Chapter 14: 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 rates in susceptible household contacts from 65%–86%. 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. 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.[1]

Varicella severity and complications are increased among immunocompromised persons, neonates, children less than 1 year of age, and adults.[2,3] However, healthy children and adults may also develop serious complications and even die from varicella.[3-6] Serious complications include secondary bacterial infections (most notably those caused by group A beta-hemolytic streptococcus including cellulitis, necrotizing fasciitis, septicemia, and toxic shock syndrome), pneumonia, encephalitis, cerebellar ataxia, Reye syndrome, and death.

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. 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 two trimesters of pregnancy.

Although immunity following varicella infection is considered to be long lasting, second cases of varicella do occur rarely among immunologically normal persons.[7] VZV remains in a latent state in human nerve tissue and reactivates in approximately 15% of infected persons, resulting in herpes zoster (shingles). Herpes zoster usually presents as a vesicular rash with pain and itching in a dermatomal distribution. This disease increases with increasing age 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 early age. Loss, or a relative absence, of cell-mediated immunity is considered to be the common factor in development of herpes zoster in these groups.

II. Background

Before the availability of varicella vaccine in the United States, almost everyone developed varicella. Thus, the number of cases approximated the birth cohort over time, resulting in the early 1990s in an estimated 4 million cases of varicella with approximately 11,000 hospitalizations and 100 deaths each year in the pre-vaccine era. 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.[2] In the 1990s, the highest rate of disease has been reported in the preschool age group. This may be due to increasing attendance at childcare and preschool.[8,9]

Varicella vaccine was licensed in 1995 and is recommended for routine use in infants 12–18 months of age and for susceptible older children, adolescents, and adults.[10,11] National vaccine coverage among children 19–35 months was 73% in 2000, with state and urban estimates ranging from 48%–87%.[12] In active surveillance areas, varicella disease incidence and hospitalizations have declined approximately 70%-80% from 1995 to 2000. During this same period, varicella vaccine coverage among children aged 19–35 months has risen to 74%–84% with some evidence of catch-up vaccination among older children.[13] Among state that have consistently reported a high proportion of cases to the National Notifiable Disease Surveillance System (NNDSS) relative to their birth cohort (e.g., West Virginia and Michigan), there has also been a reduction in cases noted during 1999, 2000, and 2001, consistent with findings from the active surveillance sites.

III. Importance of rapid identification

Although rapid case identification of all suspected cases of varicella is not feasible or necessary at this stage of the vaccination program, reporting of varicella outbreaks (in childcare centers, schools, institutions, barracks) will facilitate public health action. In addition, in certain high-risk settings (e.g., hospitals and other health-care settings), 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.[10]

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.

Surveillance data can be used to evaluate vaccine effectiveness under conditions of routine use. Increased use of vaccine among children has lowered the overall burden of disease. However, among the greatly reduced number of remaining cases, a higher proportion will occur among older children, adolescents and adults. Pre-licensure studies, using different vaccine formulations, showed vaccine efficacy ranging from 70% - 90% for all disease and > 95% for severe disease. Post-licensure studies under conditions of community use have demonstrated vaccine effectiveness most commonly in the range of 70% - 86% for prevention of all disease with several lower estimates (40% - 59%) and > 95% for severe disease.[14] However, in some settings field effectiveness may be affected by improper storage and handling of vaccine at any stage of the cold chain. While mild "breakthrough" varicella may be expected to occur in 10% - 20% of vaccinated children, the rate of varicella (mild or severe) among vaccinated children should be monitored; if the rate of breakthrough disease is higher than expected (e.g., ≥ 30%), the cause of the problem should be investigated.

Many states report aggregate varicella cases to NNDSS, and two states instituted case-based surveillance in 2001. 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 surveillance to monitor these expected changes. Surveillance data will be used to assess progress towards the year 2010 disease reduction goals.

Varicella deaths became nationally notifiable in 1999.

