



Varicella

Last updated: September 5, 2018



DISEASE AND VACCINE CHARACTERISTICS

Varicella-zoster virus (VZV) causes both varicella (chickenpox) by primary infection and herpes zoster (HZ or shingles) by endogenous reactivation from latency. VZV circulates worldwide. Acquisition of infection tends to be at a younger age in temperate countries (> 90% infected by adolescence in absence of vaccination programme), compared to an older distribution in tropical countries. Varicella shows a winter/spring or cool/dry month predominance, and can occur in large outbreaks every 2–5 years. VZV is highly contagious with secondary attack rates from varicella cases ranging from 61–100%. The virus spreads person-to-person primarily by inhalation of aerosols from vesicular fluid of skin lesions, by direct contact with rash and possibly by infected respiratory tract secretions. Without vaccination, almost everyone in the population acquires wild-type varicella infection by adulthood. The incubation period for varicella from time of contact to rash onset is generally 14–16 days, with a range of 10–21 days. A prodrome of fever, malaise and anorexia can precede the rash by several days. The rash consists of new crops of skin lesions which progress over five to seven days from macules to papules, pruritic vesicles and then scabs, with unvaccinated individuals often typically having approximately 300 lesions. VZV can be transmitted one to two days before rash onset and until the lesions have crusted. Varicella is usually self-limited, rarely causing severe complications such as pneumonia,

cerebellar ataxia, encephalitis, haemorrhagic conditions and bacterial superinfection of skin lesions. Although serious disease with visceral organ involvement occurs more commonly in immunocompromised persons, the greatest number of varicella deaths occurs in healthy children since varicella is so common. High-risk groups for more serious disease and complications of primary VZV infection include infants < 1 year old, pregnant women, adults and immunocompromised persons.

Latent VZV infection can reactivate later in life and result in HZ, a vesicular rash usually in a single dermatome accompanied by radicular pain, which can last from two to four weeks. Active HZ can transmit VZV to susceptible people, causing varicella. A common and often debilitating consequence of HZ is post-herpetic neuralgia, a persistent pain for months or even years after resolution of the rash.

Varicella vaccines are live-attenuated VZV vaccines, given in a one- or two-dose schedule. A single dose has been found to be approximately 80% effective against all severities of varicella disease and higher for severe disease. A two-dose schedule is > 92% effective (1). After the vaccine is introduced but before it reaches 80% coverage, modelling has predicted a theoretical risk of a shift in primary varicella incidence to older ages, when it is usually more severe (2).

BOX

1

Herpes zoster surveillance

Herpes zoster (HZ) surveillance is an optional adjunct to varicella surveillance in countries with a national varicella vaccination programme or HZ vaccination programme. In countries with a HZ vaccination programme, the primary objective of HZ surveillance is to monitor changes in HZ burden and epidemiology, and to monitor effectiveness and impact of vaccination on HZ. In countries with varicella vaccine but not HZ vaccine, the primary objective of HZ surveillance is to understand the impact of varicella vaccine on HZ epidemiology. Countries with sufficient resources can consider implementing HZ surveillance or alternatively, conducting special studies to understand this impact. Moreover, countries considering introduction of HZ vaccines in the future might consider undertaking HZ surveillance to inform vaccine policy decisions.

This document does not provide guidance on how to conduct HZ surveillance. Some member states are conducting HZ surveillance, and guidance on potential case definitions and approaches to surveillance can be found elsewhere (3) (4) (5) (6).



RATIONALE AND OBJECTIVES OF SURVEILLANCE

- Objectives of varicella surveillance include the following:
- in countries where varicella vaccine has not been introduced, inform potential introduction by providing data on varicella burden and epidemiology
 - in countries where vaccine has been introduced, monitor changes in varicella burden and epidemiology, and monitor effectiveness and impact of vaccination on varicella.



TYPES OF SURVEILLANCE RECOMMENDED

Recommended surveillance depends on vaccine introduction status and programme goals.

