants whose mothers developed varicella around the time of delivery (5 days before to 2 days after delivery), immunocompromised patients, pregnant women without evidence of varicella immunity, premature infants 28 or more weeks' gestation who are exposed during the neonatal period and whose mothers have no evidence of varicella immunity, and premature infants less than 28 weeks' gestation or who weigh 1000g or less at birth and were exposed during the neonatal period, regardless of the mother's history of varicella disease or vaccination.[32, 67] After the only U.S. licensed manufacturer of VZIG announced it had discontinued production of VZIG, an investigational (not licensed) VZIG product, VariZIG, became available in February 2006 under an investigational new drug application (IND) submitted to the Food and Drug Administration. This new product can be obtained from the distributor (FFF Enterprises, Inc., Temecula, CA) by calling 800-843-7477.[67]

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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.

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.

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 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?

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 presents other problems that are often less well recognized. As an example, in response to a small measles outbreak, an urban health department recently approached pediatric infectious disease practitioners in the community and requested them to participate in active surveillance for a limited time. City public health officials were surprised and disappointed when the clinicians were unwilling to participate in active surveillance, a standard recommendation for public health response to outbreaks (see Chapter 7, "Measles"). Although many factors may have contributed to the failure to recruit clinicians to participate in this effort, this episode highlighted the difficulty of improving completeness of reporting of rare diseases.

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).

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.

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. This is already recommended 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 such as outbreaks. 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- or hospital-based surveillance, laboratory-based surveillance, population-based surveillance,[1] and sentinel surveillance. 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]

Efforts should be made to increase healthcare providers' awareness of their responsibility to report suspected cases.

The National Notifiable Diseases Surveillance System (NNDSS) 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).[3, 4] 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.[5] These data are usually 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.[6] 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,[7] each state has laws or regulations stipulating which diseases are reportable.[5] Efforts should be made to increase healthcare providers' awareness of their responsibility to report suspected cases.[8–12]

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.[13] 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.[14] A study on mandatory chronic disease reporting by physicians suggests that public health should emphasize both the legal and public health bases for reporting.[15]

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.[16] 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 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.[17]

IV. Improving the Completeness of Reporting

Complete reporting involves accounting for as many cases of vaccine-preventable diseases as is possible. Completeness of reporting be enhanced in many ways,[18] including using electronic laboratory reporting,[19–22] 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.[9] Likewise, hospital discharge records may also be reviewed for specific discharge diagnoses,[8, 23] 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.[16, 24] 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.

In general, the most complete surveillance systems at the state and local levels involve multiple sources of reporting.

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.[25, 26] However, unless extensive efforts are made to validate diagnoses, misclassification is likely.[27] 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.[28]

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.[16, 24, 29–32] 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 in 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

Active surveillance, in which the health department initiates contact with the healthcare provider to identify cases, involves regular (e.g., weekly) contact with healthcare providers.[10, 13, 16, 29, 33, 34] This regular contact with individual providers promotes increased awareness of reporting responsibilities and increased cooperation with the health department. Active surveillance is generally 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.

Using sentinel surveillance systems

Sentinel surveillance,[13, 16, 29] 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.

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Chapter 20: Analysis of Surveillance Data

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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., tabulating reports manually and filling in a summary data sheet, or 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, 2004

Age group	Frequency	%	Cumulative %
<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 yr	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, 2004

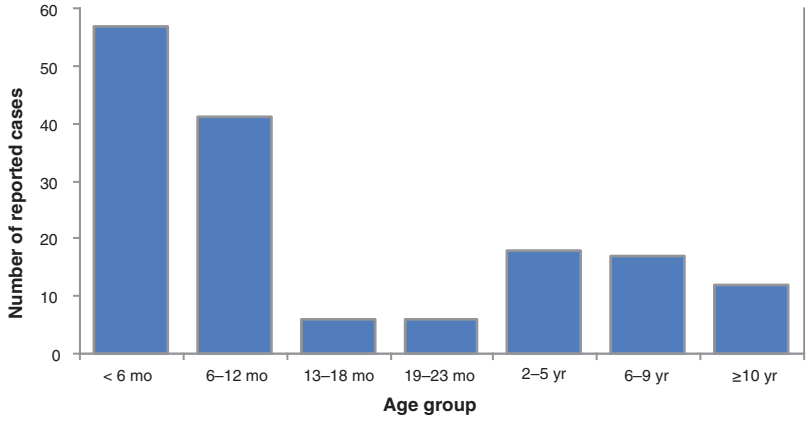
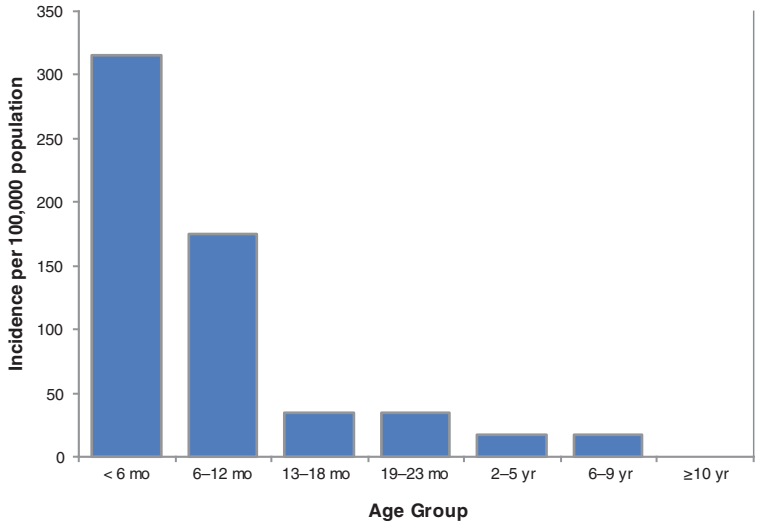


