Chapter 17: Varicella

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I. Disease Description

Varicella (chickenpox) is a febrile rash illness resulting from primary infection with the varicella-zoster virus (VZV). Humans are the only source of infection for this virus. Varicella is highly infectious, with secondary infection occurring in 61%–100% of susceptible household contacts.[1–5] Transmission occurs from person to person by direct contact with persons with either varicella or herpes zoster (shingles) lesions or by airborne spread from respiratory secretions or lesions of persons with chickenpox. The incubation period for varicella is 10–21 days, most commonly 14–16 days. Varicella is characterized by a pruritic, maculopapular vesicular rash that evolves into noninfectious dried crusts over a 5- to 6-day period.[6]

Varicella severity and complications are increased among immunocompromised persons, children younger than 1 year of age, and adults.7–10 However, healthy children and adults may also develop serious complications and even die from varicella.[8–15] Severe complications include secondary bacterial infections (most notably those caused by group A beta-hemolytic *Streptococcus*, e.g., cellulitis, necrotizing fasciitis, septicemia, and toxic shock syndrome), pneumonia, encephalitis, cerebellar ataxia, Reye syndrome, and death.[7]

Congenital varicella syndrome, characterized by hypoplasia of an extremity, skin abnormalities, encephalitis, microcephaly, ocular abnormalities, mental retardation, and low birth weight, may occur among 0.4%–2.0% of infants born to women infected with varicella during the first or second trimester of pregnancy.[16–18] Infants born to women who develop varicella within the period of 5 days before delivery to 2 days after delivery are at risk of neonatal varicella, which may be severe.

Immunity following varicella infection is considered to be long-lasting and second cases of varicella are thought to be rare. However, second cases may occur more commonly among immunocompetent persons than previously considered.[19, 20]

VZV remains in a latent state in human nerve tissue and reactivates in approximately one in three infected persons during their lifetime, resulting in herpes zoster.[21, 22, 23] Herpes zoster usually presents as a vesicular rash with pain and itching in a dermatomal distribution. Herpes zoster incidence increases with increasing age, especially after age 50, is more common among immunocompromised persons, and among children with a history of intrauterine varicella or varicella occurring within the first year of life; the latter have an increased risk of developing herpes zoster at an earlier age.[24–26] A decline or a relative absence of cell-mediated immunity is considered to be an important factor in development of herpes zoster in these groups. A zoster vaccine (Zostavax™, Merck & Co., Inc.) is licensed and recommended for adults 60 years of age and older in the United States.[23]

II. Background

Before the availability of varicella vaccine in the United States, almost everyone had varicella. Thus, the number of cases approximated the birth cohort over time, and in the early 1990s (the prevaccine era) this resulted in an average of 4 million cases of varicella, 10,500–13,000 hospitalizations (range, 8,000–18,000), and 100–150 deaths each year.[10, 27-30] Varicella affected mainly children, with approximately 90% of cases occurring before the age of 15 years. In the 1970s and 1980s, the highest rates of disease were among children 5–9 years of age, followed closely by children 1–4 years of age.[8] In the 1990s, the highest rate of disease was reported in the preschool age group. This might have been due to increasing attendance at child care and preschool.[31-32]

Varicella vaccine was licensed in 1995. Two doses are now recommended for routine use, with the first dose given to infants 12–15 months of age and the second dose to children 4–6 years of age. Persons 13 years of age and older without evidence of immunity to varicella should also routinely receive two doses of varicella vaccine 4–8 weeks apart.[33] One-dose varicella

vaccination coverage among children 19–35 months of age was 89.6% nationally in 2009, with state and city estimates ranging from 76% to 95%.[34] In active surveillance areas, varicella vaccination coverage among children age 19–35 months has risen to 92%, and varicella disease incidence declined approximately 90% from 1995 to 2005.[35] Among the states that in the prevaccine era consistently reported a high proportion of varicella cases to the National Notifiable Disease Surveillance System (NNDSS) relative to their birth cohort (West Virginia, Illinois, Texas, and Michigan), a 41% to 81% decline in cases has been reported as of 2009. In reports of varicella as the underlying cause of death, national varicella mortality rates among children younger than 10 years of age declined by 90% comparing the period of 1990-1994 to 1999-2001.[36] During 2000-2006, national varicella-related hospitalization rates declined by 71% compared with rates during the period 1988–1995.[37]