MINIMUM SURVEILLANCE

Minimal surveillance is aggregate, passive, subnational (district, province), health facility-based and without laboratory confirmation. A country can choose to do this type of surveillance nationwide, but the surveillance burden might be large given how common varicella is prior to vaccine introduction. Facility-based surveillance will also underestimate the total burden of varicella since many cases never present for health care. At a minimum, collect age group of cases for aggregate surveillance. In addition, collection of data on severe disease, such as hospitalizations and deaths, can provide useful complementary data on burden. This type of surveillance is frequently done prior to vaccine introduction as there can be a large disease burden without the vaccine and outbreak response is limited. This type of surveillance can also be done post-vaccine introduction, though it may have limited ability to inform the programme.

ENHANCED SURVEILLANCE

Enhanced surveillance can be either:

- Case-based, nationwide, passive, with or without laboratory confirmation, and with additional information collected on cases, such as vaccination status. This is usually ideal in settings where vaccine has already been introduced and there is already evidence of substantial vaccine impact and a decline in varicella incidence.
- Case-based, sentinel site, passive or active, with or without laboratory confirmation, and with additional information collected on cases, such as vaccination status. For varicella surveillance, sentinel sites might not be restricted to health facilities as a large proportion of cases might not present to health facilities. Sentinel sites could be defined as outpatient clinics or paediatric offices, schools, daycare centres, etc. The objectives of surveillance will determine the age groups and sites selected. Some countries have chosen to focus on specific age groups or only on severe cases (such as adults, who have lower incidence and higher severity of disease.) It may be necessary to select a large number of sites to capture sufficient cases to inform the programme, due to the rarity of disease post-vaccine introduction.



CASE DEFINITIONS AND FINAL CLASSIFICATION

SUSPECTED CASE DEFINITION FOR CASE FINDING

Acute onset of a generalized maculopapulovesicular rash with concomitant presence of papules, blisters, pustules or crusts appearing on trunk and face and spreading to extremities, without other apparent cause.

In countries that have achieved high varicella vaccination coverage for a few years, the suspected case definition should be changed to capture modified varicella in a vaccinated person (see **Other definitions** below).

FINAL CASE CLASSIFICATION

Laboratory-confirmed. A suspected case with laboratory evidence of acute VZV infection by one of the following methods:

- detection of VZV DNA (using PCR)
- direct antigen detection of VZV from an appropriate clinical specimen (for example, direct fluorescent antibody (DFA) testing)
- isolation using viral culture*
- seroconversion* or a significant rise (fourfold or greater) in varicella-zoster IgG titer between acute and convalescent sera by any validated serologic assay.

*These laboratory methods are not commonly used due to the logistical constraints of specimen collection and lack of timeliness in receiving results (see **Laboratory testing** section).

Epidemiologically linked confirmed case. A suspected case that is epidemiologically linked to a laboratory confirmed case, another case confirmed by epidemiologic linkage, or another clinically compatible case of VZV.

Epidemiologic linkage requires contact between two people involving a plausible mode of transmission at a time when:

- one of them is likely to be infectious (one to two days before rash onset until lesions have crusted)

AND

- the other has illness 10–21 days after contact (the incubation period).

Clinically compatible case. A case that meets the suspected case definition, is not laboratory-confirmed and is not epidemiologically linked to another clinically compatible or confirmed case.

OTHER DEFINITIONS

Vaccine associated varicella. A varicella-like rash in a person vaccinated 5–42 days prior to rash onset, or isolation of vaccine-type virus from rash that occurs during that interval after vaccination. These cases should result in the same public health response as wild-type varicella, as these are infectious and can be spread, particularly to immunocompromised persons. Note that in the early years after vaccine introduction when varicella incidence remains high, most varicella-like rashes among recently immunized persons will still be due to wild-type varicella.

Modified varicella in a vaccinated person. Modified varicella, also known as breakthrough varicella, is varicella due to wild-type virus that occurs in vaccinated people (> 42 days after vaccination). Modified varicella is usually mild, with < 50 lesions, low or no fever, and shorter duration of rash. The rash may be atypical in appearance with predominance of maculopapular lesions and fewer vesicles. Modified varicella is contagious, although less so than varicella in unvaccinated people.