V. Disease reduction and vaccine coverage goals

Proposed Healthy People 2010 goals for varicella include: > 90% reduction in the current number of varicella cases, > 90% vaccine coverage among children 19–35 months, and > 95% vaccine coverage among children at school entry.[15]

VI. Case definitions

The following case definitions were approved by the Council of State and Territorial Epidemiologists (CSTE) for varicella in June 1999[16] and for varicella deaths in 1998.[17]

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 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

- Positive serologic test for varicella-zoster immunoglobulin M (IgM) antibody
- Isolation of varicella-zoster virus (VZV), demonstration of VZV antigen by direct fluorescent antibody (DFA) or by polymerase chain reaction (PCR) tests from a clinical specimen
- Significant rise in serum varicella immunoglobulin G (IgG) antibody level by any standard serological assay

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 definition and case classification

The following surveillance definitions are proposed and use existing public health surveillance definitions for 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) rashes. While varicella remains a fairly common disease, a varicella-like rash in a recently vaccinated person may be caused by either wild- or vaccine-type virus. Approximately 4% of children receiving varicella vaccine develop a generalized rash (as compared with 2% of placebo recipients),[18] with a median of five lesions 5–26 days post vaccination, and 4% develop a localized rash, with a median of two lesions, 8–19 days post vaccination. The rash may be atypical in appearance (maculopapular with no

vesicles). However, approximately 2% of children who received a placebo in the clinical trials also developed varicella-like rashes, indicating that not all rash following vaccination is attributed to the vaccine. Rash occurring within 7 or > 42 days of vaccination should be considered wild-type virus, and rash occurring 7–42 days post vaccination may be due to either wild- or vaccine-type virus. Attribution of disease to 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. Breakthrough disease is defined as 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 may be less infectious than varicella in unvaccinated persons because of the lower number of lesions, though isolated cases have been found to be highly infectious.

Secondary transmission of vaccine virus. Secondary transmission of vaccine virus is defined as a varicella-like rash occurring 10–21 days after exposure to a person recently vaccinated. No transmission of vaccine virus has ever been documented from a person in the absence of vaccine rash. Since 1995, only 3 cases of transmission of vaccine virus from a healthy vaccinee to a healthy contact have been documented with the Oka/Merck vaccine. Transmission of vaccine strain virus can only be confirmed by strain differential real-time PCR or by PCR combined with RFLP.

VII. Laboratory testing

Laboratory testing for varicella is not routinely required but is indicated to confirm the diagnosis in severe or unusual cases or to determine varicella susceptibility. As varicella is the most common disease confused with smallpox, rapid laboratory confirmation of VZV diagnosis in cases of vesicular-pustular rash illness that fall into the category of "moderate risk" for smallpox according to the CDC algorithm is required. As disease continues to decline, laboratory confirmation will become standard practice. Diagnostic tests used to confirm recent varicella infection include virus isolation and identification, in addition to serologic tests. For additional information on laboratory support for vaccine-preventable disease surveillance, see Chapter 19, "Laboratory Support for Surveillance of Vaccine-Preventable Diseases."

Virus isolation and identification

- **Rapid varicella zoster virus identification.** Rapid virus identification techniques are indicated for a case with severe or unusual disease to initiate specific antiviral therapy. The direct fluorescent antibody (DFA) test is the method of choice for rapid clinical diagnosis. This test is sensitive, specific, and widely available. Results are available within several hours. Specimens are best collected by unroofing a vesicle, preferably a fresh fluid-filled vesicle, and then rubbing the base of a skin lesion with a polyester swab.

Crusts from lesions are also excellent specimens. Other specimen sources such as nasopharyngeal secretions, saliva, blood, urine, bronchial washings, and cerebrospinal fluid are considered less desirable sources than skin lesions since positive test results from such specimens are much less likely. Because viral proteins persist after cessation of viral replication, DFA may be positive when viral cultures are negative.