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

III. Importance of Rapid Case Identification

Reporting of varicella cases in child care centers, schools, institutions, military barracks and other group settings will facilitate public health action and outbreak control. In addition, in certain high-risk settings (e.g., hospitals and other healthcare settings, schools that may have students who are immunocompromised), rapid case identification and public health action are important to prevent infection of susceptible persons at high risk for serious complications of varicella, such as immunocompromised persons and pregnant women, and susceptible individuals for whom varicella vaccine is contraindicated.[33]

IV. Importance of Surveillance

Surveillance data are needed to

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

With vaccine coverage increasing and the disease burden declining, varicella disease surveillance is especially important to monitor changes in varicella epidemiology. All states should establish or enhance varicella case-based surveillance to monitor these changes. Surveillance data will be used to assess progress towards the year 2020 disease reduction goals, and determine whether any improvements to the vaccination policy are needed. *Healthy People 2020* goals for varicella include a greater than 80% reduction in the estimated number of varicella cases among children < 18 years of age compared to 2008, greater than 90% vaccine coverage among children 19–35 months, greater than 95% vaccination coverage with 2 doses of varicella vaccine among children in kindergarten, and greater than 90% 2-dose vaccine coverage among adolescents.[39]

V. Case Definition

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

Varicella clinical case definition

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

Laboratory criteria for diagnosis

- Isolation of varicella-zoster virus (VZV) or demonstration of VZV DNA by direct fluorescent antibody (DFA) or by polymerase chain reaction (PCR) tests from a clinical specimen, ideally scabs, vesicular fluid, or cells from the base of a lesion [See the following website for more details: http://www.cdc.gov/shingles/lab-testing/index.html.] These tests are also useful for diagnosing breakthrough disease (Table 1).
- Positive serologic test for varicella-zoster IgM antibody using a capture assay
- Fourfold or greater rise in serum varicella IgG antibody titer by any standard serologic assay

For both unvaccinated and vaccinated persons, DNA detection methods (PCR, DFA) and culture are the methods of choice for laboratory confirmation. Of these, **PCR is the most reliable and sensitive method for confirming infection.**

In unvaccinated persons, experience is limited with IgM antibody tests and with timing of the IgM response. In vaccinated persons, even less experience with serologic methods for laboratory confirmation is available. Therefore, DNA detection methods are the laboratory methods of choice for diagnosis. A negative IgM result should not be used to rule out the diagnosis. A positive IgM in the absence of rash should not be used to confirm a diagnosis. A fourfold rise in IgG antibody may not occur in vaccinated persons.

Varicella case classification

Probable: A case that meets the clinical case definition, is not laboratory confirmed, and is not epidemiologically linked to another probable or confirmed case.

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

Note: *Two probable cases that are epidemiologically linked are considered confirmed, even in the absence of laboratory confirmation.*

Varicella deaths case classification

Probable: A probable case of varicella that contributes directly or indirectly to acute medical complications that result in death.

Confirmed: A confirmed case of varicella that contributes directly or indirectly to acute medical complications that result in death.

Other definitions

Varicella-like (vaccine) rash: A varicella-like rash in a recently vaccinated person that may be caused by either wild- or vaccine-type virus. Approximately 4% of children receiving varicella vaccine (compared with 2% of placebo recipients) develop a generalized rash with a median of five lesions 5–26 days postvaccination, and 4% develop a localized rash with a median of two lesions 8–19 days postvaccination.[43] The rash may be atypical in appearance (maculopapular with no vesicles). Approximately 2% of children who received a placebo in the clinical trials also developed generalized rashes, some of which were varicella-like, indicating that not all rashes following vaccination are attributable to the vaccine.[43] Rash occurring within 2 weeks of or more than 42 days after vaccination are more likely to be wild-type virus, and rash occurring 15–42 days postvaccination are more likely to be vaccine-type virus.[44] Attribution of disease to vaccine strain VZV can only be confirmed by strain differential real-time PCR or by PCR combined with restriction fragment length polymorphism (RFLP) analysis.