BOX

2

Congenital varicella syndrome

Congenital varicella syndrome (CVS) is a rare condition that results from VZV infection in pregnant women infected during the first 20 weeks of gestation (< 2% of VZV-infected pregnant women) (7). Affected newborns can be born with low birth weight, skin scarring, limb malformation, neurologic abnormalities, and cataracts and other ocular abnormalities. The skin abnormalities do not look like the typical varicella rash, and neonates with CVS would not fulfill the varicella surveillance criteria for detection described in this chapter. Administration of VZV-immune globulin is recommended for non-immune pregnant women as soon as possible after exposure to VZV. In addition to preventing severe varicella in the woman, it might decrease viremia and transmission to the fetus. Women infected in the first 20 weeks of gestation should be followed through delivery.

**CASE INVESTIGATION**

Individual case investigations are not routinely done if aggregate surveillance is being conducted, and data are typically limited to age of case and vaccination status (if possible). If case-based surveillance is being conducted, additional case information can be collected, such as severity of disease based on number of lesions, risk factors for severe disease, complications, vaccination status, pregnancy status of women and outcomes.

Although investigations of all cases of varicella may not be feasible in all settings, they are warranted in some specific circumstances, including deaths associated with varicella, cases with severe complications, outbreaks in populations with high varicella vaccine coverage and outbreaks involving exposure of persons at high risk (including health care workers).

**SPECIMEN COLLECTION**

The diagnosis of varicella is usually made clinically by the characteristic clinical presentation of the rash with fever. If a country chooses to conduct laboratory testing, several types of specimens can be collected.

- Skin lesions are the preferred specimen, which is collected by unroofing a vesicle (preferably a fresh fluid-filled vesicle) with a sterile needle and swabbing the base of the lesion with a sterile polyester swab with sufficient vigour to ensure epithelial cells are collected. Do not use cotton swabs.
- If the rash comprises only macules or papules, scrape the lesion (with the edge of a glass microscope slide, for example), swab the abraded lesion with a polyester swab, and then use the same swab to collect any material that was accumulated on the object that was used to scrape the lesion. If direct fluorescent antibody (DFA) testing will be done, take care to avoid contaminating the sample with blood, as serum antibodies can interfere with binding of the fluorescent detection antibody and cause a false-negative result. Swabs can be used for PCR, DFA or

viral culture. Swabs for PCR should be transported dry or in universal transport media for culture. Successful viral culture depends on inoculating the sample into tissue culture immediately following collection.

- Crusts or scabs from skin lesions are excellent specimens for PCR testing but not for DFA or culture. To collect these, crusts should be lifted off the skin, placed into an empty tube and transported dry.

The swabs and crusts should be transported at ambient temperature and arrive at the laboratory as soon as possible.

If paired IgG antibody testing is desired and available, a venipuncture blood specimen can be collected and sent to the laboratory for testing. Blood collection tubes can be those for serum or plasma. Serum and plasma samples may be stored for up to five days at 2–8 °C or four weeks

at –20 °C. An acute specimen should be taken within the first few days of illness, and the convalescent specimen should be taken at least three weeks later.

For acute varicella, cheek and throat swabs and oral fluid are nearly as reliable as skin lesion samples and scabs. However, they are substantially less reliable samples for confirming HZ cases. Other specimens, such as peripheral blood, plasma and urine are not recommended, as they rarely contain detectable virus even in cases that have been confirmed with skin lesion samples. For presentations involving complications (such as pneumonia or encephalitis) or death, other types of specimens such as bronchial washings, cerebrospinal fluid or biopsied tissues may be collected. Since these are considered secondary sources, the methods are not described here but are available elsewhere (8).