- **PCR.** PCR is a powerful technique that permits the rapid amplification of specific sequences of viral DNA that would otherwise be present in clinical specimens at concentrations well below detectable limits. Carefully designed RNA primers that target selected small stretches of viral DNA can be used to replicate small quantities of viral DNA extracted from clinical samples. If a PCR product of the expected size is produced, it is evidence that the virus was present in the lesion. This technique has been extended for VZV by amplifying pieces of varicella DNA that include a mutation in the base sequence that distinguishes the vaccine strain from wild-type varicella strains. Highly specific cutting enzymes (restriction endonucleases) can be selected that will cut the fragment from either wild-type strains or the vaccine strain, but not both. This provides a convenient means for discriminating between them. More recently, it has been possible to apply these methods to real-time PCR machines that permit direct, single-step discrimination of vaccine from wild-type on the basis of such indicators as the difference in temperature at which the strands from vaccine versus wild-type DNA fragments reanneal on cooling. This type of approach has reduced the time required to identify a vaccine adverse event from two days to several hours.

- **Virus strain identification.** Strain identification can distinguish wild-type VZV from the vaccine (Oka/Merck) strain using polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) analysis. Such testing is important in situations where it is important to distinguish wild-type from vaccine-type virus suspected vaccine adverse events. More recently, rapid real-time PCR methods using Light Cycler or TaqMan technology have made it possible to discriminate vaccine strain from wild-type VZV in a single tube assay requiring only a few hours. Post-vaccination situations for which specimens should be tested include 1) rash with more than 50 lesions ≥ 7 days after vaccination; 2) suspected secondary transmission of the vaccine virus; 3) herpes zoster in a vaccinated person; or 4) any serious adverse event. The National VZV Laboratory at CDC has the capacity to distinguish wild-type VZV from Oka strain using both conventional and real-time PCR methods. Call the National VZV laboratory at 404-639-0066, 404-639-3667, or email vzvlab@cdc.gov for details about collecting and submitting specimens for testing.

- **Virus culture.** The diagnosis of VZV infection may be confirmed by culture (isolation) of VZV. Although the virus is difficult to culture, virus isolation should be attempted in cases of severe disease, especially in immunocompromised persons, in order to confirm the diagnosis of varicella. Newer, more sensitive and rapid culture techniques may 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 CSF, especially in immunocompromised patients. Viable VZV cannot be recovered from crusted lesions.

- **Serologic testing.** For confirmation of disease a) IgM, and b) acute and convalescent IgG: Serological tests are available for IgM and IgG antibodies to VZV. Testing using commercial kits for IgM antibody is not recommended since available methods lack sensitivity and specificity; false positive IgM results are common in the presence of high IgG levels. The National VZV Laboratory at CDC has developed a reliable IgM capture assay. Call 404-639-0066, 404-639-3667, or email vzvlab@cdc.gov for details about collecting and submitting specimens for testing.

- **Testing susceptibles.** Single serological IgG tests may be used to identify the immune status of individuals whose history of varicella is negative or uncertain, and who may be candidates for varicella zoster immune globulin (VZIG) or vaccination. Paired acute and convalescent antibody tests are used in situations of mild or atypical presentation of disease when immediate therapy is not indicated and when, for clinical reasons, a confirmed diagnosis of the acute illness is important, e.g., a suspected second infection due to varicella. Recent evidence suggests that the latex agglutination method may result in false positive tests that could mistakenly categorize a susceptible person as immune; less sensitive commercial ELISAs are recommended for the purpose of screening.[19] Routine testing for varicella immunity following vaccination is not recommended.

VIII. Reporting

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

Reporting to CDC

Varicella deaths. In 1998, the Council of State and Territorial Epidemiologists recommended that varicella-related deaths be placed under national surveillance,[17] and varicella-related deaths became nationally notifiable on January 1, 1999.

Varicella deaths can be identified through death certificates, which may be available through the 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, health-care practitioners, and hospitals report varicella deaths that occur in their community.

