Chapter 17: Varicella

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I. Disease Description

Varicella (chickenpox) is a febrile rash illness resulting from primary infection with the varicella-zoster virus (VZV). Humans are the only source of infection for this virus. Varicella is highly infectious, with secondary infection occurring in 61%–100% of susceptible household contacts.[1–5] Transmission occurs from person to person by direct contact with persons with either varicella or herpes zoster (shingles), inhalation of aerosols from vesicular fluid of skin lesions of persons with varicella or zoster, and through infected respiratory secretions that also may be aerosolized. 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 3- to 7-day period.[6]

Varicella severity and complications are increased among immunocompromised persons, pregnant women, children younger than 1 year of age, and adults.[7–10] However, healthy children 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 who develop 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 high risk of severe neonatal varicella.

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 1 in 3 infected persons during their lifetime, resulting in herpes zoster.[21–23] Herpes zoster usually presents as a vesicular rash with pain and itching in a dermatomal distribution. Herpes zoster incidence increases with 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 during childhood.[24–25] 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. Two zoster vaccines (Zostavax™, Merck & Co., Inc.; and Shingrix, GlaxoSmithKline [GSK]) are licensed and recommended in the United States for adults 50 years of age and older (recombinant vaccine)[26] and 60 years of age and older (live attenuated vaccine).[27]

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, 28–29] Varicella primarily affected 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 childcare centers and preschools.[8, 30]

Varicella vaccine was licensed in the United States in 1995. Two doses are now recommended for routine use, with the first dose given to children 12–15 months of age and the second dose at 4–6 years of age.[31] Persons 13 years of age and older without evidence of immunity to varicella should routinely receive 2 doses of varicella vaccine 4–8 weeks apart.[31] Persons who previously received 1 dose of varicella vaccine should receive their second dose.

Since implementation of the varicella vaccination program in 1996, there have been substantial declines in varicella morbidity and mortality in the United States. One-dose varicella vaccination coverage among children 19–35 months of age was 91% in 2016,[32] and ≥2-dose varicella vaccination coverage among adolescents 13–17 years of age without history of varicella was 86% nationally in 2016.[33] Overall, from prevaccine years, varicella incidence declined an average of 97.4% (from 1993–1995 to 2013–2014) based on data from 4 states that have been continuously reporting varicella to the National Notifiable Disease Surveillance System (NNDSS)[34] since before the varicella vaccination program.The second dose of varicella vaccine was added to the national program in 2007.[31] During the 2-dose era, data from 40 states that reported varicella cases to NNDSS have shown an 85% decline in varicella incidence from 2005–06 to 2013–14, with the greatest declines among children 5–14 years of age (85%–89%).[34]

Medical claims data for varicella outpatient visits and hospitalizations demonstrated declines of 84% and 93%, respectively, by 2012 compared to the prevaccination period (1994–95).[35] Furthermore, in reports of varicella as the underlying cause of death to the National Vital Statistics System, national varicella mortality rates declined 87% for all ages, and 99% for persons <20 years of age in 2008–2011 as compared to pre-vaccine years (1990–1994).[36]

Although increased vaccination of children has lowered the overall burden of disease, a higher proportion of reported cases now occur among older children, adolescents, and adults who may have escaped varicella disease or vaccination, although age specific incidence remains significantly lower than during the prevaccine years for all age groups. As vaccination rates have increased, the majority of varicella cases now occur among vaccinated persons. Cases of varicella in vaccinated persons (i.e., breakthrough cases) are generally much milder, often with fewer than 50 lesions and fewer vesicles compared with 300 or more lesions and many vesicles typically seen in unvaccinated persons.[37] Persons with breakthrough cases are also less likely to have fever and more likely to have fewer days of illness.[38] Given its modified clinical presentation, breakthrough varicella illness can be challenging for practitioners and parents to recognize clinically.