LABORATORY TESTING

Laboratory confirmation is not routinely recommended as part of a minimum standard surveillance system, as the suspected case definition is specific in the pre-vaccine setting. However, in populations with high vaccine coverage and low disease rates, laboratory testing is important for diagnosis of vaccine-modified varicella. In modified (breakthrough) varicella among vaccinated persons, rash illness is often limited to a few lesions, typically maculopapular, with few or no accompanying symptoms. Diagnosis based on clinical grounds alone is challenging and laboratory testing may be required.

Confirmation methods for lab testing are the following:

- PCR to detect VZV DNA is the most reliable and sensitive method, and is now considered the gold standard. False-negative PCR results are more likely to occur from lesions in vaccinated persons.
- Direct immunofluorescence (DFA) to detect VZV antigen is the second choice; sensitivity is only 60–70% of cases detectable by PCR (2),

Other methods to confirm VZV infection, which are less preferable and less commonly used today, are described below.

Viral culture of VZV is possible but is insensitive, time-consuming and expensive because it requires special media.

Serologic tests may be used to confirm disease but are less reliable than PCR or DFA for virus identification. A four-fold or greater rise in serum varicella IgG titers from acute- and convalescent-phase samples indicates a recent VZV infection. However, persons in whom vaccination produced a high VZV IgG titer may not achieve the required four-fold increase in the convalescent sample. Serologic tests are also less useful in immunocompromised people who are less likely to mount an effective immune response.

Testing for VZV IgM by using commercial kits is not recommended because available methods lack sensitivity and specificity.



DATA COLLECTION, REPORTING AND USE

RECOMMENDED DATA ELEMENTS

If conducting aggregated data collection, collect the number of total cases by age group (suggested age groups: < 1 year, 1–4 years, 5–9 years, 10–19 years, ≥ 20 years), month, geographical area, and, if used in national programme, immunization status.

If conducting case-based data collection:

► Demographic information

- » Name (if confidentiality is a concern the name can be omitted so long as a unique identifier exists)
- » Unique case identifier
- » Date of birth (or age if date of birth not available)
- » Sex
- » Place of residence (city, district and province)

► Reporting information

- » Date of notification to public health
- » Lowest administrative unit (e.g. district)
- » Date of investigation

► Clinical

- » Pre-existing medical conditions (including pregnancy, immunocompromised condition)
- » Dates of rash onset
- » Complications of disease (bacterial superinfection, varicella pneumonitis, encephalitis, etc.)
- » Hospitalization status
- » Severity of disease (guidance on how to count lesions available elsewhere) (9)
 - Mild: fewer than 50 lesions (can be counted in 30 seconds)
 - Average: 50–249 lesions (some skin was affected, but there was a clear area at least as big as the child's hand)
 - Moderate: 250–499 lesions (some skin was affected, and clear areas were not large enough to fit the child's hand without touching other lesions)
 - Severe: 500 or more lesions (confluence of lesions in many skin areas) or any complications such as bacterial superinfection, varicella pneumonitis, encephalitis, hospitalization or death

- » Outcome (patient survived, died, unknown)
- » Treatment, if any

► Varicella vaccination status

- » Number of varicella vaccine doses received
- » Dates of doses (or age received if card not available)

► Epidemiologic data

- » Transmission setting (daycare, school, institution, hospital, etc.)
- » Source of transmission
 - Contact with a probable case, confirmed case or person with a rash illness suspected of being varicella or HZ
 - Date of contact

► Laboratory methods and results

- » Type(s) of specimen(s) (crusts, vesicular fluids, blood, CSF)
- » Date(s) of specimen(s) collection
- » Date specimen(s) sent to laboratory
- » Date specimen(s) received at laboratory
- » Method(s) of testing
- » Test result(s) for each method used
- » Reporting date of results

► Final classification

REPORTING REQUIREMENTS AND RECOMMENDATIONS

Reporting of aggregate and case-based data to the next higher administrative level should be done according to a pre-defined weekly or monthly schedule. In enhanced surveillance, zero reporting should be done when there are no cases. There are no global reporting requirements for varicella at this time by the International Health Regulations (IHR) or on the Joint Reporting Form (JRF).

