Varicella: epidemiological surveillance and immunoprophylaxis


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Chickenpox: epidemiological surveillance and immunoprophylaxis

INTRODUCTION

Varicella is an acute, immune preventable, highly contagious infectious disease caused by the varicella-zoster virus (VZV) characterized by the presence of fever and widespread vesicles throughout the body.\textsuperscript{1,2} Its main clinical feature is the polymorphism of skin lesions, which present in the evolving forms of macules, papules, vesicles, pustules, and crusts, accompanied by pruritus.\textsuperscript{1} Reactivation of latent VZV infection causes herpes zoster.\textsuperscript{1}

About 90\% of individuals who have never had the disease or have not been vaccinated have the possibility of developing varicella after close contact with a confirmed case.\textsuperscript{3} Transmission occurs from person to person through direct contact with skin lesions or respiratory secretions, through airborne dissemination of viral particles or aerosols.\textsuperscript{2} The transmissibility period initiates one to two days before the rash appearances and extends until all lesions are crusting.\textsuperscript{1,2}

On average, the incubation period is 14 to 16 days, and may range from 10 to 21, being shorter in immunocompromised patients and longer after passive immunization.\textsuperscript{1,2} Infection can occur throughout the year, but a seasonal pattern of increased numbers of cases is observed in the period extending from late winter to spring.\textsuperscript{4}

In healthy children, it is usually a benign and self-limited disease.\textsuperscript{1} In children under 1 year of age, adolescents, adults, pregnant women, and individuals with immune compromising conditions, the clinical picture tends to be more severe.\textsuperscript{2,3}

The complications of varicella can be secondary bacterial skin infection, which can lead to systemic sepsis, dehydration, acute cerebellar ataxia, encephalitis, and thrombocytopenia; pneumonia; varicella hemorrhagic in immunocompromised children; and rare complications such as Reye’s syndrome related to the use of acetylsalicylic acid, glomerulonephritis, hepatitis, and arthritis. Involvement during pregnancy can lead to fetal infection, capable of causing embryopathy, with congenital varicella syndrome, at risk of fetal death.\textsuperscript{1,2,3}

Since 2001, in the state of São Paulo (ESP) varicella outbreaks in restricted environments such as daycare centers, schools and hospitals are duly reported in the Sinan Net Outbreak Notification Bulletin, in order to investigate and adopt appropriate control measures against the spreading of the disease.\textsuperscript{5} According to the Ordinance # 1,271, of July 6, 2014, varicella is of compulsory notification in Brazil, and only hospitalized severe cases and deaths should be notified, through the Individual Notification Form.\textsuperscript{2}

In 2013 the MMRV vaccine (against measles, mumps, rubella, and varicella) was introduced in the National Vaccination Calendar for 15-month-old children, as long as they have already been vaccinated with the first dose of the MMR (triple viral vaccine). In the unavailability of the MMRV vaccine, this
dose should be given with MMR and varicella (attenuated) simultaneously. In 2018 varicella vaccine was also added for children aged between 4 years and 6 years, 11 months, and 29 days. This is administered as the second dose of varicella vaccine (attenuated) given in MMRV form.

The vaccine against the disease is also available at Reference Center for Special Immunobiological (CRIES) for specific patients who have a higher susceptibility to varicella. Among them, health care professionals and organ transplant candidates.

In the year the vaccine was introduced nationwide (2013), there were 3,689 outbreaks (25,052 cases) and 12 deaths in São Paulo. In 2021, the state recorded 62 outbreaks (316 cases) and no deaths.

VARICELLA OUTBREAKS

An outbreak of varicella is characterized by the occurrence of a number of cases above the expected limit, based on previous years, or aggregate cases in environments at high risk of disseminating the disease - closed or semi-closed institutions, such as healthcare units, long-term care facilities for seniors, shelters, daycare centers and schools, and prison units, among others. Because it is a highly contagious disease, when a single case is identified in these environments, control measures should be taken as soon as possible, as there is potential to trigger an outbreak.