Figure 2. Pertussis incidence by age group, 2004



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, 2004

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

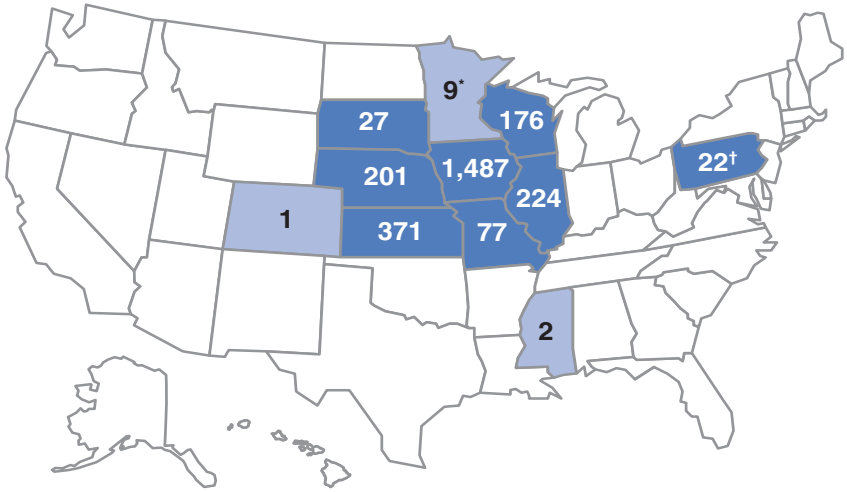
Describe the persons with vaccine-preventable diseases (cases) detected by your surveillance system by geographic location. Location may be defined as the place where the case was first reported, place of residence of the case-patient, or place of hospitalization. Location may be a state, city, county, 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.

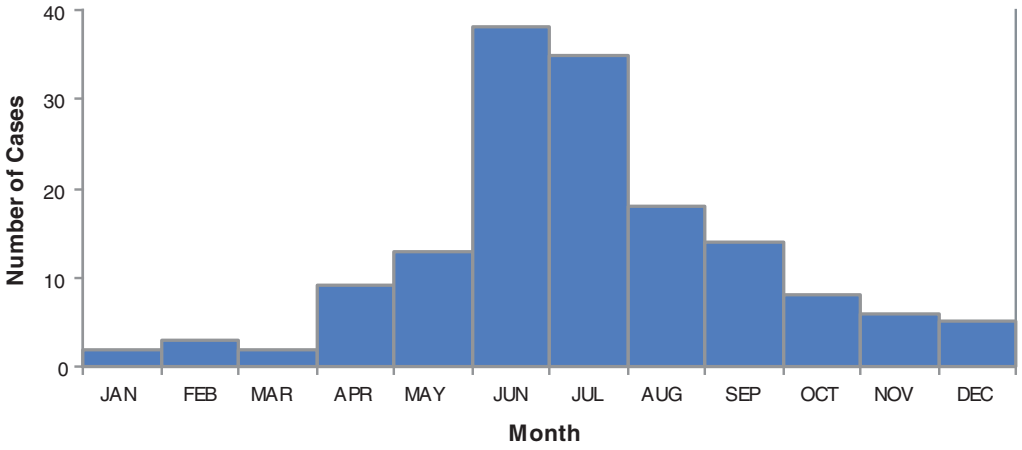
Compare the number of cases occurring in a current time period with the number reported during the same time period in each of the last 5 years. Compare the cumulative number of cases year-to-date with the cumulative number of cases year-to-date of previous years.

Example 5. Reported pertussis cases, 2004, 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	2	1.3	4.4
Feb	3	1.9	6.3
Mar	2	1.3	7.6
Apr	9	5.7	13.3
May	13	8.2	21.5
Jun	38	24.0	45.6
Jul	35	22.2	67.7
Aug	18	11.4	79.1
Sep	14	8.9	88.0
Oct	8	5.1	93.0
Nov	6	3.8	96.8
Dec	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 2004. Note that in this dataset of cases reported during 2004 there are a number of cases with onset during 2003. Reports in 2005 should be reviewed to look for cases with onset in 2004 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 2004 by month of onset, omitting the cases with onset in 2003, and including the few additional cases reported in 2005 but with onset in the latter months of 2004.

Figure 4. Reported pertussis cases by month of onset, 2004



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 yr	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

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I. Public health importance

Immunizations have reduced the incidence of many vaccine-preventable diseases in the United States (and many other countries) by more than 95% compared with the prevaccine era (Table 1).[1, 2] For example, wild-type paralytic poliomyelitis has been eliminated from the Western Hemisphere[3] and endemic rubella virus transmission in the United States has ceased.[4] As the proportion of the vaccinated population increases, however, there is also an increase in the number of persons who experience an adverse event following vaccination—an event due either to reactions caused by the vaccination or to coincidental events not caused by the vaccination (e.g., an upper respiratory infection occurring after inactivated influenza vaccine). In recent years, the annual number of reports to the national Vaccine Adverse Event Reporting System (VAERS), a passive surveillance system that monitors vaccine safety, has exceeded the total number of reports of routine childhood vaccine-preventable diseases (excluding varicella and pertussis). This historic decrease in disease rates is shown in Table 1. With the lower rates of disease, benefits of vaccination may be overshadowed by reports of vaccine adverse events, and media attention may result in loss of public confidence in the vaccine. This can result in resurgence of vaccine-preventable diseases, as experienced in several countries with pertussis[5–7] and in the United Kingdom with mumps.[8]

One of the best ways to enhance our understanding of vaccine safety is to improve surveillance for vaccine adverse events.