All deaths due to varicella should be investigated to understand why a death resulted from this vaccine-preventable disease. The 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/NIP Varicella Activity (404-639-8230) and to NNDSS via the National Electronic Telecommunications Surveillance System (NETSS) or the National Electronic Disease Surveillance System (NEDSS), when available.

Information to collect

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 potentially distinguish varicella from herpes zoster)
  - Medications

- Vaccination status including:
  - Number of doses of varicella vaccine
  - Date(s) of vaccination
  - If not vaccinated, describe reason

- Clinical and epidemiological 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

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Information to collect (con't.)

  - Hemorrhagic
  - Reye syndrome

- Treatment including:
  - Medications given (e.g., antiviral drugs, VZIG, aspirin, non-steroidal anti-inflammatory drugs)
  - Duration of therapy

- Laboratory information including:
  - Virus isolation
  - PCR
  - DFA
  - Serology

- Epidemiological information including:
  - Transmission setting
  - Source of transmission (e.g., age, vaccination status, relationship to decedent)

Varicella case reporting

In 1999, CSTE recommended that all states carry out some form of ongoing systematic morbidity surveillance to monitor the impact of varicella vaccination on the incidence of varicella.[21] States are encouraged to report varicella cases to the NNDSS via the NETSS or NEDSS. Two states commenced case-based varicella surveillance in 2001. Contact your state health department for specific requirements in your state.

Although detailed investigation of all cases of varicella may not be feasible in all areas, action may be required to prevent transmission to susceptible persons at high risk of serious complications of varicella, such as might occur in a hospital setting.[10, 22] A worksheet has been designed to provide guidelines for varicella case investigations in these special circumstances (see **Appendix 20**).

IX. Vaccination

The Oka/Merck live attenuated varicella vaccine was licensed in the United States in March 1995. Because of the thermolability of the vaccine, 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.[10]

Recommendations for the use of varicella virus vaccine

For children, vaccine recommendations include the following:

- Routine administration of live attenuated varicella virus vaccine for children 12–18 months of age.
- Catch-up vaccination for children 19 months through 12 years.
- One dose of vaccine is **required** for children aged < 13 years. A positive history of varicella is considered reliable evidence of immunity.

For adolescents and adults, vaccination is desirable for all susceptible persons.[10] Specific vaccine recommendations for adolescents and adults include the following:

- For persons ≥ 13 years of age, the Advisory Committee on Immunization Practices (ACIP) recommends varicella vaccination for susceptible adolescents and adults who may have close contact with susceptible persons at high risk for serious complications (such as health-care workers and family contacts of immunocompromised persons).

- The ACIP also recommends varicella vaccination for those at increased risk of exposure or transmission (teachers of young children, childcare employees, residents and staff in institutional settings or correctional facilities; nonpregnant women of childbearing age; adolescents and adults living in households with children; and international travelers).[10,11]

- Adolescents ≥ 13 years of age and adults require 2 doses of varicella vaccine given 4 to 8 weeks apart. Serologic testing of adolescents and adults with an uncertain or negative history is likely to be cost-effective because 70%–90% of these individuals are likely to be varicella-immune.[10]

Contraindications[10]
Contraindications to varicella vaccine include the following:

- Allergy to vaccine components.
- Severe illness. Vaccination of persons with severe illness should be postponed until recovery.
- Altered immunity from a malignant condition, including blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.
- For children, conditions that require steroid therapy.

Additional precautions include:

- Vaccinees in whom vaccine-related rash develops, particularly health-care workers and household contacts of immunocompromised persons, should avoid contact with susceptible persons who are at high risk for severe complications.

- 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.
- Avoid the use of salicylates for 6 weeks after receiving varicella virus vaccine because of the association between aspirin use and Reye syndrome following varicella disease.