Breakthrough disease: A case of wild-type varicella infection occurring more than 42 days after vaccination. Such disease is usually mild with a shorter duration of illness, fewer constitutional symptoms, and fewer than 50 skin lesions. Breakthrough cases with fewer than 50 lesions have been found to be one third as contagious as varicella in unvaccinated persons with 50 or more lesions, but breakthrough cases with 50 or more lesions can be just as contagious as cases in unvaccinated persons.[45]

Secondary transmission of vaccine virus: A varicella-like rash occurring 10–21 days after exposure to a person recently vaccinated. It is extremely rare. Since 1995, only eight secondary cases of transmission of vaccine virus from seven vaccinees have been documented with the varicella (Oka/Merck) vaccine, five of which occurred in e immunocompetent people. Most secondary transmissions occur from vaccine recipients who develop at least a limited rash illness. One case of secondary transmission was reported from a woman vaccinated post-partum who developed no vaccine rash to her infant. All laboratory-confirmed cases of Oka vaccine secondary transmission have resolved without complications. Transmission of vaccine strain VZV can only be confirmed by strain differential real-time PCR or by PCR combined with restriction fragment length polymorphism analysis. In addition to these episodes, there have been two reports of transmitted vaccine virus from herpes zoster that occurred 5 months after varicella vaccination.

Evidence of immunity to varicella

Evidence of immunity to varicella includes any of the following:[34]

1. Documentation of age-appropriate vaccination
   - Preschool-aged children 12 months of age or older: 1 dose
   - School-aged children, adolescents, and adults: 2 doses
   - For children younger than 13 years of age, the minimum interval between the two doses is 3 months. However, if the child received the first dose before age 13 years and the interval between the two doses was at least 28 days, the second dose is considered valid.
2. Laboratory evidence of immunity or laboratory confirmation of disease
   - Commercial assays can be used to assess disease-induced immunity, but they lack sensitivity to always detect vaccine-induced immunity (i.e., they may yield false-negative results).
3. Born in the United States before 1980
   - For healthcare workers, immunocompromised persons, and pregnant women, birth before 1980 should not be considered evidence of immunity.
4. A healthcare provider diagnosis of varicella or verification of history of varicella disease
   - Verification of history or diagnosis of typical disease can be done by any healthcare provider (e.g., school or occupational clinic nurse, nurse practitioner, physician assistant, physician). For persons reporting a history of or presenting with atypical and/or mild cases, assessment by a physician or designee is recommended and either one of the following should be sought: a) an epidemiologic link to a typical varicella case or laboratory-confirmed case, or b) evidence of laboratory confirmation, if testing was performed at the time of acute disease. When such documentation is lacking, persons should not be considered as having a valid history of disease, because other diseases may mimic mild, atypical varicella.
5. History of herpes zoster based on healthcare provider diagnosis.

VI. Laboratory Testing

As varicella disease has declined with introduction of vaccine, the need for laboratory confirmation has grown because fewer physicians have direct experience with breakthrough infections, which are often atypical in appearance, result in fewer lesions, and may lack characteristic vesicles. Varicella hospitalizations and deaths, as well as other severe or unusual disease, should routinely be laboratory confirmed. Postvaccination situations for which specimens should be tested include 1) rash with more than 50 lesions occurring 7 to 42 days

after vaccination; 2) suspected secondary transmission of the vaccine virus; 3) herpes zoster in a vaccinated person; or 4) any serious adverse event. In an outbreak, it is recommended that three to five cases be confirmed, regardless of vaccination status. The preferred diagnostic tests to confirm varicella infection include DNA detection methods for virus identification. For additional information on laboratory support for vaccine-preventable disease surveillance, see Chapter 22, "Laboratory Support for Surveillance of Vaccine-Preventable Diseases."

Specimen collection

Skin lesions are the preferred specimen for laboratory confirmation of varicella disease. Blood specimens are preferred to test for varicella immunity. Specimens from skin lesions are best collected by unroofing a vesicle, preferably a fresh fluid-filled vesicle, and then rubbing the base of a skin lesion with a polyester swab. Scabs from skin lesions are also optimal specimen types for PCR detection of VZV DNA. Other specimen sources such as nasopharyngeal secretions, saliva, blood, urine, bronchial washings, and cerebrospinal fluid are considered less desirable sources than vesicular fluid and skin lesions since they are less likely to give positive results. Collecting skin lesion specimens from breakthrough cases can be especially challenging because the rash is often maculopapular with few or no vesicles. A video demonstrating the techniques for collecting various specimens for varicella confirmation, including specimens from breakthrough cases, can be found at http://www.cdc.gov/shingles/lab-testing/collecting-specimens.html#video. Additional information about collecting and submitting specimens for testing can be found on the CDC shingles web site or by calling the National VZV laboratory at 404-639-0066 or 404-639-2192 or emailing dds1@cdc.gov or kjr7@cdc.gov.