Vaccinations are usually administered to healthy persons and often are mandated; therefore, they are held to a higher standard of safety than other medications.[9] However, as with all medications, no vaccine is perfectly safe or effective. Vaccines can induce minor adverse events such as fever or local reactions at the injection site. Very rarely, they can induce serious adverse events such as seizures or severe allergic reactions. To reduce the occurrence of vaccine adverse events and maintain public confidence in vaccines, it is important to improve the understanding of vaccine safety, and, thereby, foster the development and use of safer vaccines.[10] One of the best ways to enhance our understanding of vaccine safety is to improve surveillance for vaccine adverse events.

Table 1. Decline in vaccine-preventable disease morbidity in the United States during the 20th century*

Disease	Baseline 20th century morbidity	2005 morbidity	% Decrease
Smallpox	48,164	0	100
Diphtheria	175,885	0	100
Pertussis	147,271	25,616	>82
Tetanus	1,314	27	>97
Poliomyelitis	16,316	1	>99
Measles	503,282	66	>99
Mumps	152,209	314	>99
Rubella	47,745	11	>99
Congenital rubella	823	1	>99
Haemophilus influenzae disease (<5 years of age)	20,000 (estimated)	226 (serotype b or unknown serotype)	>98

**See references 1,2*

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. 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. During prelicensure testing, detection of uncommon adverse events with delayed onset is not highly sensitive. Postlicensure or postmarketing surveillance—the continuous monitoring of vaccine safety in the general population after licensure—is needed to identify and evaluate such adverse events.[9]

The history of postmarketing surveillance for vaccine adverse events in the United States has been reviewed elsewhere.[10] From 1978 through 1990, the Centers for Disease Control (CDC) and the Food and Drug Administration (FDA) divided the responsibility for postmarketing surveillance of vaccines in the United States. Reports of adverse events following administration of vaccines purchased with public funds were submitted to CDC's Monitoring System for Adverse Events Following Immunization (MSAEFI); the FDA received reports of adverse events after administration of vaccine purchased with private funds. Although collaboration was maintained between the two agencies, the use of different reporting forms and reporting requirements made combined analysis difficult.

The passage of the National Childhood Vaccine Injury Act of 1986 (NCVIA) and its mandatory reporting requirement was an opportunity to correct these shortcomings. With enactment of the NCVIA, vaccine manufacturers licensed in the United States and healthcare providers who administer vaccines are required by law to report certain serious adverse events following specific vaccinations.[11] 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 (liability concerns, inadequate supply of vaccine, rising vaccine costs).[12] The NCVIA stipulates the vaccines, the adverse events, and the time of occurrence after vaccination for which reporting 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. 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 adverse events following immunization.[13] This led to the establishment of the Vaccine Adverse Event Reporting System (VAERS), which is cosponsored by CDC and FDA. Programs 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 safety monitoring efforts around the world.

Table 2. VAERS Table of Reportable Events Following Vaccination*

Vaccine/Toxoid	Event	Interval from Vaccination
Tetanus in any combination; DTaP, DTP, DTP-Hib, DT, Td, TT, Tdap	Anaphylaxis or anaphylactic shock	7 days
	Brachial neuritis	28 days
	Any acute complications or sequelae (including death) of above events	Not applicable
	Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Pertussis in any combination; DTaP, DTP, DTP-Hib, Tdap	Anaphylaxis or anaphylactic shock	7 days
	Encephalopathy (or encephalitis)	7 days
	Any acute complications or sequelae (including death) of above events	Not applicable
	Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert

Table 2. VAERS Table of Reportable Events Following Vaccination*

Vaccine/Toxoid	Event	Interval from Vaccination
Measles, mumps and rubella in any combination; MMR, MR, M, MMRV, R	A. Anaphylaxis or anaphylactic shock	7 days
	B. Encephalopathy (or encephalitis)	15 days
	C. Any acute complications or sequelae (including death) of above events	Not applicable
	D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Rubella in any combination; MMR, MMRV, MR, R	A. Chronic arthritis	42 days
	B. Any acute complications or sequelae (including death) of above event	Not applicable
	C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Measles in any combination; MMR, MMRV, MR, M	A. Thrombocytopenic purpura	7-30 days
	B. Vaccine-strain measles viral infection in an immunodeficient recipient	6 months
	C. Any acute complications or sequelae (including death) of above events	Not applicable
	D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Oral Polio (OPV)	A. Paralytic polio	
	– in a non-immunodeficient recipient	30 days
	– in an immunodeficient recipient	6 months
	– in a vaccine-associated community case	Not applicable
	B. Vaccine-strain polio viral infection	
	– in a non-immunodeficient recipient	30 days
	– in an immunodeficient recipient	6 months
	– in a vaccine-associated community case	Not applicable
	C. Any sequelae (including death) of above events	Not applicable
	D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Inactivated Polio (IPV)	A. Anaphylaxis or anaphylactic shock	7 days
	B. Any sequelae (including death) of the above event	Not applicable
	C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Hepatitis B	A. Anaphylaxis or anaphylactic shock	7 days
	B. Any acute complications or sequelae (including death) of the above event	Not applicable
	C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Hemophilus influenzae type b (conjugate)	Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Varicella	Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert

Table 2. VAERS Table of Reportable Events Following Vaccination*

Vaccine/Toxoid	Event	Interval from Vaccination
Rotavirus	A. Intussusception	30 days
	B. Any acute complications or sequelae (including death) of the above event	Not applicable
	C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Pneumococcal conjugate	Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Hepatitis A	Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Influenza	Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert

* ***Effective date: July 01, 2005.*** *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, individuals are encouraged to report any clinically significant or unexpected events (even if you are 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.*

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.