III. Importance of Rapid Case Identification

Reporting of varicella cases in childcare centers, schools, other institutions, military barracks, and other group settings will facilitate public health action and outbreak control. In addition, in certain high-risk settings (e.g., hospitals and other healthcare settings, schools that may have students who are immunocompromised), rapid case identification and public health action are important to prevent infection of susceptible persons at high risk for serious complications of varicella, such as immunocompromised persons and pregnant women, for whom varicella vaccine is contraindicated.[31]

IV. Importance of Surveillance

Surveillance data are needed to

- document and monitor the impact of a vaccination program on disease incidence, morbidity, and mortality;
- evaluate the effectiveness of prevention strategies; and
- evaluate vaccine effectiveness under conditions of routine use.

With varicella vaccine coverage increasing and 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 *Healthy People 2020* disease reduction goals,[39] and determine whether any improvements to the vaccination policy are needed. *Healthy People 2020* goals for varicella include a greater than 80% reduction in the estimated number of varicella cases among children <18 years of age

compared to 2008; greater than 90% vaccine coverage among children 19–35 months of age; greater than 95% vaccination coverage with 2 doses of varicella vaccine among children in kindergarten; and greater than 90% 2-dose vaccine coverage among adolescents.[39]

V. Case Definition

The following case definitions were approved by the Council of State and Territorial Epidemiologists (CSTE) for varicella cases in June 1999 with an update in June 2009[40–41] and varicella deaths in 1998.[42]

Varicella clinical case definition

An illness with acute onset of diffuse (generalized) maculopapulovesicular rash without other apparent cause. In vaccinated persons, varicella that develops more than 42 days after vaccination (breakthrough disease) due to infection with wild-type VZV, is usually mild, with fewer than 50 skin lesions and of shorter duration of illness. The rash may also be atypical in appearance (maculopapular with few or no vesicles).

Laboratory criteria for diagnosis

- Demonstration of VZV DNA by polymerase chain reaction (PCR) tests from a clinical specimen, ideally scabs, vesicular fluid, or cells from the base of a lesion is the preferred method for varicella diagnosis. [See the varicella web site(https://www.cdc.gov/chickenpox/lab-testing/index.html) for more details.] PCR is also useful for confirming breakthrough disease (Table 1). Other methods, such as DFA and culture, are available for diagnosis but are less sensitive and specific than PCR.
- Positive serologic test for varicella-zoster IgM antibody when varicella-like symptoms are present
- Four-fold or greater rise in serum varicella IgG antibody titer by any standard serologic assay between acute and convalescent sera

For both unvaccinated and vaccinated persons, **PCR is the most reliable method for confirming infection**.

Data are limited regarding IgM antibody tests and the timing of the IgM response in unvaccinated persons. Even less information is available on serologic methods for laboratory confirmation for vaccinated persons. Therefore, a negative IgM result should not be used to rule out the diagnosis, and a positive IgM in the absence of rash should not be used to confirm a diagnosis. Furthermore, a 4-fold rise in IgG antibody may not occur in vaccinated persons. VZV IgG avidity testing is a method that can be used to distinguish between primary VZV infection and past infection but this method is not widely available. Therefore, DNA detection methods are the laboratory methods of choice for diagnosis.

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 rash in vaccine recipients: A varicella-like rash in a recently vaccinated person may be caused by either wild- or vaccine-type virus or have other etiologies. Approximately 4% of children receiving varicella vaccine develop a generalized rash with a median of 5 lesions 5–26 days post-vaccination, and 4% develop a localized rash at the injection site with a median of 2 lesions 8–19 days postvaccination.[43] The rash may be atypical in appearance (maculopapular with no vesicles). Approximately

2% of children who received a placebo in the clinical trials also developed generalized rashes, some of which were varicella-like, indicating that not all rashes following vaccination are attributable to the vaccine.[44] Rashes occurring within 2 weeks of or more than 42 days after vaccination are more likely to be wild-type virus, and rashes occurring 15–42 days postvaccination are more likely to be vaccine-type virus.[45] Attribution of disease to vaccine strain VZV can only be confirmed by strain differential, real-time PCR, or by PCR combined with restriction fragment length polymorphism (RFLP) analysis.

