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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