3. ***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).
4. ***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.

III. Objectives of VAERS

- To detect previously unrecognized reactions from both existing and newly licensed vaccines
- To detect apparent increases or decreases in previously reported events
- To detect preexisting conditions that may promote reactions and may represent contraindications or precautions to additional doses
- To detect vaccine lots associated with unusual numbers and types of reported events
- To trigger further clinical, epidemiologic, or laboratory investigations regarding a possible causal relationship between a vaccine and adverse event
- To provide descriptive epidemiologic data on national numbers of reported adverse events following immunization (AEFI)
- To closely monitor the safety of newly licensed vaccines

Scope of reports sought

Table 2 lists the events mandated for reporting to VAERS. However, more importantly, reports should be submitted to VAERS for all serious and unusual events 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 an emergency department visit or hospitalization, prolongation of a hospital stay, or any illness resulting in a permanent disability, as well as less serious but previously unrecognized adverse events attributable to vaccination.

Reports should be submitted to VAERS for all serious and unusual events occurring after vaccination, in all age groups, even if the causal relationship to vaccination is uncertain.

The VAERS form allows description of the adverse event in narrative form by the reporter. Unlike other public health disease surveillance systems for which a distinct case definition exists, many adverse events reported to VAERS are clinical syndromes that may be poorly defined or understood or are diagnoses of exclusion. The Brighton Collaboration (http://brightoncollaboration.org) is an international voluntary collaboration whose primary aim is to develop globally accepted standardized case definitions of AEFI. These definitions are useful in defining the adverse events reported to VAERS. The term "adverse event" rather than "reaction" is used because attribution of causality to the vaccine usually is not possible. Some examples of case definitions developed by the Brighton Collaboration to date include seizure, intussusception, fever, persistent crying, nodule at injection site, and hypotonic–hyporesponsive episode. The VAERS form is designed to permit description of the adverse event, the type of vaccine(s) received, the timing of vaccination and the adverse event, demographic information about the recipient, concurrent medical illness or medications, and prior history of AEFI (see Appendix 22). Adverse events 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 if they assist in clarifying any aspects of the report

IV. Reporting to VAERS

Anyone can report any vaccine adverse event to VAERS. Healthcare providers and manufacturers are mandated by law to report certain adverse events after vaccination, and they are encouraged to report any serious or unusual event occurring after vaccination, even if they are not certain the event is causally related to a vaccine or vaccines. A table listing 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 patients, parents and caregivers. Lay persons who report 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 adverse event. It is primarily by analyzing all reports in aggregate that possible causal relationships between vaccines and adverse events can be properly evaluated.

Reporting to VAERS can be done in one of three ways:

- Online through a secure website: https://secure.vaers.org/VaersDataEntryIntro.htm
- Fax a completed VAERS form to 877-721-0366

- 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://www.VAERS.hhs.gov/pdf/vaers_form.pdf or can be requested by telephone at 800-822-7967. The Vaccine Information Statements (VIS) developed by CDC for all U.S.-licensed vaccines also contain instructions on how to report adverse events 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.

Upon receipt by VAERS, reports are entered into a database, verified, and coded using a standard set of coding terms. The person reporting is sent a letter from VAERS verifying receipt of the form and is requested to supply any critical information that is missing. The FDA reviews reports of deaths and other serious events and conducts analyses of reports by vaccine lots. CDC routinely reviews selected serious outcomes (e.g., anaphylaxis, Guillain-Barré syndrome) and conducts additional analyses as needed to address specific concerns and to evaluate trends in reporting.

Completion of VAERS form and submission of reports

Instructions for completing the VAERS form are on the back of the form.

Note: *Report adverse events associated with vaccines on the VAERS form. Do not use MEDWATCH or the old MSAEFI forms to report vaccine adverse events.*

Do not report events associated with tuberculosis screening tests (Tine, PPD, or Mantoux), immune globulins, or other nonvaccine injectable 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 obtain them from www.vaers.hhs.gov. Clinic staff at the local level are responsible for completing a VAERS report when an adverse event 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 nonserious events, all clinically significant adverse events 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, date, 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. 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.

- *Critical boxes*—Certain items are crucial to the analysis of VAERS data and have been designated as critical boxes. 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 adverse events, symptoms, etc.
  - Box 8: Indicates whether a report is regarded as serious or nonserious, and identifies the most serious reports for 60-day and annual follow-up
    - Serious
      - Patient died and date of death
      - Life-threatening illness
      - 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 adverse event (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 follow-up investigation.

State health coordinator responsibilities

The SHC receives VAERS reports from local health departments or immunization projects and is responsible for the following activities:

- 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 2006 begins with AZ, followed by 06, followed by 057, and should look like this: AZ06057. 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 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. In the case of a patient death, include date of death and supporting documentation (copies of hospital records, autopsy report, and death certificate) as available.