Breakthrough disease: A case of wild-type varicella infection occurring more than 42 days after vaccination. Such disease is usually mild with a shorter duration of illness, fewer constitutional symptoms, and fewer than 50 skin lesions. Breakthrough cases with fewer than 50 lesions have been found to be one-third as contagious as varicella in unvaccinated persons, but breakthrough cases with 50 or more lesions can be just as contagious as cases in unvaccinated persons.[46] Though generally mild, about 25%–30% of breakthrough cases among 1-dose vaccinated children have clinical features more similar to those in unvaccinated children and rare, severe presentations with visceral dissemination have been reported.[47] Persons who received 2 doses of vaccine are less likely to have breakthrough disease than those who received 1 dose. Additionally, breakthrough varicella may be further attenuated among 2-dose vaccine recipients though the difference was not always statistically significant.[47] No cases of breakthrough varicella with visceral dissemination have been reported.

Secondary transmission of vaccine virus: A varicella-like rash due to Oka-VZV (i.e., the vaccine-strain variant of VZV) occurring in a non-vaccinated contact of a person who received varicella vaccine. Secondary transmission can occur within 10–21 days after exposure either to a person recently vaccinated or to a person who develops herpes zoster due to vaccine-strain virus. It is extremely rare; since 1995, only 11 secondary cases of transmission of vaccine virus from 9 healthy vaccinees have been documented with the varicella vaccine; 7 were acquired from vaccinees with varicella-like rashes soon after vaccination and 4 from children with HZ caused by Oka strain.[31,45,48–57] All secondary transmissions occurred from vaccine recipients who developed at least a limited rash illness. One additional report was of neonatal varicella with vaccine-strain VZV diagnosed after maternal postpartum vaccination; the mother did not have a rash but the newborn was in the room when she was vaccinated. It is considered more likely that transmission occurred by aerosolization when the syringe was cleared by flushing air bubbles rather than from the mother.[58] All laboratory-confirmed cases of Oka vaccine secondary transmission resolved without complications. Transmission of vaccine-strain VZV can only be confirmed by strain differential real-time PCR or by PCR combined with RFLP analysis.

VI. Evidence of Immunity to Varicella

Evidence of immunity to varicella includes any of the following:[31]

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 2 doses is 3 months. However, if the child received the first dose before 13 years of age and the interval between the 2 doses was at least 28 days, the second dose is considered valid.
     - For persons 13 years of age or older the minimum interval between doses is 4 weeks (28 days).
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, pregnant women, and immunocompromised persons, 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 to have a valid history of disease, because other diseases may mimic mild, atypical varicella.

5. A healthcare provider diagnosis of herpes zoster or verification of history of herpes zoster

VII. Laboratory Testing

As varicella disease has declined with introduction of vaccine, the need for laboratory confirmation has concomitantly grown. This is because fewer physicians have direct experience with natural infection and breakthrough disease is often atypical in appearance, results in fewer lesions, and may lack characteristic vesicles. Varicella hospitalizations and deaths, as well as other severe or unusual disease, should routinely be laboratory confirmed. Postvaccination situations for which specimens should be tested include 1) rash occurring 7–42 days after vaccination; 2) suspected secondary transmission of the vaccine virus; 3) herpes zoster in a vaccinated person; or 4) any serious adverse event. In an outbreak, it is recommended that 3–5 cases be confirmed, regardless of vaccination status. The preferred diagnostic test to confirm varicella infection is detection of viral DNA. For additional information on laboratory support for vaccine-preventable disease surveillance, see Chapter 22, Laboratory Support for Surveillance of Vaccine-Preventable Diseases (https://www.cdc.gov/vaccines/pubs/surv-manual/chpt22-lab-support.html).