RECOMMENDED DATA ANALYSES

- **Aggregate.** Number of cases and incidence by age group and geographic location (such as district), and number of cases by vaccination status.
- **Case-based.** Number of cases and final classification by age group, incidence rates, and other variables of interest, such as vaccination status by age, severity of disease and complications.
- monitor changes in the epidemiology of varicella, such as changing incidence among adults
- monitor the impact of a vaccination programme, such as decreasing incidence in children
- determine where gaps exist in the vaccination programme, which might lead to changes in vaccination policy (high-risk vaccination strategies, need for additional doses and timing of doses, etc.).

USING DATA FOR DECISION-MAKING

Data may be used to do any of the following:

- assess the epidemiology of varicella to inform vaccine introduction



SURVEILLANCE PERFORMANCE INDICATORS

Regular monitoring of surveillance indicators can identify specific areas of the surveillance and reporting system that need improvement. Some suggested

surveillance indicators to monitor include those listed in Table 1. Modify these based on the type of surveillance being conducted.

TABLE
1

Varicella surveillance indicators

SURVEILLANCE ATTRIBUTE	INDICATOR	TARGET	HOW TO CALCULATE (NUMERATOR/DENOMINATOR)	COMMENTS
COMPLETENESS OF REPORTING	Percentage of designated sites reporting varicella data	≥ 80%	# designated reporting sites reporting varicella data / # designated reporting sites for varicella surveillance x 100 (for a given time period)	For nationwide or subnational, could be administrative units, like districts, provinces. For sentinel surveillance, could be number of facilities, schools, etc.
TIMELINESS OF REPORTING	Percentage of designated sites reporting varicella data to the national level on time (based on local reporting schedules)	≥ 80%	# of designated reporting sites in the country reporting varicella data by the deadline / # of designated reporting sites in the country x 100	At each level reports should be received on or before the requested date.
TIMELINESS OF INVESTIGATION	Percentage of all suspected varicella cases that have had an investigation initiated within two days of notification	≥ 80%	# of suspected cases of varicella for which an investigation initiated within two days of notification / # of suspected varicella cases x 100	Only applicable when the country requires cases to be investigated. Can be restricted to varicella deaths or high risk or unusual epidemiological groups (e.g. infants, adults) if desired



CLINICAL CASE MANAGEMENT

Treatment of varicella with antiviral medication such as acyclovir are recommended only for patients with generalized varicella and persons at high risk for severe varicella, given the expense and minimal clinical benefit in otherwise healthy persons. Immunocompromised individuals and patients with severe complications are generally treated with intravenous antiviral medication.

Nosocomial transmission of VZV should be prevented due to the increased likelihood of exposure of susceptible patients at high risk of complications. Airborne and contact isolation of hospitalized patients who have confirmed or suspected VZV infection should be undertaken; guidelines for prevention of nosocomial VZV transmission are available from member states (10) (11) (12) (13). Patients should be placed under both airborne and contact precautions if in institutional or

health care settings. If negative airflow rooms are not available, varicella case patients should be isolated in closed rooms, having no contact with persons who lack evidence of immunity.

To prevent spread, persons with varicella should avoid leaving home until their lesions are crusted and dry. Cases should stay home from work or school until this occurs. Vaccinated persons with varicella may develop lesions that do not crust (macules and papules only); isolation guidance for these persons is to avoid leaving home until no new lesions appear for a 24-hour period.

Post-exposure prophylaxis with immunoglobulin can be considered in non-immune contacts at high risk of severe disease and complications.



CONTACT TRACING AND MANAGEMENT

Universal contact tracing is not currently considered an essential strategy in stopping the spread of disease. Contact management is most commonly implemented

in outbreak settings (see **Contact management during an outbreak** below).