Quarterly reports are submitted to VAERS by mail, fax, or email.

Mail: VAERS
P.O. Box 1100
Rockville, MD 20849-1100
Fax: 877-721-0366
E-mail: info@vaers.org

- Updates 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

Approximately 20,000 reports of AEFI are now received by VAERS each year. All reports are accepted and entered without case-by-case determination of whether the adverse event could have been caused by the vaccine in question. To put the number of reports of adverse events in perspective, it should be noted that each year over 200 million doses of vaccine are distributed in the United States. Additionally, the type and severity of events reported vary from minor local reactions or fever to death. Of the reports received between 1991 and 2001, 1.7% reported death as the outcome; 12.6% reported a serious nonfatal adverse event, and 85.8 % reported less serious events.[14]

From 1991 through 2001, vaccine manufacturers submitted 36.2% of the VAERS reports; 20% were from private healthcare providers. State and local health departments accounted for 27.6% of the reports, patients or parents submitted 4.2% of the reports, and 7.3% came from other sources.[14]

Direct reporting to VAERS or to the SHC by healthcare providers is encouraged, as these reports arrive on a more timely basis than those 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 less serious vaccine-associated events may be delayed.

Usefulness

The data from VAERS have been used by FDA, CDC, and the Division of Vaccine Injury Compensation at the Health Resources and Services Administration (HRSA). The FDA investigates all deaths, reports classified as serious according to the Code of Federal Regulations, and certain nonserious events that have unusual characteristics. Assessments of lot-specific reporting rates are conducted weekly, using manufacturer-supplied data on lot size. The FDA has regulatory authority to withdraw a vaccine lot if it is determined that the rate of reported vaccine-associated adverse events is unusually high.

CDC has used VAERS data in analyses of the safety of acellular versus whole-cell pertussis vaccine; the rates of allergic reactions after first and second doses of measles-containing vaccines; intussuception occurring after the earlier rotavirus vaccine Rotashield®, which is no longer licensed; the safety of newly licensed vaccines such as meningococcal conjugate, the tetanus-diphtheria-acellular pertussus combined vaccine, and the human papillomavirus vaccine; the association between influenza vaccinations and Guillain-Barré syndrome; the suspected potential association between meningococcal conjugate vaccine and Guillain-Barré syndrome; evaluation of reporting efficiency; and use of safety profiles as tools for assessing

vaccine safety. VAERS data, without identifying information, are available to the public through the VAERS website (http://vaers.hhs.gov/) and are updated monthly.

VAERS data have also been used by the Institute of Medicine (IOM) Vaccine Safety Committee (http://www.iom.edu/?id=4705&redirect=0) in an extensive assessment of the causal relations between common childhood vaccines and adverse events. 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,[15] Thimerosal-Containing Vaccines and Neurodevelopmental Disorders,[16] Multiple Immunizations and Immune Dysfunction,[17] Hepatitis B Vaccine and Demyelinating Neurological Disorders,[18] SV40 Contamination of Polio Vaccine and Cancer,[19] Vaccinations and Sudden Unexpected Death in Infancy,[20] Influenza Vaccines and Neurological Complications,[21] and Vaccines and Autism.[22] 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 adverse events.

Reporting sensitivity

The completeness of reporting of adverse events associated with certain vaccines varies according to the severity of the event and the specificity of the clinical syndrome to the vaccine.

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 adverse event, 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 adverse events associated with certain vaccines varies according to the severity of the event and the specificity of the clinical syndrome to the vaccine.[23, 24]

Table 3 shows the reporting efficiency to VAERS for various adverse events. For example, the reporting efficiency for paralytic poliomyelitis following oral polio vaccine (severe event, very specific vaccine association, and very rare) was 68%, yet the reporting efficiency for rash following MMR is <1% (mild event, many causes).

Table 3 Reporting efficiency To VAERS for various adverse events

Event *	Reporting efficiency %
OPV and vaccine-associated paralytic polio	68%
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%

**See References 23,24*

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.

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.[23]

Biased and stimulated reporting. Reports to VAERS may not be representative of all adverse events 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 rotavirus vaccine.

Confounding by drug and disease. Many reports to VAERS describe events that may have been caused by medications or underlying disease processes. Many adverse event reports encompass clinical syndromes that are poorly defined, not clearly understood, or represent diagnoses of exclusion (e.g., sudden infant death syndrome). Often multiple vaccines are administered at the same visit, making attribution of causation to a single vaccine or antigen difficult.

Inability to determine causation. VAERS reports are usually not helpful in assessing whether a vaccine actually caused the reported adverse events because they lack either unique laboratory findings or clinical syndromes necessary to draw such conclusions.[9] Reports to VAERS are useful for generating hypotheses, but controlled studies are necessary to confirm any hypotheses generated by VAERS observations.[9, 25–27]

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 should be reviewed for completeness and accuracy. The reporter should be contacted if any information is missing. For death and serious outcomes after vaccination, efforts should be made to obtain additional documentation (e.g., hospital discharge summaries, laboratory reports, death certificates, autopsy reports). The VAERS staff contacts reporters and parents or vaccine recipients routinely to obtain missing information or to correct inaccurate information for all reports of deaths, serious adverse events, and selected clinically significant events.