Skin lesions are the preferred sample for laboratory confirmation of varicella. Peripheral blood samples (serum or plasma) are preferred to test for varicella immunity. Samples from skin lesions should be collected by unroofing a vesicle, preferably a fresh fluid-filled vesicle, and then rubbing the base of a skin lesion with a polyester swab. If only macules or papules are present, suitable samples can often be obtained by scraping the lesion (e.g., with the edge of a glass microscope slide), swabbing the abraded lesion with a polyester swab, and then collecting any material that was accumulated on the object that was used to scrape the lesion on the same swab. Scabs from skin lesions are also excellent samples for PCR detection of VZV DNA. Other sources such as nasopharyngeal secretions, saliva, blood, urine, bronchial washings, and cerebrospinal fluid are less likely to provide an adequate sample than vesicular swabs and scabs from skin lesions, and can often lead to false negative results. Collecting skin lesion specimens from breakthrough cases can be 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 on the CDC varicella web site (https://www.cdc.gov/chickenpox/lab-testing/collecting-specimens.html). Additional information about collecting and submitting specimens for testing can also be found on the CDC varicella web site (https://www.cdc.gov/chickenpox/lab-testing/collecting-specimens.html) or by calling the National VZV laboratory at 404-639-0066, or emailing dds1@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 confirmation of a clinical diagnosis. This test is sensitive, specific, and widely available. Short turnaround times of several hours are possible. PCR is a powerful technique that permits the rapid amplification of specific sequences of viral DNA that would otherwise be present in clinical samples at concentrations well below detectable limits.
- **DFA.** If PCR is not available, the DFA test can be used, although it is only about 60% as sensitive as 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. At the same time, care must 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 and viral particles persist 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 and the American Public Health Laboratory Association Vaccine Preventable Diseases Reference Centers (VPD-RCs, https://www.aphl.org/programs/infectious_disease/Documents/ID_VPDQuickReferenceGuide_updated62016.pdf) have the capacity to distinguish wild-type VZV from Oka strain using both strain differential real-time PCR or PCR combined with restriction fragment length polymorphism (RFLP) analysis. VPD-RCs are located in the state laboratories of Wisconsin, California, New York, and Minnesota, and each VPD-RC receives specimens from a designated group of states.

Virus culture: The diagnosis of VZV infection may be confirmed by culture (isolation) of VZV, but is generally not recommended because of the length of time for results and the insensitivity of the approach compared with PCR. Although newer, more sensitive and rapid culture techniques can provide results within 2–3 days, they are still substantially less sensitive than PCR, and may fail to confirm as many as 50% of varicella infections. 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: IgM serology can provide evidence for a recent active VZV infection, but cannot discriminate between a primary infection and reinfection or reactivation from latency since specific IgM antibodies are transiently produced on each exposure to VZV. IgM tests are also inherently prone to poor specificity. Paired IgG acute- and convalescent-phase antibody tests are used in situations of mild or atypical presentation of disease when immediate therapy is not indicated and when, for clinical reasons, a confirmed diagnosis of the acute illness is important, e.g., a suspected second infection due to varicella. In addition, the laboratory at CDC has developed an IgG avidity assay, which can be used to identify recent primary VZV infection using a single VZV IgG-seropositive serum specimen. IgM detection does not confirm a primary infection, since specific IgM antibodies are transiently produced on each exposure to VZV, whether through reinfection or reactivation from latency.

Single serologic IgG tests may be used to determine the immune status of persons whose history of varicella is negative or uncertain and who may be candidates for varicella zoster immune globulin (VZIG) or vaccination. Commercial enzyme-linked immunosorbent assays (ELISAs) are recommended for the purpose of screening.[59] Routine testing for varicella immunity following vaccination is not recommended. Commercially available serologic IgG tests are not sufficiently sensitive to detect low levels of antibody following vaccination. There is evidence to suggest that the latex agglutination method, another method to test for serologic IgG, may result in false-positive results that could mistakenly categorize a susceptible person as immune.[60]