Virus isolation and identification

Table 1 provides a summary of the laboratory tests used for varicella, the types of specimens appropriate for each test, and comments about the tests. Further details about the most commonly used laboratory tests for varicella are provided below.

Rapid varicella zoster virus identification:

- **PCR.** PCR is the method of choice for rapid clinical diagnosis. This test is sensitive, specific, and widely available. Results are available within several hours. PCR is a powerful technique that permits the rapid amplification of specific sequences of viral DNA that would otherwise be present in clinical specimens at concentrations well below detectable limits.
- **DFA.** If PCR is not available, the DFA test can be used, although it is less sensitive than PCR and requires more meticulous specimen collection and handling. A vesicle should be unroofed and scrubbed with sufficient vigor to ensure that cellular matter is collected at the base. Care must also be taken to avoid bleeding from the lesion as serum antibodies can interfere with the test and generate false-negative results. Crusts from lesions are not suitable for use with DFA.

Because viral DNA persists after cessation of viral replication or after viral death, DFA or PCR may be positive when viral cultures are negative.

Virus strain identification: Methods are available in specialized laboratories to identify VZV strains and distinguish wild-type VZV from the vaccine (Oka/Merck) strain. Such testing is used in situations when it is important to distinguish wild-type from vaccine-type virus, e.g., in suspected vaccine adverse events. The National VZV Laboratory at CDC has the capacity to distinguish wild-type VZV from Oka strain using both strain differential real-time PCR or PCR combined with restriction fragment length polymorphism analysis.

Virus culture: The diagnosis of VZV infection may be confirmed by culture (isolation) of VZV. Newer, more sensitive and rapid culture techniques can provide results within 2–3 days, although they are less sensitive than PCR. Infectious VZV is usually recoverable from fluid from varicella lesions for 2–3 days and from zoster lesions for 7 days or longer. VZV may be cultured from other sites such as blood and cerebrospinal fluid, especially in immunocompromised patients. Viable VZV cannot be recovered from crusted lesions.

Serologic testing: Serologic tests are available for confirmation of disease. They include capture IgM or fourfold rise from acute- and convalescent-phase IgG antibodies to VZV. Testing using commercial kits for IgM antibody is not recommended because available methods lack sensitivity and specificity; false-positive IgM results are common in the presence of high IgG levels. The National VZV Laboratory at CDC has developed a reliable IgM capture assay. Paired IgG acute- and convalescent-phase antibody tests are used in situations of mild or atypical presentation of disease when immediate therapy is not indicated and when, for clinical reasons, a confirmed diagnosis of the acute illness is important, e.g., a suspected second infection due to varicella. In addition, the laboratory at CDC has developed an IgG avidity assay, which can be used to identify recent primary VZV infection using a single VZV IgG-seropositive serum specimen.

Single serologic IgG tests may be used to determine the immune status of persons whose history of varicella is negative or uncertain and who may be candidates for varicella zoster immune globulin (VZIG) or vaccination. Commercial ELISAs are recommended for the purpose of screening.[46] Routine testing for varicella immunity following vaccination is not recommended. Commercially available serologic IgG tests are not sufficiently sensitive to detect low levels of antibody following vaccination. There is evidence to suggest that the latex agglutination method, another method to test for serologic IgG, may result in false-positive results that could mistakenly categorize a susceptible person as immune.[47]

Table 1. Laboratory tests available for varicella confirmation

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

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

VII. Reporting

Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.[48] These regulations and laws list the diseases to be reported and describe those persons or institutions responsible for reporting, including healthcare providers, hospitals, laboratories, schools, child care facilities, and other institutions. Persons reporting should contact the state health department for state-specific reporting requirements.

Varicella deaths

In 1998, the Council of State and Territorial Epidemiologists recommended that varicella-related deaths be placed under national surveillance,[42] and varicella-related deaths became nationally notifiable on January 1, 1999.

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

Because varicella is preventable with vaccine, all deaths due to varicella should be investigated. Investigation may provide insight into risk factors for varicella mortality and may help identify missed opportunities for, and barriers to, vaccination. A worksheet is provided to guide varicella death investigations (see Appendix 19). Deaths should be reported to CDC/NCIRD/DVD/Epidemiology Branch (404-639-8230) and to NNDSS via the National Electronic Telecommunications Surveillance System (NETSS) or the National Electronic Disease Surveillance System (NEDSS), when available.