Evaluation of system attributes

Surveys have been conducted to assess the knowledge, attitudes, and beliefs of both private and military healthcare providers about reporting to VAERS. 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]

Promoting awareness

Current outreach and education efforts to promote VAERS include general information brochures in English and Spanish and an online public use data set (http://www.vaers.hhs.gov/info.htm). 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.

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.

Despite its limitations, VAERS is useful in that it generates signals that trigger further investigations.

To complement VAERS' role in hypothesis generation, CDC created the Vaccine Safety Datalink (VSD) project in 1990 to test and validate hypothesized vaccine adverse events.[29] The VSD links computerized vaccination and medical records for approximately 5.5 million persons (2% of the total U.S. population) at eight geographically diverse health maintenance organizations (HMOs). Because the databases are usually generated during routine administration of the HMO, the problems of underreporting or recall bias are minimized. Because these programs have enrollees numbering from thousands to millions, large cohorts may be assembled to examine less frequent adverse events. Denominator data and control groups are also readily available. Hence the VSD provides an economical and rapid means of generating and testing hypotheses related to vaccine safety.

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. The sentinel role of VAERS is particularly significant for newly licensed vaccines, as evidenced by the detection of intussusception following introduction of rhesus–human rotavirus reassortant tetravalent vaccine in 1999. Although manufacturers are now routinely asked to conduct 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 are generally not large enough to detect rare adverse events.

VII. The National Vaccine Injury Compensation Program

The NCVIA established the National Vaccine Injury Compensation Program to provide compensation for certain AEFI. VICP is not related to VAERS and is a separate government "no-fault" system to compensate individuals whose injuries may have been caused by any routinely recommended childhood vaccines. Reporting an event to VAERS does not automatically result in the filing of a claim with 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.[11, 30]

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.

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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 which specimens to collect for each VPD and how to interpret 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	(404) 639-1239 (404) 639-1231	(404) 639-4421	CDC Pertussis and Diphtheria Laboratory	
	Toxigenicity testing	Dr.M. Lucia Tondella or Ms. Pam Cassiday	(404) 639-1239 (404) 639-1231	(404) 639-4421	CDC Pertussis and Diphtheria Laboratory	
	PCR	Dr. M. Lucia Tondella or Ms. Pam Cassiday	(404) 639-1239 (404) 639-1231	(404) 639-4421	CDC Pertussis and Diphtheria Laboratory	
	Serology (antibodies to diphtheria toxin)	Dr. M. Lucia Tondella or Ms. Pam Cassiday	(404) 639-1239 (404) 639-1231	(404) 639-4421	CDC Pertussis and Diphtheria Laboratory	This test is not currently available at CDC.
Haemophilus influenzae	Culture	Dr. Leonard Mayer	(404) 639-2841 LWM1@cdc.gov	(404) 639-4421	Meningitis Laboratory	
	Serotyping	Dr. Leonard Mayer	(404) 639-2841 LWM1@cdc.gov	(404) 639-4421	Meningitis Laboratory	
	Antigen detection	Dr. Leonard Mayer	(404) 639-2841 LWM1@cdc.gov	(404) 639-4421	Meningitis Laboratory	
	Subtyping	Dr. Leonard Mayer	(404) 639-2841 LWM1@cdc.gov	(404) 639-4421	Meningitis Laboratory	
Hepatitis A		Dr. Wendi Kuhnert	(404) 639-2339	(404) 639-1563	Hepatitis Reference Laboratory	
Hepatitis B		Dr. Wendi Kuhnert	(404) 639-2339	(404) 639-1563	Hepatitis Reference Laboratory	
Influenza	Culture/viral isolation	Dr. Michael Shaw	(404) 639-1405	(404) 639-2350	Influenza Surveillance and Diagnosis 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 cont'd	Antigen detection	Dr. Michael Shaw	(404) 639-1405	(404) 639-2350	Influenza Surveillance and Diagnosis Laboratory	
	RT-PCR/ real time RT-PCR	Dr. Michael Shaw	(404) 639-1405	(404) 639-2350	Influenza Surveillance and Diagnosis Laboratory	
	Serology	Dr. Michael Shaw	(404) 639-1405	(404) 639-2350	Influenza Surveillance and Diagnosis Laboratory	
Measles	IgM antibody	Dr. Paul Rota	(404) 639-4181	(404) 639-4187		
	IgG antibody	Dr. Paul Rota	(404) 639-4181	(404) 639-4187		
	Culture	Dr. Paul Rota	(404) 639-4181	(404) 639-4187		
	PCR	Dr. Paul Rota	(404) 639-4181	(404) 639-4187		
Meningococcal disease	Culture	Dr. Leonard Mayer	(404) 639-2841 LWM1@cdc.gov	(404) 639 4421	Meningitis Laboratory	
	SASG	Dr. Leonard Mayer	(404) 639-2841 LWM1@cdc.gov	(404) 639 4421	Meningitis Laboratory	
	PCR	Dr. Leonard Mayer	(404) 639-2841 LWM1@cdc.gov	(404) 639 4421	Meningitis Laboratory	
	Susceptibility testing	Dr. Leonard Mayer	(404) 639-2841 LWM1@cdc.gov	(404) 639 4421	Meningitis Laboratory	
	Molecular genotyping (PFGE, MLST, etc.)	Dr. Leonard Mayer	(404) 639-2841 LWM1@cdc.gov	(404) 639 4421	Meningitis Laboratory	
Mumps	Culture	Dr. Paul Rota	(404) 639-4181	(404) 639-4187		
	IgM antibody	Dr. Paul Rota	(404) 639-4181	(404) 639-4187		
	IgG antibody	Dr. Paul Rota	(404) 639-4181	(404) 639-4187		
Pertussis	Culture	Dr. M. Lucia Tondella or Ms. Pam Cassiday	(404)-639-1239 (404) 639-1231	(404)639-4421	CDC Pertussis and Diphtheria Laboratory	
	PCR	Dr. M. Lucia Tondella or Dr. Kathy Tatti	404-639-1239 (404) 639-3797	(404)639-4421	CDC Pertussis and Diphtheria Laboratory	
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	