Table 1. Laboratory tests available for varicella confirmation

Test	Specimen	Comments
PCR	Vesicular swabs or scrapings; scrapings from maculopapular lesions; scabs from crusted lesions; biopsy tissue	Very sensitive and specific for detecting VZV. Results rapidly available (within 3 hours). Real-time methods (not widely available and require special equipment) have been designed that distinguish vaccine strain from wild-type.
DFA	Vesicle scraping; swab of lesion base (must include cells)	Identifies VZV. More rapid and sensitive than culture. Less sensitive than PCR.
Tissue culture	Vesicular fluid; biopsy specimens from sterile sites (e.g., CSF, joint fluid)	Used to detect the presence of viable VZV. Culture is considerably less sensitive than VZV PCR. Requires up to a week for results.
Tzanck smear	Vesicle scraping; swab of lesion base (must include cells)	Detects multinucleated giant cells with inclusions. Diagnostic of alpha herpes viruses (VZV, herpes simplex viruses). Less sensitive than DFA.
IgM	Acute or convalescent serum specimens for VZV IgM	IgM is inconsistently detected, even among patients with PCR-confirmed disease. Not a reliable method for routine confirmation, especially in vaccinated persons, but a positive result in presence of varicella-like symptoms indicates current/recent VZV infection. However, positive results in the absence of clinical disease would not be considered confirmation of active varicella disease due to limits in specificity.
EIA	Acute and convalescent serum specimens for IgG	Requires special equipment. Specific but may not be sensitive enough to identify vaccine-induced immunity.
LA	Acute and convalescent serum specimens for IgG	Rapid (15 min). No special equipment needed. More sensitive but less specific than EIA. Can produce false-positive results.
IFA	Acute and convalescent serum specimens for IgG	Requires special equipment. Good sensitivity and specificity; however, accurate interpretation requires an experienced operator.
gpELISA	Acute and convalescent serum specimens for IgG	Highly specific and sensitive but not widely or commercially available. Suitable for evaluation of vaccine-induced seroconversion.

Abbreviations: *CSF, cerebrospinal fluid; DFA, direct fluorescent antibody; EIA, enzyme immunoassay; gpELISA, glycoprotein-based enzyme-linked immunosorbent assay; IFA, indirect fluorescent antibody; LA, latex agglutination; PCR, polymerase chain reaction; VZV, varicella-zoster virus.*

Specimen collection

Specimen collection and shipping are important steps in obtaining laboratory diagnosis or confirmation for vaccine preventable diseases. Guidelines have been published for specimen collection and handling for microbiologic agents (https://stacks.cdc.gov/view/cdc/7590). Information is also available on using CDC laboratories as support for reference and disease surveillance (https://www.cdc.gov/ncezid/dsr/specimen-management-branch.html); this includes

- a central website (https://www.cdc.gov/laboratory/specimen-submission/index.html) for requesting lab testing;
- the form required for submitting specimens to CDC (See Appendix 23, Form # CDC 50.34);
- information on general requirements for shipment of etiologic agents (Appendix 24, https://www.cdc.gov/vaccines/pubs/surv-manual/appx/appendix24-etiologic-agent.pdf)—although written to guide specimen submission to CDC, this information may be applicable to submission of specimens to other laboratories; and
- the CDC Infectious Diseases Laboratories Test Directory (https://www.cdc.gov/laboratory/specimen-submission/list.html), which not only contains a list of orderable tests for that institution, but also detailed information on appropriate specimen types, collection methods, specimen volume, and points of contact.

The APHL/CDC Vaccine Preventable Disease Reference Centers (https://www.aphl.org/programs/infectious_disease/Documents/ID_VPDQuickReferenceGuide_updated62016.pdf} can perform RT-PCR to detect measles RNA and measles genotyping.

Specific instructions for specimen collection and shipping may be obtained from the CDC varicella website (https://www.cdc.gov/chickenpox/lab-testing/collecting-specimens.html) or by contacting the CDC Viral Vaccine Preventable Diseases Branch at 404-639-0066. Specimens for virus identification 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 and Case Notification

Case reporting within a jurisdiction

Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[61] 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, childcare facilities, and other institutions. Persons reporting should contact the state health department for state-specific reporting requirements.