Varicella vaccination is contraindicated for all persons with moderate or severe cellular immunodeficiency due to human immunodeficiency virus (HIV) infection and is not recommended for adults who are HIV infected. However, vaccination should be considered for HIV-infected children if they have asymptomatic or mildly symptomatic HIV infection, in CDC class N1 or A1 with age-specific CD4+ T-lymphocyte percentages of > 25%. These children should receive two doses of varicella vaccine with a 3 month interval between the doses.

Varicella vaccination is contraindicated in pregnancy. Women should avoid pregnancy for 1 month after receiving a dose of varicella vaccine. If inadvertent vaccination of a pregnant woman occurs, the incident should be reported to the Varivax® in Pregnancy Registry at 1-800-986-8999. In the first 5 years of data collection, there have been no reported cases of congenital varicella syndrome or other patterns of birth defects although an extremely low risk cannot be excluded.[23]

Post-exposure use of varicella vaccine
The ACIP recommends the use of varicella vaccine for susceptible persons following exposure to varicella and for outbreak control as discussed below.[24]

X. Establishing or enhancing surveillance

Varicella vaccination coverage has now increased to > 70%, and in states and localities where vaccine coverage is in this range and surveillance is adequate to monitor disease trends, varicella disease is declining. In the June 2002 meeting, CSTE passed a resolution making varicella a nationally notifiable disease starting in 2003. Varicella surveillance is needed to facilitate public health action at the state and local level and 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 surveillance system where feasible.

Reporting aggregate cases by age group
States are encouraged to report aggregate case counts by age group for varicella to the National Notifiable Diseases Surveillance System (NNDSS). Reporting varicella by age group improves the ability to detect changes in age-specific incidence for varicella. Reporting sources could include schools, childcare centers, and health-care providers.

Conducting sentinel and school-based surveillance
Schools, childcare centers, physicians' practices, and hospitals should be encouraged to report aggregate case counts of varicella by age group or grade.

School reporting is influenced by the support of the principal, teachers, and secretarial staff, as well as parental awareness of the importance of reporting varicella to the school. Some states conduct sentinel or school-based surveillance even though statewide case reporting is not required. 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. Some states have started sentinel surveillance with plans to expand to statewide surveillance within several years.

Conducting individual case reporting

States are encouraged to progressively implement individual case reporting. This can be done by establishing statewide or sentinel surveillance. The following data are epidemiologically important and should be collected in the course of case investigation. Additional information may be collected at the direction of the state health department. Individual case reporting should include:

Information to collect

- Demographic information
  - Name
  - Address
  - Date of birth
  - Age
  - Sex
  - Ethnicity
  - Race
  - Country of birth

- Reporting source
  - County
  - Earliest date reported

- Clinical
  - Pre-existing medical conditions
  - History of varicella (to potentially distinguish varicella from herpes zoster)
  - Medications

- Vaccination status including:
  - Number of doses of varicella vaccine
  - Date(s) of vaccination
  - If not vaccinated, describe reason

- Clinical and epidemiological data
  - Dates of rash
  - Duration of rash
  - Rash presentation
  - Symptoms and date of onset
  - Hospitalizations

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Information to collect (con't.)

- Complications

- Outcome (case survived or died)
  - Date of death

- Laboratory
  - Serological test dates and results
  - Virus isolation date and result

- Vaccination status
  - Number of doses of varicella vaccine received
  - Dates of varicella vaccinations
  - Manufacturer of vaccine
  - Vaccine lot number
  - If not vaccinated, reason

- Epidemiological
  - Transmission setting
  - Source of transmission

- Laboratory information including:
  - Virus isolation
  - PCR
  - DFA
  - Serology

XI. Case investigation

Although investigation of all cases of varicella may not be feasible in all areas, action may be required to prevent transmission to susceptible persons at high risk of serious complications of varicella. In addition, investigation is warranted in some specific circumstances, including deaths associated with varicella, outbreaks involving exposure of potentially susceptible persons at high risk of serious complications of varicella, and documentation of severe complications such as invasive group-A streptococcal infections. Because of the stringent cold-chain requirements of this vaccine, an investigation should be considered when a high proportion of cases occur among vaccinated persons. For more information or for assistance with case, outbreak, and death investigations, contacts your state health department. For varicella post-exposure prophylaxis of contacts, see Section XII, "Outbreak investigation."