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 cont'd	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	(404) 639-1237	(404) 639-4215	CDC Streptococcus Laboratory	
Poliomyelitis	Culture	Dr. Steve Oberste	(404) 639-2749	(404) 639-4011	Polio/Picornavirus Laboratory	
	Intratypic differentiation	Dr. Steve Oberste	(404) 639-2749	(404) 639-4011	Polio/Picornavirus Laboratory	
	Serology	Dr. Steve Oberste	(404) 639-2749	(404) 639-4011	Polio/Picornavirus Laboratory	
Rotavirus	Antigen EIA	Dr Jon Gentsch	(404) 639-2860	(404) 639-3645	Gastroenteritis Virus Laboratory	
	Intratypic differentiation	Dr Jon Gentsch	(404) 639-2860	(404) 639-3645	Gastroenteritis Virus Laboratory	
	Serology	Dr Jon Gentsch	(404) 639-2860	(404) 639-3645	Gastroenteritis Virus Laboratory	
	Culture	Dr Jon Gentsch	(404) 639-2860	(404) 639-3645	Gastroenteritis Virus Laboratory	
Rubella	IgG antibody	Dr. Joe Icenogle	(404) 639-4557	(404) 639-1516		
	IgM antibody	Dr. Joe Icenogle	(404) 639-4557	(404) 639-1516		
	Culture	Dr. Joe Icenogle	(404) 639-4557	(404) 639-1516		
	PCR	Dr. Joe Icenogle	(404) 639-4557	(404) 639-1516		
Congenital rubella syndrome	IgG antibody	Dr. Joe Icenogle	(404) 639-4557	(404) 639-1516		
	IgM antibody	Dr. Joe Icenogle	(404) 639-4557	(404) 639-1516		
	Culture	Dr. Joe Icenogle	(404) 639-4557	(404) 639-1516		
	PCR	Dr. Joe Icenogle	(404) 639-4557	(404) 639-1516		
	Serology	Dr. Joe Icenogle	(404) 639-4557	(404) 639-1516		
Varicella	DFA	Dr. Scott Schmid	(404) 639-0066	(404) 639-4056		
	Culture	Dr. Scott Schmid	(404) 639-0066	(404) 639-4056		
	Viral typing/ strain identification	Dr. Scott Schmid	(404) 639-0066	(404) 639-4056		

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 also is 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 laboratory.

Table 2. Confirmatory and other useful tests for the surveillance of vaccine-preventable diseases

Disease	Confirmatory tests	Other useful tests
Diphtheria	Culture Toxigenicity testing	PCR Serology (antibodies to diphtheria toxin)
Haemophilus influenzae	Culture	Serotyping (identification of capsular type of encapsulated strains) Antigen detection Subtyping
Hepatitis A	IgM anti-HAV (positive)	Total anti-HAV (marker of immunity) PCR
Hepatitis B	IgM anti-HBc (acute infection) HBsAg (acute or chronic infection)*	Anti-HBs (marker of immunity) Total anti-HBc (marker of past or present infection)
Influenza	Culture Antigen detection (EIA, IFA, EM) Serology PCR	
Measles	IgM Paired sera for IgG	Culture (for molecular epi) PCR
Meningococcal disease	Culture	Serogroup-specific PCR Slide agglutination serogrouping PCR
Mumps	Culture IgM IgG	IgG—for immunity testing
Pertussis	Culture PCR	Serology
Pneumococcal disease	Culture PCR	Antibiotic resistance -serotyping -PCR deduction of serotypes - strain identification (MLST,PFGE)
Poliomyelitis	Culture-from stool, pharynx, or CSF	Intratypic differentiation (wild vs. vaccine type) Paired serology CSF analysis
Rotavirus	Culture Paired serology	Nucleic acid electrophoresis PCR genotyping

Table 2. Confirmatory and other useful tests for the surveillance of vaccine-preventable diseases

Disease	Confirmatory tests	Other useful tests
Rubella	Paired sera for IgG IgM Culture	PCR
Tetanus	There are no lab findings characteristic of tetanus	Serology to test for immunity
Varicella	Culture Serology	Viral typing/strain identification 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 ≥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.
	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 not currently 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			

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
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	
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.

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
Measles cont'd	IgM antibody	Serum	ASAP, and repeat 72 hours after onset if first negative			IgM is detectable for at least 28 days after rash onset.
	IgG antibody	Paired sera	Acute: ASAP after rash onset (7 days at the latest) Convalescent: 10–30 days after acute			
Meningococcal disease	Culture*	Blood	ASAP	TI medium preferred. 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 preferred. 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 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.		
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 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 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. Negative culture does NOT rule out pertussis.