SURVEILLANCE, INVESTIGATION AND RESPONSE IN OUTBREAK SETTINGS

The approach to varicella outbreaks varies depending on if and when varicella vaccine was introduced into the national immunization programme. Before vaccine introduction, outbreaks can be used as an opportunity to learn more about the epidemiology of varicella to help guide potential future vaccination strategies. Because varicella outbreaks are so widespread in the absence of a vaccine programme, investigations should be prioritized among potentially high-risk individuals in well-circumscribed settings such as hospitals, jails and daycare facilities with infants. In the early years after vaccine introduction, outbreaks will still be common in settings with many unvaccinated children, such as schools and daycare centres; prioritization of investigation should

still be among high-risk settings. Sites where outbreaks would provide particularly useful information about the vaccine programme or affect high-risk individuals (daycare centres with infants, health care facilities, residential facilities for adults, military barracks, etc.) should be educated to rapidly report cases to public health authorities. As the vaccination programme matures, outbreaks will reduce in number and size. When this happens, outbreak investigation and response might limit the size of the outbreak through vaccination and provide useful information to evaluate the programme (vaccine impact, changing epidemiology, etc.).

DEFINITION OF OUTBREAK

In pre-vaccination settings and in countries recently having introduced vaccine, an outbreak is an increase in varicella cases over baseline, tightly clustered in place and time. In the absence of vaccine, because varicella is so widespread, discrete outbreaks are hard to define. In countries that have a mature programme, an outbreak is a cluster of five or more suspected cases that are related in place and epidemiologically linked. Cases should be considered part of an outbreak if they occur within at least one incubation period (21 days) of the previous case.

CHANGES TO SURVEILLANCE DURING AN OUTBREAK

In the absence of vaccination, laboratory confirmation is not necessary because the clinical and epidemiologic presentations will be characteristic of varicella. Countries with mature vaccination programmes and laboratory confirmation capacity can confirm an outbreak of rash illness as varicella when at least one case is confirmed with lab testing (ideally, three to five cases). Future cases should be epidemiologically linked, and there is no need to overwhelm the laboratory by requesting laboratory confirmation on subsequent cases. Once an outbreak is confirmed, enhanced surveillance with line listing is recommended to keep track of cases and document outcomes, particularly complications. If not already established, surveillance should continue through two full incubation periods (42 days) after the rash onset of the last identified case to ensure that the outbreak has ended.

CONTACT MANAGEMENT DURING AN OUTBREAK

Contacts are those who have exposure to the case one to two days before rash onset until lesions have crusted over. Universal contact tracing is not currently considered an essential strategy in stopping spread of disease. Instead, contacts in congregated settings, particularly schools, are deemed the most at risk and should be followed up to ensure vaccination is provided, if available. Single-dose varicella vaccine administered

within three to five days of exposure has proved to be highly effective for prevention of disease (> 70%), the earlier after exposure the higher the efficacy. Countries with national varicella vaccination programmes should recommend that those without evidence of immunity be vaccinated, regardless of number of days since exposure. Evidence of immunity is defined as having had prior natural infection, serological evidence of infection, or having received age-appropriate vaccination with varicella vaccine according to the national schedule. If vaccination is contraindicated or refused, countries can choose to exclude the person from school or work for up to 21 days after the last case is identified to prevent infection. This is most important for contacts at the highest risk of having severe disease.

When available, VZV immune globulin can be effective for post-exposure prophylaxis if given soon after exposure, to reduce disease severity in persons at high risk for severe varicella such as pregnant women, immunocompromised persons and neonates. Post-exposure prophylaxis with antiviral medications has been shown to prevent clinical disease in immunocompromised children.

PUBLIC HEALTH RESPONSE

In countries without varicella vaccination, vaccine is unlikely to be given in response to outbreaks. In countries with a national vaccine programme, vaccination is recommended to control the outbreak and prevent spread. This is usually manageable several years after introduction when the number of outbreaks has started to decrease. The country should select the groups prioritized for vaccination depending on the goal of the programme and the epidemiology of the outbreak. For example, the objective to decrease mortality and morbidity would lead a country to focus on vaccinating groups such as adolescents and adults, who are at increased risk for severe disease, while the objective to prevent future outbreaks might lead a country to vaccinate all persons in the outbreak area.



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