In 2002, CSTE recommended that states establish case-based surveillance for varicella and that it be included in NNDSS. All states were encouraged to conduct ongoing varicella surveillance to monitor vaccine impact on morbidity.[62] States are encouraged to report varicella cases to NNDSS via the National Electronic Disease Surveillance System (NEDSS). As of 2017, 38 states are conducting case-based varicella surveillance. Persons reporting should contact the state health department for state-specific reporting requirements.

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, childcare 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 the number of sites as they develop their system with the intention of eventually having statewide surveillance.

Case notification to CDC

Notifications for cases with confirmed, probable, and unknown case status of varicella should be sent to CDC using event code 10030 in the NNDSS via NEDSS. Case notifications should not be delayed because of incomplete information or lack of confirmation. Data can be updated electronically as more information becomes available. The state in which the patient resides at the time of diagnosis should submit the case notification to CDC. The Varicella Surveillance Worksheet is included as Appendix 20 https://www.cdc.gov/vaccines/pubs/surv-manual/appx/appendix20-varicella-surv-wksht.pdf, to serve as a guide for data collection to be included in case investigations and case notification to CDC. Additional inquiries can be directed to the CDC National Center for Immunization and Respiratory Disease, Division of Viral Diseases, Viral Vaccine Preventable Diseases Branch (ncirddvdmmrhp@cdc.gov)

The Reporting Line List for Varicella Outbreak Surveillance at https://www.cdc.gov/vaccines/pubs/surv-manual/appx/appendix20-varicella-list.xlsx is included to serve as a guide for outbreak reporting.

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

- Age—to monitor the impact of vaccination on disease reduction in specific age groups and any shift in disease to older persons.
- Varicella vaccination status—to determine the proportion of cases occurring in vaccinated persons and assess crude vaccine effectiveness.
    - Number of doses of varicella vaccine
    - Date(s) of vaccination

        - Type and manufacturer of vaccine
        - Vaccine lot number
        - If not vaccinated, reason
- Severity of disease—to assess the severity of varicella (based on number of lesions) in vaccinated persons, to monitor the impact of vaccination on disease severity, and to determine if vaccine-induced immunity wanes over time.
    - Number of lesions
        - Mild: fewer than 50 lesions
        - Mild/moderate: 50–249 lesions
        - Moderate: 250–499 lesions
        - Severe: 500 or more lesions or any complications such as bacterial superinfection, varicella pneumonitis, encephalitis, hospitalization, or death
        - Hospitalization
            - » Reason for hospitalization, if known
- Laboratory information
    - Virus isolation test dates and results
    - PCR test dates and results
    - DFA test dates and results
    - Serologic test dates and results

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
    - Complications
- Outcome (patient survived or died)
    - Date of death
- Epidemiologic data
    - Transmission setting
    - Source of transmission
    - Vaccination status of source patient

Varicella deaths reporting

In 1998, CSTE recommended that varicella-related deaths be placed under national surveillance,[42] and varicella-related deaths became nationally notifiable on January 1, 1999.

Varicella deaths can be identified through death certificates, which may be available through state vital records systems and may be more readily available soon after death in states using electronic death certificates. State public health departments may also request that local health departments, healthcare practitioners, and hospitals report varicella deaths that occur in their community.

Because varicella is a vaccine-preventable disease, 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) at (https://www.cdc.gov/vaccines/pubs/surv-manual/appx/appendix19-2-varicella-wrsh.pdf). Deaths should be reported to the CDC National Center for Immunization and Respiratory Diseases, Division of Viral Diseases, Viral Vaccine Preventable Diseases Branch (ncirddvdmmrhp@cdc.gov), and to NNDSS via NEDSS.