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

- Demographic information
  - Name
  - Address
  - Date of birth
  - Age
  - Sex
  - Ethnicity
  - Race
  - Country of birth
  - Date of death
- Medical history
  - Pre-existing medical conditions
  - History of varicella (to distinguish varicella from herpes zoster)
  - Medications
- Vaccination status
  - Number of doses of varicella or herpes zoster vaccine
  - Date(s) of vaccination
  - Type and manufacturer of vaccine
  - If not vaccinated, reason

- Clinical data
  - Date of rash onset
  - Hospitalization, date of hospital admission
  - Postmortem examination results
  - Death certificate diagnoses
- Complications
  - Pneumonia
  - Infections (e.g., invasive group A beta-hemolytic streptococcal [GAS], cellulitis, sepsis, necrotizing fasciitis, other)
  - Encephalitis
  - Neurologic condition (specify)
  - Hemorrhagic condition (specify)
  - Reye syndrome
- Treatment
  - Medications given (e.g., antiviral drugs, VZIG, aspirin, nonsteroidal anti-inflammatory drugs)
  - Duration of therapy
- Laboratory information
  - Virus isolation test dates and results
  - PCR test dates and results
  - DFA test dates and results
  - Serology test dates and results
- Epidemiologic information
  - Transmission setting
  - Source of transmission (e.g., age, vaccination status, relationship to decedent)

Varicella case reporting

In 2002, CSTE recommended that varicella be included in NNDSS. All states were encouraged to conduct ongoing varicella surveillance to monitor vaccine impact on morbidity.[49] States are encouraged to report varicella cases to NNDSS via NETSS or NEDSS. As of 2010, 36 states were conducting case-based varicella surveillance. Persons reporting should contact the state health department for state-specific reporting requirements.

Individual case reporting: States not conducting case-based surveillance are encouraged to progressively implement individual case reporting. This can be done by establishing statewide or sentinel surveillance. Statewide surveillance involves adding varicella to the list of notifiable diseases that are reported to the state health department. Sentinel site surveillance involves identifying sites such as schools, child care centers, physicians' practices, hospitals, colleges, and other institutions to perform surveillance for varicella. Sentinel sites can be limited to a geographic area, such as a county or city, or selected to be representative of the entire state population. States may also consider requesting reports from sites that already participate in other surveillance networks. Some states have initiated surveillance using sentinel or school-based surveillance even though statewide case reporting is not required. States can expand their number of sites as they develop their system with the intention of eventually having statewide surveillance.

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

- Age—to monitor the impact of vaccination on disease reduction in specific age groups and any shift in disease to older persons.

- Varicella vaccination status—to determine the proportion of cases occurring in vaccinated persons and assess crude vaccine effectiveness.
- Number of varicella vaccine doses received – to monitor number of cases with one, two, or no doses of vaccine.
- Severity of disease—to assess the severity of varicella in vaccinated persons, to monitor the impact of vaccination on disease severity, and to determine if vaccine-induced immunity wanes over time (based on number of lesions)
  - Number of lesions:
    - Mild: fewer than 50 lesions
    - Mild/moderate: 50–249 lesions
    - Moderate: 250–499 lesions
    - Severe: 500 or more lesions or any complications such as bacterial superinfection, varicella pneumonitis, encephalitis, hospitalization, or death.
  - Hospitalization

Additional information to collect can include the following:

- Demographic information
  - Name
  - Address
  - Date of birth
  - Sex
  - Ethnicity
  - Race
  - Country of birth
- Reporting source
  - County
  - Earliest date reported
- Clinical data
  - Pre-existing medical conditions
  - History of varicella (to distinguish varicella from herpes zoster or to document reported second infections)
  - Medications
  - Dates of rash onset
  - Duration of rash
  - Symptoms and date of onset
  - Complications
- Vaccination status
  - Date(s) of vaccination
  - Type and manufacturer of vaccine
  - Vaccine lot number
  - If not vaccinated, reason
- Outcome (patient survived or died)
  - Date of death
- Epidemiologic data
  - Transmission setting
  - Source of transmission
  - Vaccination status of source patient

- Laboratory information
  - Virus isolation test dates and results
  - PCR test dates and results
  - DFA test dates and results
  - Serologic test dates and results

CDC has designed a worksheet to provide guidance for individual varicella case investigations (see Appendix 20).