XII. Outbreak investigation

Childcare centers and schools are the most common sites for varicella outbreaks; children aged 1-9 years attending these facilities currently have the highest varicella susceptibility and disease incidence. Despite low susceptibility among adults (generally < 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. As vaccine coverage among young children increases and disease incidence declines, a higher proportion of older children and adolescents may escape exposure. When alerted of outbreaks in middle and high schools, states should evaluate whether further control measures are warranted. Investigation of outbreaks of vaccine-preventable diseases helps us to understand whether outbreaks are occurring due to the failure of vaccine (lower than expected vaccine effectiveness) or failure to vaccinate (low vaccine coverage rates and therefore high susceptibility). Investigation of varicella outbreaks can provide estimates of varicella vaccine effectiveness in different outbreak settings and may identify risk factors for vaccination failure. In the course of investigation, health authorities may use information on susceptibility and reliability of history of disease in order to develop an appropriate screening and vaccination policy for the affected population (e.g., correctional facilities, residential institutions, the military). Although varicella outbreaks are less common than in the pre-vaccine era, some will continue to occur, especially among children. State and local health departments may wish to focus investigation and control efforts on outbreak situations that present the greatest risk of severe morbidity from varicella (see **Table 1**).

A systematic approach to investigation and control of outbreaks includes confirming the outbreak, identifying susceptible persons, offering vaccine, establishing surveillance, analyzing data, and using data to make recommendations. These steps are outlined in **Table 2**.

Assessing vaccine effectiveness

Vaccine effectiveness can be evaluated by comparing rates of disease among vaccinated and unvaccinated persons in outbreak settings such as in schools, and childcare centers.[25] It is particularly important to evaluate whether varicella among vaccinated children is occurring at a rate higher than expected. To calculate vaccine effectiveness, varicella case patients, as well as non-case patients, should be interviewed for history of receipt of vaccine. Low vaccine effectiveness could indicate improper storage and handling of the vaccine, which has stringent cold-chain requirements.

Controlling outbreaks

Varicella vaccine is recommended by the ACIP for outbreak control.[11] Varicella vaccine, if administered within 72 hours and possibly up to 120 hours following

varicella exposure, may prevent or significantly modify disease.[24, 26, 27] If exposure to varicella does not cause infection, post-exposure 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.

The response to an outbreak may involve one or a combination of measures that include isolation of infected persons and vaccination with varicella vaccine either through a recommendation to parents or through outbreak control efforts offered by the health department. Vaccination during school outbreaks will shorten the duration of the outbreak.[28]

Isolation (exclusion) or cohorting of individuals with varicella until all of their lesions have crusted is routinely recommended for outbreak control. However, because substantial transmission of chickenpox occurs before rash onset, exclusion may have limited value as an outbreak control measure.[29] Exclusion is also recommended for exposed susceptible individuals who may be in contact with persons at high risk of serious complications (e.g., health-care workers, family members of immunocompromised persons). In these situations, exclusion is required for the duration of the period of communicability (i.e., from the 10th until the 21st day post-exposure).[10, 22]

In outbreaks involving children covered by childcare or school requirements, unvaccinated children with no history of varicella should be instructed to be vaccinated immediately or excluded from school for the duration of the period of communicability (i.e., from 10–21 days post exposure or for the duration of the outbreak).

For outbreaks in childcare centers and schools, the minimum public health response must include informing parents and caregivers of the occurrence of the outbreak, providing them with information on varicella and its potential to cause severe complications, and providing information about the availability of the vaccine. A sample letter to parents is provided in **Appendix 21**. This letter recommends that parents and caregivers contact their regular health-care provider to discuss the use of the vaccine for their child or for children under their care. To facilitate use of the vaccine, health departments may choose to send letters to all childcare facilities and elementary schools in the state encouraging vaccination of students. A Vaccine Information Statement (VIS) for varicella should be included with the letter.