Potential interventions for subjects without evidence of immunity who are exposed to a suspected or confirmed case of the disease include: varicella vaccine, given ideally within five days of exposure, or Human Varicella-Zoster Immunoglobulin, recommended within four days of exposure.

OPERATIONAL DEFINITIONS

Suspected case of varicella

Patient with moderate fever, sudden onset, and lasting two to three days; nonspecific generalized symptoms (indisposition, adynamia, anorexia, headache, and others); and a papulovesicular eruption that starts on the face, scalp, or torso (centripetal distribution - head and torso).

Severe Varicella

A report that meets the definition of a suspected case and requires hospitalization or has evolved to death.
Communicants

Any person who has had close and prolonged contact with a suspected or confirmed case of varicella, during its transmissibility period, for more than one hour, in an enclosed environment.  

Susceptible

Individual with no evidence of having had the disease (clinical diagnosis or verbal information) or not having been vaccinated.

Hospital environment

In a hospital environment, a single confirmed case is characterized as an outbreak. In such outbreak control situations, even if the vaccine is used, it is important to remember that there is a possibility that a small percentage of people will develop the disease.

Day Care Centers

Considering that the disease in children who attend day care centers can be more severe, the varicella vaccine is indicated from the time of the first case.

RECOMMENDATIONS

1. Identify all subjects who did not have varicella and who visited the institution in the last four weeks, from the identification of cases, regardless of the number of hours they stayed in the institution.

2. Identify the number of employees in the institution who have not had varicella but have a contact history with the cases.

3. Identify the number of immunocompromised individuals and the susceptible pregnant women who have had contact with cases. Write down the weight to calculate the specific immunoglobulin dosage (VZIG).
4. Apply the specific immunoglobulin within the appropriate period for blocking clinical manifestations (96 hours).

5. Track the emergence of new cases.

6. It is recommended that the daycare/school not accept enrollment of susceptible children until 21 days have elapsed from the last case. In case of new admissions, you should check if the child’s varicella vaccination status is up to date according to the indications of the State Vaccination Calendar.

7. After 21 days of no new cases, the outbreak is considered to be under control.

CONTROL MEASURES

Objectives

- Restrict the spread of the varicella virus.
- Reduce the occurrence of severe disease cases.
- Reduce the number of hospitalizations, complications, and deaths related to varicella.²

VARICELLA VACCINE (ATTENUATED)

Composition

Currently, the varicella vaccines registered for use in Brazil are those from Merk Sharp & Dohme (MSD), GlaxoSmithKline (GSK), and Green Cross Corporation (GCC). Its composition is described in Table 1.

Dosage, route of administration and storage

Each dose is equivalent to 0.5 ml and should be administered subcutaneously. After its reconstitution it should be administered immediately. Products currently available should be stored in refrigerated form at +2°C to 8°C. (36° F and 46° F).³
Table 1. Information on varicella vaccine according to the producing laboratory.

<table>
<thead>
<tr>
<th>Brazilian Nonproprietary Name (DCB)</th>
<th>Varicella vaccine (attenuated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Producer Laboratory</td>
<td>Merk Sharp &amp; Dohme (MSD)</td>
</tr>
<tr>
<td></td>
<td>GlaxoSmithKline (GSK)</td>
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<tr>
<td></td>
<td>Green Cross Corporation (GCC)</td>
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**Indication**

- For individuals from 12 months of age.
- For individuals from 9 meses of age.
- For individuals from 12 months of age.

**Posology**

- **Children aged 12 months to 12 years should receive a dose of 0,5 mL administered subcutaneously. If a second dose**
  - Each 0,5 mL of the reconstituted vaccine contains one immunizing dose.
  - Children from 9 months to 12 years of age should receive two doses of the vaccine to ensure maximum protection against varicella.