Varicella Outbreaks

Although varicella outbreaks are not nationally notifiable, states are encouraged to report varicella outbreaks to CDC on an annual basis. The information is important for understanding the epidemiology of varicella and monitoring the impact of the routine two dose varicella vaccination program. An example of the varicella outbreak reporting worksheet can be found online here (http://www.cdc.gov/vaccines/vpd-vac/varicella/outbreaks/appx.htm#a). Reporting worksheets can be faxed to CDC/NCIRD/DVD/Epidemiology Branch (404-639-8665)

The following data are epidemiologically important. Additional information may be collected at the direction of the state health department.

- Outbreak setting
- Outbreak duration
- Outbreak size (i.e., # varicella cases)
- Ages of cases
- Vaccination status of cases
- Number of laboratory confirmed cases

VIII. Vaccination

Two varicella-containing vaccines are now available in the United States. The live attenuated single-antigen varicella vaccine (Varivax®, Merck & Co., Inc.) was licensed in March 1995. A combination varicella-containing vaccine, Measles, Mumps, Rubella, Varicella (MMRV) (ProQuad®, Merck & Co., Inc.), was licensed in 2005 for use in children 12 months through 12 years of age. Because of the thermolability of the vaccines, the manufacturer's requirements for maintaining the cold chain must be followed strictly. Vaccine that is not properly stored before administration could have suboptimal potency.[33, 50]

Prelicensure studies of one dose of varicella vaccine, using various vaccine formulations, showed vaccine efficacy ranging from 70% to 90% for all disease and greater than 95% for severe disease.[4, 51, 52] Postlicensure studies under conditions of community use have demonstrated vaccine effectiveness in the range of 80%–85% for prevention of all disease. However, several lower estimates (40%–59%), and some higher estimates (100%) have been reported.[53-59]

The efficacy of two doses of varicella vaccine was evaluated in a randomized clinical trial. Over a 10-year observation period, the estimated vaccine efficacy of two doses was 98.3% compared with 94.4% for one dose. The difference was statistically significant ($p<0.001$).[60] A second dose of vaccine reduced varicella attack rates by 3.3-fold.[60] A case control study evaluating the effectiveness of two doses found the 2-dose vaccine effectiveness to be 98.3% [61], similar to what was seen in the clinical trial. The two dose vaccine effectiveness estimate calculated from an outbreak investigation was found to be lower, 89%.[62] High two-dose vaccine coverage should greatly decrease outbreaks that have been reported among groups of school children with high vaccination coverage.

Recommendations for the use of varicella-containing vaccines[33]

Routine administration of two doses of live attenuated varicella virus–containing vaccine:

- All children should routinely receive their first dose at 12–15 months of age. The second dose is recommended routinely when children are aged 4–6 years (i.e., before a child enters kindergarten or first grade), but can be administered at an earlier age provided the interval between the first and second dose is at least 3 months.
- Persons 13 years of age or older without evidence of varicella immunity should receive two doses of single-antigen varicella vaccine administered 4–8 weeks apart. Serologic testing of adults with an uncertain or negative history may be cost-effective.
- Healthcare workers without laboratory evidence of immunity to varicella, laboratory confirmation of disease, or provider-confirmed history of varicella or herpes zoster should receive two doses of varicella-containing vaccine.
- Documentation of vaccination or evidence of immunity to varicella should be required for children and adults entering or working in child care, school, college, other post–high school educational institutions, and healthcare settings.
- Second-dose catch-up varicella vaccination is recommended for children, adolescents, and young adults who previously received one dose.
- Prenatal assessment of women for evidence of varicella immunity is recommended. Upon completion or termination of their pregnancy, women without evidence of varicella immunity should receive a first dose of varicella vaccine before discharge from the hospital, birthing center, or healthcare facility. The second dose can be given 4 or more weeks after the first dose (e.g., at the postpartum visit). Postpartum vaccination need not be delayed because of breastfeeding.
- Asymptomatic or mildly symptomatic HIV-infected children in CDC clinical class N, A, or B with age-specific CD4+ T-lymphocyte counts of higher than 15% and without evidence of varicella immunity may receive two doses of single-antigen varicella vaccine 3 months apart. Data on the use of varicella vaccine in older HIV-infected persons are lacking. However, based on expert opinion, vaccination for HIV-infected adults with similar immune function should be considered.
- A two-dose vaccination policy is recommended for outbreak control. Persons without evidence of immunity or those who received one dose of varicella vaccine should be offered vaccine.