In institutional outbreaks or outbreaks involving adolescents and adults, vaccination of susceptible persons should be strongly considered because it is likely to limit or control the outbreak by interrupting transmission. Health department personnel and officials in other institutions (health-care settings, correctional facilities) should evaluate available resources and consider vaccination of susceptible persons for outbreak control. Health-care personnel have increased potential for close contact with persons at high risk for developing severe disease and serious complications. Outbreak control should be

considered at any stage of an outbreak if there are remaining susceptible persons.

Using varicella vaccine and VZIG post exposure

The ACIP recommends the use of varicella vaccine for susceptible persons following exposure to varicella.[11] If administered within 72 hours and possibly up to 120 hours following varicella exposure, varicella vaccine may prevent or significantly modify disease.[24,26,27] Post-exposure vaccine use should be considered following exposures in health care settings, where transmission risk should be minimized at all times, and in households. If exposure to varicella does not cause infection, post-exposure 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 post-exposure prophylaxis of susceptible persons who are at high risk for developing severe disease and when varicella vaccine is contraindicated.[10] VZIG is most effective in preventing varicella infection when given within 96 hours of varicella exposure. The decision to administer VZIG to a person exposed to varicella should be based on 1) whether the person is susceptible, 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 children, susceptible pregnant women, hospitalized premature infants > 28 weeks gestation whose mother had no history of varicella, and premature infants < 28 weeks gestation, regardless of the mother's history of varicella.[10] Varicella zoster immune globulin can be ordered from the distributor (FFF Enterprises, Inc., Temecula, CA) by calling 800-843-7477.

Table 1. Varicella outbreaks: priorities for investigation

Step	Outbreak Description
1	Outbreaks among patients and staff in health-care settings
2	Outbreaks associated with severe complications (e.g., pneumonia, encephalitis, serious infectious complications such as invasive Group A streptococcal infection or hemorrhagic complications) and/or hospitalizations
3	Outbreaks among persons who are immunocompromised due to HIV infection, cancer, or immunosuppressive therapy
4	Outbreaks involving adolescents and adults
5	Outbreaks occurring among vaccinated populations
6	Clusters of reports (may suggest improper storage and handling of vaccine)
7	Outbreaks involving a large number of cases

Table 2. Steps for investigation and control of varicella outbreaks

Step	Description and details
1	**Confirm outbreak, investigate all persons exposed in the outbreak, and determine varicella susceptibility.** a. Define cases and confirm outbreak. b. Screen outbreak cohort for susceptibility to varicella. i. Use history of disease and vaccination ii. Use serologic testing. c. Investigate cases to characterize illness including onset, severity, duration, pre-existing medical conditions and medications, and complications.
2	**Initiate outbreak control and treat cases (if appropriate).** a. Isolate or cohort infective cases. b. Exclude non-vaccinated persons without history of disease from school or contact with children. c. Recommend treatment of active cases with antiviral therapy (adolescents and adults only). d. Offer vaccine to susceptible persons. i. Distribute letters recommending vaccination. ii. Offer vaccine through on-site clinics. e. Offer VZIG to exposed, susceptible persons at high risk of severe disease.
3	**Establish surveillance for:** a. Additional varicella cases *(Note: If cases continue despite recommendation 2.d.ii, consider a vaccination clinic.)* b. Vaccine-associated adverse events.
4	**Analyze collected data.** a. Describe cases and transmission (date of rash onset, age, sex, country of birth, severity, etc.). b. Describe serological status (if serology testing performed). c. Evaluate outbreak control efforts. d. Calculate vaccine effectiveness.
5	**Investigate low vaccine effectiveness (if present).**

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