- **Individuals from 13 years and older should receive a dose of 0.5 mL administered subcutaneously and a second dose of 0.5 mL after 4 to 8 weeks.**
  - It is preferable to administer the second dose at least six weeks after the first; under no circumstances such administration should occur before four weeks.

- **Individuals aged 13 years and older: two doses.**
  - After reconstitution with the provided diluent, inject a single 0.5 mL dose subcutaneously.

**Presentation**

- Single-dose vial: one dose + diluent.
- Single-dose vial (one dose + diluent in a filled syringe or ten ampoules - ampoule + ten ampoules with diluent).
- Single-dose vial: one dose + diluent.

**Pharmaceutical Form**

- Lyophilized powder + diluent.
- Lyophilized powder + diluent.
- Lyophilized powder + diluent.

**Route of administration**

- Subcutaneous
- Subcutaneous
- Subcutaneous

**Composition per 0.5 mL dose**

- Each 0.5 mL dose of reconstituted varicella vaccine (attenuated) contains a minimum of 1,350 PFU (Plate Forming Units) of Oka/Merck strain virus.
- Each 0.5 mL dose of reconstituted vaccine contains live attenuated varicella-zoster virus (VZV), Oka strain, no less than 2,000 PFUs.
- Each vial (0.7 mL, when reconstituted) contains live attenuated VZV virus, Strain MAV/06, NLT 1,400 PFUs.

- Excipients: sucrose, gelatin (hydrolyzed porcine), urea, sodium chloride, sodium glutamate monobasic, sodium phosphate dibasic, potassium phosphate monobasic, and potassium chloride.
- Excipients: amino acid supplement, lactose, sorbitol, and mannitol.
- Excipients: sucrose, glycine, sodium L-glutamate, gelatin, L-cysteine, disodium edetate, Na2HPO412H2O, Na2HPO42H2O.

**Preservation**

- Store at +2°C to +8°C (36° F and 46° F) and protected from light.
- Store at +2°C to +8°C (36° F and 46° F) and protected from light.
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**Storage after reconstitution**

- Immediate use.
- Immediate use.
- Immediate use.

Source: vaccines leaflet
EFFECTIVENESS AND PROTECTION DURATION

Approximately 85% of immunocompetent children over 12 months of age who have been vaccinated against varicella develop cellular and humoral immunity responses at levels associated with disease protection. Protection levels are significantly higher when two doses of the vaccine are given.\(^{10}\)

The effectiveness with one dose ranges from 70% to 90% against infection and 95% against the severe form of the disease. In post-licensing studies, the vaccine has been shown to be highly effective in preventing severe forms of varicella. They have also shown that immunocompetent children vaccinated with two doses have 3.3 times less risk of developing the disease over a ten-year period post-immunization than those receiving a single dose.\(^{10}\)

Since the pre-licensing studies of the vaccine, subjects older than 13 years of age have shown lower one-dose seroconversion rates than those observed in children, ranging from 72% to 94%. When the second dose is given 4 to 8 weeks after the first, these rates increase to 94% to 99%.\(^{10}\)

In general, the varicella that develops in vaccinated patients tends to be less intense in terms of clinical manifestations than that which occurs in unvaccinated patients. Vaccinated persons usually have few skin lesions (<50) and tend to recover more quickly from the disease - sometimes the clinical manifestations of varicella in this group are so discrete that diagnosis is difficult. However, even with few lesions, the contagion risk exists.\(^{10}\)

Regarding the duration of immunity produced by the vaccine, studies developed in Japan indicate persistence of antibodies for at least 20 years. Nevertheless, the studies have been conducted in a period when the wild virus was circulating significantly in the community, inducing reinforcement of natural immunity. With increasing vaccination coverage in countries where the vaccine is part of the national vaccination schedule, further studies are needed to assess the antibody persistence and long-term protection granted against the disease.\(^{10}\)

INDICATION

In Routine

Varicella vaccination is routinely available in public health services, according to the following scheme.