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, and discharge diagnoses
  - Postmortem examination results
  - Death certificate diagnoses
- Complications
  - Pneumonia
  - Infections (e.g., invasive group A beta-hemolytic streptococcal infection, 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)

IX. Vaccination

Two varicella vaccines are now available in the United States. The live attenuated single-antigen varicella vaccine (Varivax®, Merck & Co., Inc.) was licensed in March 1995 for use in persons 12 months of age and older. A combination vaccine, Measles, Mumps, Rubella, and 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 freezer storage for the vaccine must be followed strictly. Vaccine that is not properly stored before administration could have suboptimal potency.[31,63]

Prelicensure studies of 1 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.[4,64,65] Post-licensure studies under conditions of community use in the United States have demonstrated 1-dose vaccine effectiveness of 82% (range of estimates, 44%–100%) for prevention of all disease and 100% effectiveness in preventing severe varicella.[66–74]

The efficacy of 2 doses of varicella vaccine was evaluated in a randomized clinical trial. Over a 10-year observation period, the estimated vaccine efficacy of 2 doses was 98.3% compared with 94.4% for 1 dose. The difference was statistically significant ($p<0.001$).[75] A second dose of vaccine reduced varicella attack rates by 3.3-fold.[75] Post-licensure studies in the United States found 2-dose vaccine effectiveness was 94%–98% though 2 studies found lower 2-dose vaccine effectiveness of 84% and 88%.[74,76–80]

Recommendations for the use of varicella vaccines[31]

Routine administration of 2 doses of live attenuated varicella vaccines

- All children should routinely receive their first dose at 12–15 months of age. The second dose is recommended routinely when children are 4–6 years of age (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.
  - Because MMRV vaccine is associated with a higher risk for fever and febrile seizures among young children, CDC recommends that MMR vaccine and varicella vaccine be administered for the first dose at 12-47 months old unless the parent or caregiver expresses a preference for MMRV vaccine.
- Persons 13 years of age or older without evidence of varicella immunity should receive 2 doses of single-antigen varicella vaccine administered 4–8 weeks apart. Serologic testing of adults with an uncertain or negative history of varicella may be cost-effective.
- Second-dose catch-up varicella vaccination is recommended for children, adolescents, and adults who previously received 1 dose.
- Healthcare workers without laboratory evidence of immunity to varicella, laboratory confirmation of disease, or provider-confirmed history of varicella or herpes zoster should receive 2 doses of varicella-containing vaccine. See Chickenpox for Healthcare Professionals (https://www.cdc.gov/chickenpox/hcp/index.html) for more guidance for healthcare workers.
- Evidence of immunity to varicella should be required for children and adults entering or working in childcare, school, college, other post-high school educational institutions, and healthcare settings.

- 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.
- Vaccination should be considered for HIV-infected children with age-specific CD4+ T-lymphocyte counts of 15% or higher and without evidence of varicella immunity; eligible children should receive 2 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 may be considered. Combination MMRV vaccine should not be administered as a substitute for the component vaccines when vaccinating HIV-infected children.
- A 2-dose vaccination policy is recommended for outbreak control. Persons without evidence of immunity or those who had received 1 dose of varicella vaccine should be offered vaccine.

Contraindications:[31]

- 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.
- A family history of congenital or hereditary immunodeficiency in first-degree relatives (e.g., parents and siblings) unless the immune competence of the potential vaccine recipient has been demonstrated. Hypogammaglobulinemia and dysgammaglobulinemia are contraindications for MMRV administration.
- 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.[81]
- Pregnancy. Varicella vaccination is contraindicated during pregnancy. Women should avoid pregnancy for 1 month after receiving a dose of varicella vaccine. To monitor pregnancy outcomes of women inadvertently vaccinated with VZV-containing vaccines immediately before or during pregnancy, Merck and CDC established the Merck/CDC Pregnancy Registry for VZV-Containing Vaccines in 1995. This registry was closed as of October 16, 2013.[82] During 1995 through March 2012, the pregnancy registry received 860 prospective and 68 retrospective reports and no cases of congenital varicella syndrome or other patterns of birth defects were reported, although a small risk cannot be excluded.[82, 83] New cases of exposure immediately before or during pregnancy or other adverse events after vaccination with Varivax, ProQuad, or Zostavax, should be reported to Merck (telephone, 1-877-888-4231) and to the Vaccine Adverse Event Reporting System (https://vaers.hhs.gov/index).