Contraindications:[33]

- Allergy to vaccine components.
- Altered T-cell immunity from a malignant condition, including blood dyscrasias, leukemia, lymphomas of any type, other malignant neoplasms affecting the bone marrow or lymphatic systems, or HIV, except as discussed above.
- For children receiving high doses of systemic steroids (i.e., at least 2 mg/kg prednisone) for 2 weeks or longer, vaccination should be delayed until steroid therapy has been discontinued for at least 1 month, in accordance with the recommendations of ACIP for live-virus vaccines.[63]
- Pregnancy. Varicella vaccination is contraindicated during pregnancy. Women should avoid pregnancy for 1 month after receiving a dose of varicella vaccine. If a pregnant woman is inadvertently vaccinated, the incident should be reported to the Varivax in Pregnancy Registry at 1-800-986-8999. In the first 10 years of data collection, no reported cases of congenital varicella syndrome or other patterns of birth defects have been reported, although an extremely low risk cannot be excluded.[64]

Additional precautions:

- Severe illness. Vaccination of persons with severe illness should be postponed until recovery.
- Because of the potential inhibition of the response to varicella vaccination by passively transferred antibodies, varicella vaccine should not be administered for 3-11 months, depending on dosage, after administration of blood (except washed red blood cells), plasma, or IG. In addition, varicella vaccine should not be administered for at least 5 months after administration of VZIG. Persons who have received varicella vaccine should not be given antibody-containing product for 2 weeks after vaccination unless the benefits exceed those of vaccination.
- Vaccination of leukemic children who are in remission and who do not have evidence of immunity to varicella should be undertaken only with expert guidance and with the availability of antiviral therapy in case complications occur.
- Salicylates (i.e., aspirin and related medications) should not be used for 6 weeks after receiving varicella vaccine because of the association between aspirin use and Reye syndrome following varicella disease.

IX. Establishing or Enhancing Surveillance

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

Case investigation

Although investigation of all cases of varicella may not be feasible in all settings in all states, action may be required to prevent transmission to persons without evidence of immunity to varicella who are at high risk of serious complications of varicella.[33] In addition, investigation is warranted in some specific circumstances, including deaths associated with varicella, cases with severe complications such as invasive group-A streptococcal infections, outbreaks involving exposure of persons without evidence of immunity to varicella who are at high risk of serious complications of varicella, and outbreaks in populations with high two-dose varicella vaccine coverage. For more information or for assistance with case, outbreak, and death investigations, the state health department should be contacted. Varicella postexposure prophylaxis of contacts should also be considered.[33]

Outbreak investigation

Although varicella vaccination coverage has increased and disease incidence has declined, outbreaks of varicella continue to occur, increasingly among highly vaccinated populations. Elementary schools are now the most common sites for varicella outbreaks, although they continue to occur in daycare settings and in middle and high schools. Because younger children are targeted for vaccination, a higher proportion of older children and adolescents may have escaped exposure and vaccination at a younger age and thus be more vulnerable to disease. Additionally, despite low susceptibility among adults (generally less than 5%), outbreaks have been reported from a variety of adult settings, including correctional facilities, hospitals, military training facilities, refugee centers, immigration detention facilities, homeless shelters, other residential institutions, and cruise ships. Outbreak response is particularly important in settings that present the greatest risk for severe disease (e.g., healthcare settings). Additionally, with implementation of the two-dose varicella vaccine policy, investigations of outbreaks provide data to monitor the effectiveness of the varicella vaccination program.

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

1. improve existing knowledge of the epidemiology of varicella;
2. identify virus transmission patterns;

3. describe disease burden;
4. determine risk factors for severe varicella;
5. provide additional estimates of varicella vaccine effectiveness; and
6. describe risk factors for vaccine failure.

Information about strategies for the investigation and control of varicella outbreaks can be found at: http://www.cdc.gov/vaccines/vpd-vac/varicella/outbreaks/manual.htm. Reporting of varicella outbreaks is also important to help monitor impact of the two dose varicella vaccination recommendation. A worksheet for reporting varicella outbreaks is available in Appendix 20.

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