- At age 4: the second dose should be with varicella vaccine (attenuated). Children who are not previously vaccinated can receive this vaccine until 6 years, 11 months, and 29 days\(^7\). If varicella vaccine is not available, this dose can be given with MMRV vaccine.\(^{11}\)
Indigenous people from 7 years old who have not been vaccinated or do not have proof of vaccination: administrate one or two doses of varicella (attenuated), depending on the producing laboratory.\(^2\)

Health professionals who are not vaccinated and who work in the care area, especially in contact with immunocompromised people, and those in the area of neonatology and pediatrics should receive one or two doses of varicella vaccine (attenuated), depending on the producing laboratory.\(^2\)

**SPECIAL SITUATIONS**

- Immunocompetent individuals from special risk groups (healthcare workers, caregivers, and family members) susceptible to the disease who are living at home or in the hospital with immunosuppressed patients.\(^{10}\)

- Immunocompetent and susceptible to the disease older than 1 year of age, at the time of admission to a unit where there is a varicella case.\(^{10}\)

- Candidates for organ transplantation, susceptible to the disease, until at least four weeks before the procedure, as long as they are not immunologically compromised.\(^{10}\)

- Individuals with chronic nephropathies.\(^{10}\)

- Individuals with nephrotic syndrome.\(^{10}\)

- Donors of solid organs and hematopoietic stem cells (bone marrow).\(^{10}\)

- Hematopoietic stem cell transplants (HSCT): for patients who have had a transplant over 24 months, being contraindicated when there is Graft versus host disease.\(^{10}\)

- HIV-infected children and adolescents susceptible to varicella in clinical categories (CDC) N, A and B with CD4>200 cells/mm3 (15%). It is recommended that exposed children are vaccinated even when HIV infection has been ruled out, to prevent the varicella transmission in household contact with people who are immunologically compromised.\(^{10}\)

- Patients with isolated humoral immunity deficiency (with preserved cellular immunity).\(^{10}\)

- Patients with severe dermatological diseases, such as ichthyosis, epidermolysis bullosa, psoriasis, severe atopic dermatitis, and similar ones.\(^{10}\)

- Individuals in chronic use of acetylsalicylic acid (suspend their use for six weeks after vaccination).\(^{10}\)
• Individuals with anatomical and functional asplenia and related diseases.\textsuperscript{10}

• Trisomy patients.\textsuperscript{10}

**POST-EXPOSURE VACCINATION**

In the event of a varicella outbreak in hospitals, daycare centers, schools, and other institutions - prisons, shelters, and homes for the elderly, among others - the number of susceptible people in contact with the disease cases must be identified. This measure aims to verify the necessary amount of vaccine and VARIZIG doses to carry out the blockade.\textsuperscript{2}

The vaccine should be administered *selectively* and according to the indications in the State Vaccination Calendar, within **120 hours** (five days); in the case of IGHAV, **96 hours** (four days) after having contact to a suspect or confirmed case of varicella. The action must be performed as described.\textsuperscript{2}

- In children under 9 months of age, pregnant women, and immunosuppressed individuals: administer VARIZIG up to 96 hours after contact with the case.\textsuperscript{2}

- Children from 9 months to 11 months and 29 days: administer one dose of varicella vaccine (attenuated), according to the producing laboratory. Do not consider this dose as valid for the vaccination routine and keep the vaccination schedule.\textsuperscript{2} If the GSK vaccine is not available, use VARIZIG for children under 1 year of age.\textsuperscript{5}

- In children between 12 and 14 months of age: anticipate the dose of MMRV in those already vaccinated with the first dose (D1) of the MMR vaccine and consider it as a valid dose for routine vaccination.\textsuperscript{2}

- Children between 15 months and under 5 years of age: vaccinate according to the recommendations of the State Vaccination Calendar.