Precautions:

- Severe illness. Vaccination of persons with severe illness should be postponed until recovery.
- Because of the potential inhibition of the response to varicella vaccination by passively transferred antibodies, varicella vaccine should not be administered for 3–11 months, depending on dosage, after administration of blood (except washed red blood cells), plasma, or immune globulin. In addition, varicella vaccine should not be administered for at least 5 months after administration of VZIG. Persons who have received varicella vaccine should not be given antibody-containing product for 2 weeks after vaccination unless the benefits exceed those of vaccination.
- Leukemic children who do not have evidence of immunity, are in remission, have restored immuno-competence and whose chemotherapy has been discontinued for at least 3 months can receive live virus vaccines. It is prudent that vaccination be undertaken with expert guidance and with the availability of antiviral therapy in case complications occur.
- The manufacturer recommends that salicylates (i.e., aspirin and related medications) should not be used for 6 weeks after receiving varicella vaccine because of the association between aspirin use and Reye syndrome following varicella disease. Vaccination with subsequent close monitoring should be considered for children who have rheumatoid arthritis or other conditions that require therapeutic aspirin.
- A personal or family (i.e., sibling or parent) history of seizures of any etiology is a precaution for MMRV administration.

X. Establishing or Enhancing Surveillance

Varicella surveillance is needed to facilitate public health action at the state and local level and to monitor the impact of the varicella immunization program. Several approaches may be used to monitor trends in varicella disease burden. States should consider their surveillance strengths and build varicella surveillance into an existing system where feasible.

Case investigation

Although investigation of all cases of varicella may not be feasible in all settings in all states, action may be required to prevent transmission to persons without evidence of immunity to varicella who are at high risk of serious complications of varicella.[31] 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 2-dose varicella vaccine coverage. For more information or for assistance with case, outbreak, and death investigations, the state health department should be contacted. Varicella postexposure prophylaxis of contacts should also be considered.[31]

Outbreak investigation

Although varicella vaccination coverage has increased and disease incidence has declined, outbreaks of varicella are still occurring. Institution of 2 doses routinely in the United States has substantially reduced the number of school outbreaks that were occurring among children who had received only 1 dose. Elementary schools are now the most common sites for varicella outbreaks, although outbreaks occur in middle and high schools. Because younger children are targeted for 2-dose vaccination, a higher proportion of older children and adolescents may have escaped exposure and vaccination at a younger age or did not receive a catch-up second dose and may thus be at risk for disease. Additionally, despite low susceptibility among adults (generally less than 5%), outbreaks have been reported from a variety of adult settings, including correctional facilities, hospitals, military training facilities, refugee centers, immigration detention facilities, homeless shelters, other residential institutions, and cruise ships. Outbreak response is particularly important in settings that present the greatest risk for severe disease (e.g., healthcare settings). Additionally, with implementation of the 2-dose varicella vaccine policy, investigations of outbreaks provide data to monitor the effectiveness of the varicella vaccination program.

Investigations of outbreaks of vaccine-preventable diseases help determine whether outbreaks are occurring because of failure of vaccine (lower than expected vaccine effectiveness) or failure to vaccinate (low vaccine coverage rates and therefore high susceptibility). Investigations of varicella outbreaks will:

- improve existing knowledge of the epidemiology of varicella;
- identify virus transmission patterns;
- describe disease burden;
- determine risk factors for severe varicella;
- provide additional estimates of varicella vaccine effectiveness; and
- describe risk factors for vaccine failure.

For more information about strategies for the investigation and control of varicella outbreaks view the varicella outbreak manual (https://www.cdc.gov/chickenpox/outbreaks/control-investigation.html). Reporting of varicella outbreaks is also important to help monitor impact of the 2-dose varicella vaccination recommendation. A worksheet for reporting varicella outbreaks is available in Appendix 20 (at https://www.cdc.gov/vaccines/pubs/surv-manual/appx/appendix20-varicella-surv-wksht.pdf).

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