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
Pertussis cont'd	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 Convalescent: 3–9 weeks after acute	-20°C		Results are presumptive and should be validated with culture. Serologic results are not currently 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.	Specimen sent 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	
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 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

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
Rotavirus gastroenteritis cont'd	Serology	Paired sera	Acute: ASAP 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			
	IgG antibody	Paired sera	Acute: within 7–10 days of onset Convalescent: 2–3 weeks after acute			
	Culture/PCR	Nasopharyngeal swab/wash, throat, urine.	Within 4 days of onset	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.
Varicella	Serology	Serum	Immune status: collect anytime except during acute illness Paired serologic diagnosis: acute within 7–10 days of onset; convalescent 2–3 weeks after acute		Single IgG assay useful to assess immune status. Paired serum used to identify recent infection, but not method of choice when rapid diagnosis 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

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 cont'd	Viral typing/ strain identification	Viral isolate (from culture)	Within 2–3 days of rash	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 persons with 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 ruled out accurately, 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 be also tested for antimicrobial susceptibility according to guidelines in M02-A9 Performance Standards for Antimicrobial Disk Susceptibility Tests (January 2006) 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 age 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).

Table 5. Interpretation of measles enzyme immunoassay results*

IgM Result	IgG Result	Previous infection history	Current infection	Comments
+	+	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 non–vaccine-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 not currently 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 ideally 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)

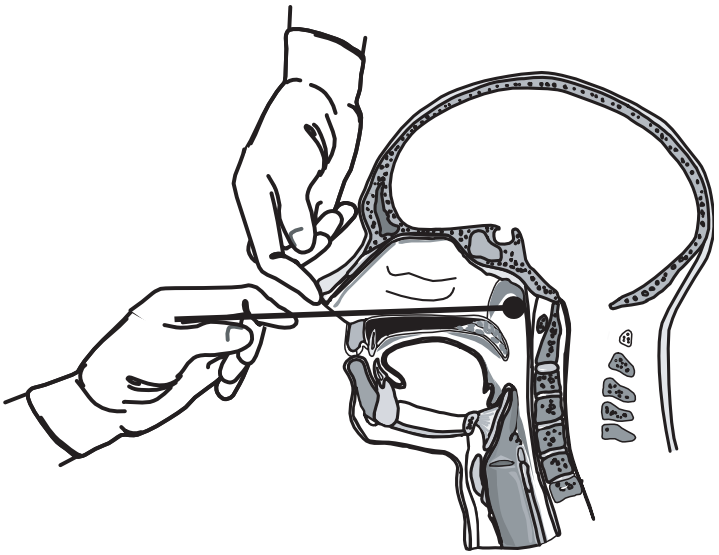
Culture
The preferred laboratory test for diagnosis of pertussis is isolation of *Bordetella pertussis* by bacterial culture.

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 cases of pertussis 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 currently is 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/PRC.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 initiated immediately (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 based primarily 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 important 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

For confirmation of disease a) IgM, and b) acute and convalescent IgG: Serologic tests are available for IgG and IgM antibodies to VZV. 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, varicella, novel influenza A virus infections, influenza-associated pediatric mortality, and varicella deaths. Cases of diseases and conditions under national surveillance, as designated by the Council of State and Territorial Epidemiologists (CSTE), are reported to CDC from state

health departments through NNDSS; these data are reported in the *Morbidity and Mortality Weekly Report (MMWR).* In general, CDC encourages state health departments to report provisional data through NNDSS before completing case investigations; however, cases are included for publication in the *MMWR* as described in the case confirmation 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 additional demographic and epidemiologic information on each case-patient reported to NNDSS.

CDC publishes NNDSS data weekly in the *MMWR*, and yearly in the *Annual Summary of Notifiable Diseases*. NNDSS data, together with data reported to supplemental surveillance systems, are analyzed by CDC staff and are disseminated through other 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] CDC and CSTE have established a policy under which state health departments report cases of selected diseases to CDC through the NNDSS. In the past, supplemental surveillance systems were developed for some diseases to gather additional epidemiologically important information. However, with the development of electronic data systems, some of these supplemental systems may no longer be needed.

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.[8]

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 report 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.[9] Poliovirus infection (asymptomatic) was added to the list of nationally notifiable diseases and conditions in 2007.[10]

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 report.

Tetanus

In 1965, the Supplemental Tetanus Surveillance System was developed to allow state health departments to report supplemental clinical and epidemiologic information on reported cases of tetanus. Data are now reported 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.[11] A 1992 study showed that only an estimated 11.6% of pertussis cases in the United States were reported.[12] 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.[13] A recent literature review of articles on surveillance data for measles, pertussis, mumps, and rubella in industrialized countries further illustrates that reporting is incomplete.[14]

The completeness of reporting to supplemental surveillance systems has been evaluated by using capture–recapture methods.[15, 16] 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.[17] 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.[12, 18] 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.[12]

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,[19] revised in 1997,[20] and have been subsequently updated as needed. However, implementation of uniform case definitions for reporting by state health departments has been incomplete.

V. Future directions

To maximize the usefulness of vaccine-preventable diseases surveillance data at the state level, the existing 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 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.

In addition, CDC, in collaboration with the states, has developed the National Electronic Disease Surveillance System (NEDSS).[6] Electronic reporting and data management were developed to provide timely access to additional demographic and epidemiologic information on each case-patient reported to 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.

There has been increasing interest in alternative approaches to traditional morbidity surveillance systems.[21, 22] Hospital discharge data sets may be useful for some purposes, although their usefulness in providing timely data for disease control purposes is limited. Ultimately, computerized medical records in physicians' offices and clinics may provide data that are timely, accurate, and complete.[23, 24] 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.[25, 26] 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, 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

This *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.