- Children 5 to 12 years old: administer one dose of varicella vaccine (attenuated).\textsuperscript{2}

- People aged 13 and older: administer one or two doses, depending on the producing laboratory. When two doses are indicated, consider an interval of 4 weeks between them.\textsuperscript{2}

- Women of child-bearing age should avoid pregnancy until one month after vaccination.\textsuperscript{2}

- The doses administered in the blockade must be recorded in the vaccination voucher and, nominally, in the adopted information system.\textsuperscript{2}
CONTRAINDICATIONS

- Immunocompromised individuals, except as indicated in the CRIE manual.\(^\text{10}\)
- During the period of three months after stopping immunosuppressive therapy or one month in case of corticotherapy.\(^\text{10}\)
- During pregnancy (women of child-bearing age vaccinated should avoid pregnancy for one month after vaccination).\(^\text{10}\)
- Anaphylactic reaction to a previous dose of the vaccine or to any of its components.\(^\text{10}\)

Note - In cases where the vaccine is contraindicated, IGHAV should be used.\(^\text{2}\)

Note - The vaccine should not be used when immunoglobulin, blood and blood products are used prior to vaccination (see intervals in Annex II of the Immunization Program Technical Standard) or within two weeks of vaccination. Revaccinate if there is application under these conditions.\(^\text{11}\)

Note - Due to the rarity of vaccinal virus transmission, varicella vaccine is not contraindicated for people who live with immunosuppressed patients, HIV-infected patients, and pregnant women.\(^\text{10}\)

PRECAUTIONS

- As a precaution, vaccinees who develop varicelliform exanthema, post-vaccination, should avoid contact with immunosuppressed patients and pregnant women. The use of IGHAVZ is not recommended in this circumstance, as the risk of transmission is considered minimal.\(^\text{10}\)
- Avoid the use of salicylates until six weeks after vaccination, due to the association with Reye’s syndrome.\(^\text{5}\)

Note - There is no age limit for varicella vaccination for healthcare workers. It is recommended, however, that health care workers aged 60 years and older undergo rigorous screening to identify possible conditions that contraindicate vaccination.\(^\text{2}\)

Note - Breastfeeding infants and health care workers can receive the vaccine because, to date, there is no evidence of transmission of the vaccine virus via breastfeeding.\(^\text{2}\)

Blood donation - According to Ordinance No. 158 of February 4, 2016, which redefines the technical regulations for hematological therapy procedures, the time of inaptitude for blood donation is four weeks after varicella vaccination.\(^\text{2}\)
SIMULTANEOUS VACCINATION

The varicella vaccine can be given at the same time with other vaccines from the State Vaccination Calendar for children, adolescents, and adults or against covid-19 or drugs. Regarding the MMR vaccines (measles, mumps, and rubella) and yellow fever, if they are not administered on the same day, it is recommended to wait for an interval of at least four weeks.

MMRV should not be given simultaneously with yellow fever vaccine for the first vaccination of children under 2 years of age, and administrations should be spaced at least four weeks apart because of the possibility of interference with the immune response to these agents.11

Note - In special situations such as travel, epidemics, block vaccination, minimizing missed opportunities, simultaneous MMRV and yellow fever vaccination can be performed.11

POST-VACCINATION ADVERSE EVENT SURVEILLANCE

The varicella vaccine is safe in immunocompetent individuals, with adverse event rates ranging from 5% to 35%. Immunosuppressed people may experience more intense, though rarely serious, adverse events.12 The clinical manifestations can be local or systemic.

- Local: symptoms such as pain, hyperesthesia (higher than normal skin sensitivity), or flushing may occur in about 20% of vaccinees in the first hours after application. About 3.5% of vaccinees may have a mild chickenpox-like rash at the application site 8 to 19 days after vaccination.10

- Systemic: fever may occur in about 15% of vaccinees up to 40 days after vaccination. Varicelliform eruption, with five lesions on average, can occur from 5 to 26 days after vaccination. Encephalitis, ataxia, polymorphous erythema, and anaphylaxis have been reported rarely, as have thrombocytopenia.10

- Allergic: anaphylaxis is rare.10

OTHER SITUATIONS ASSOCIATED TO VACCINATION

- Transmission of the vaccine virus to other people can occur but is rare (less than 1%) and only in the presence of a rash. The virus remains attenuated when it is transmitted.10

- The risk of shingles is lower after vaccination than after natural illness. In immunosuppressed
individuals, reactivation of the vaccine virus in the form of herpes-zoster is less frequent than that seen in individuals who had natural infection.\textsuperscript{10}

- The exanthema following vaccination of the immunosuppressed is usually maculopapular and vesicular and can sometimes resemble a mild form of varicella. Most lesions are maculopapular, but in more intense cases vesicles may predominate, and the risk of transmission is higher than in immunocompetent patients. The evolution may be prolonged, lasting up to two months.\textsuperscript{10}

- The frequency of manifestations can vary depending on the chemotherapy treatment and other factors. If necessary, post-vaccine manifestations can be treated with acyclovir because the vaccine virus is sensitive to this drug. Indications for treatment with acyclovir are the presence of more than 50 skin lesions or exanthema lasting more than seven days.\textsuperscript{10}

**HUMAN ANTI-VARICELLA IMMUNOGLOBULIN**

**Composition**

VARIZIG is obtained from human plasma containing high titers of IgG against varicella virus. It contains 10\% to 18\% of globulin and thimerosal as a preservative. Usually, the presentations contain 125 IU per vial, with the volume ranging from 1.25 mL to 2.5 mL. The manufacturer’s guidelines should be observed for each new batch of product.\textsuperscript{2}

**Dosage, route of administration and storage**

The dosage of VARIZIG is 125 IU for every 10 kilograms of the body weight, minimum dosage of 125 IU and maximum of 625 IU and should be applied intramuscularly no later than 96 hours after exposure. VARIZIG must be stored between +2° C and +8° C (36° F and 46° F) and cannot be frozen. The expiration dates are indicated by the manufacturers and must be strictly observed.\textsuperscript{10}

**REFERRALS**

The use of VARIZIG depends on three conditions being met: susceptibility, significant contact, and special risk condition, as defined below.\textsuperscript{2}

- That the susceptible is a person at special risk for severe varicella, that is:
  - immunocompromised children or adults;\textsuperscript{2}
- children less than 1 year of age in hospital contact with VZV;  
- pregnant women;  
- Newborns of mothers in which the varicella infection onset occurred in the last five days of gestation or up to 48 hours after delivery;  
- Preterm newborns, at 28 or more weeks of gestation, whose mother has never had varicella; and  
- preterm newborns, less than 28 weeks’ gestation (or less than 1,000 grams at birth), regardless of any maternal history of varicella.

- That the communicant is susceptible, that is:  
  - immunocompetent person and with immunological impairment without a well-defined history of the disease and/or previous vaccination; and  
  - people with severe cellular immunodepression, regardless of previous history of varicella.

- That there has been significant contact with varicella-zoster virus, i.e.,:  
  - continuous home contact - staying with the patient for at least one hour in an enclosed environment; and  
  - in hospital contact - a person who is in the same room as the patient or who has had prolonged close contact with the patient (at least one hour).

- Note: the VARIZIG has no therapeutic indication. Its use is for prophylactic purposes only.

**CONTRAINDICATIONS**

Anaphylaxis to the previous dose.

**Adverse events**

- Local: erythema, induration, and mild pain are common.

- Systemic: fever, gastrointestinal symptoms, malaise, headache, and exanthema, occasionally.

- Allergic: anaphylaxis is rare.
REFERENCES


4. Martino Mota A, Carvalho-Costa FA. Varicella zoster virus related deaths and hospitalizations before the introduction of universal vaccination with the MMRV vaccine [internet]. Sabroza PC. 2016; 92:361-6 [accessed June 29th, 2022]. Available at: https://www.scielo.br/j/jped/a/6BCZBjyTwyw3S9h9nYQRHxd/?format=pdf&lang=en


