

Varicella and Varicella Vaccines

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Introduction

Diseases resulting from infection with the Varicella-Zoster Virus (VZV) cover a broad clinical spectrum: from typical varicella to serious VZV manifestations or bacterial superinfection. Immunosuppressed individuals, pregnant women, newborns, and the elderly may suffer from severe forms of varicella or herpes zoster. The infection is endemo-epidemic leading to outbreaks in child-care centers, schools, assisted living facilities, and hospitals.^{1,2}

Efficient vaccines are available to prevent these diseases. The incidence and the hospitalization rates of varicella have changed dramatically in countries with universal varicella vaccination, as well as due to the vaccination of individuals at an increased risk of serious disease. Universal varicella vaccination significantly decreases the frequency of VZV diseases in vaccinated and unvaccinated individuals. Some vaccinated individuals acquire the disease, especially those who receive one dose of the vaccine, but the clinical manifestation is mild (fewer than 50 lesions and no fever).^{1,2}

The World Health Organization (WHO) encourages countries to implement universal varicella vaccination whenever infection by VZV is considered a public health problem and/or based on the socioeconomic impact. Sustained vaccine coverage $\geq 80\%$ may be attained with an affordable vaccine. In Latin America (LA), the varicella vaccine is included in the National Immunization Programs (NIP) in Argentina, Brazil, Colombia, Costa Rica, Ecuador, Panama, Paraguay, and Uruguay.^{1,2}

Etiology and Pathogenesis

Together with herpes simplex types 1 and 2, the VZV belongs to the family *Herpesviridae*, within the subfamily *Alphaherpesviridae*. Varicella is the manifestation of the primary infection caused by the VZV. After primary infection with VZV, the virus remains dormant in the sensory nerve ganglia and can reactivate later in life, causing herpes zoster.^{3,4}

The structure of the virus consists of a central nucleus comprising (linear double-stranded) DNA, encased within an icosahedral capsid. It is enveloped by a lipid envelope, developed upon separation from the infected cell. The envelope contains protein and glycoprotein spikes needed for attachment to the infected cell. It is heat labile at room temperature and it deactivates outside of the cell.⁴

The VZV enters the body mainly through the upper respiratory tract and via the inhalation of aerosolized droplets from respiratory tract secretions of patients with varicella. It may enter also through the conjunctiva. The vesicles comprise a large amount of the virus. Direct contact with the vesicles or aerosolized droplets from vesicular fluid may result in infection. Upon replication in the upper respiratory tract mucosa, it spreads quickly to the regional lymphatic tissues; a second round of viral replication takes place in the liver and spleen at days 4 to 6, followed by a secondary viremia at 14 to 16 days following the onset of the infection. The secondary viremia invades capillary endothelial cells and the epidermis, producing intercellular and intracellular edema leading to the formation of the vesicles. The incubation period, the time from when the virus entered the body to when vesicles appeared on the skin (exanthema) and mucosal membrane vesicles (enanthema), ranges mainly between 14 and 16 days, with a minimum of 10 days and a maximum of 21 days. The incubation period may extend up to 28 days if the individual received post-exposure prophylaxis with gammaglobulin. Affected individuals are contagious one to two days prior to exanthema and until all of the lesions have crusted over.¹⁻⁶

The VZV remains dormant in neurons or satellite cells of the sensory ganglia, without being recognized by the immune system. Seemingly, this "immune evasion" allows them to remain intact.^{3,6}

Varicella infection usually confers immunity for life to immunocompetent individuals; clinical reinfection after re-exposure to the VZV is rare but does not prevent latent infection. Cellular and humoral immunity are acquired a few days after onset; cellular immunity limits primary infection and prevents reactivation. The antibodies (immunoglobulins A, M, and G) peak at 4 to 8 weeks after varicella or herpes zoster infection and remain high for 6 months. IgG antibodies remain detectable for decades in immunocompetent individuals.¹⁻⁶

Immune mothers confer protection to their newborns in the first few months of life through the passive transfer of antibodies in the placenta. Modification of cellular immunity predisposes individuals to herpes zoster infection but does not completely compromise immunological response to VZV. For example, older adults with reduced cellular immune response have no recurrent varicella. On the other hand, younger children may suffer from varicella even with detectable levels of prenatal antibodies and there are cases of modified or breakthrough varicella in previously vaccinated children who suffer from leukemia, in spite of having a detectable humoral or cellular immune response to VZV.⁴

Epidemiology

Varicella is a disease with worldwide distribution and variable epidemiology dependent on the climate, population density, and the risk of exposure linked with universal varicella vaccination. In temperate countries without universal varicella vaccination, most of the individuals are infected before their early adult life (10% remain susceptible); incidence is higher in individuals younger than 15 years of age, predominately between 1 and 4 years of age; incidence peaks in winter and spring. In tropical countries, acquisition of infection occurs at older ages; amongst children younger than 15 years of age, predominately in the 5 to 9 years of age. Adolescents and adults are highly susceptible. Incidence peaks over the dry months. Seroprevalence in adults is lower for populations residing on islands or in rural areas.^{1,2,7}

Human beings are the exclusive VZV reservoir and the virus is highly contagious. Upon exposure, it infects individuals who have not acquired the disease or received vaccination. Individuals infected with varicella or herpes zoster transmit the disease from person to person, there is no fomite transmission.¹⁻⁴

Pregnant women are rarely infected since they are usually seropositive due to an earlier varicella infection or vaccination. The clinical manifestation in pregnant women is more severe if they become infected during the third quarter due to the frequency of VZV-induced pneumonia and visceral dissemination. Fetal infection results from prenatal or hematogenous transmission of the virus during the viremic phase of the maternal infection, and it is more likely to develop when infection occurs before week 20 of the pregnancy.¹⁻⁴

Varicella-infected patients are highly contagious in the family setting as well as at schools, recreational facilities, residential facilities, prisons, military units, and hospitals. The attack rate in susceptible cohabitants is between 80% and 90% and there is a higher number of vesicles in these cases. Without universal varicella vaccination, 10% of individuals remain susceptible in the early adult years; many may have an increased risk of exposure or acquisition of severe infection, such as individuals who work with children (teachers), health workers, pregnant women, individuals with severe chronic diseases or immunosuppressed individuals.^{1,2,4-6}

In countries with universal varicella vaccination, there may be a shift in the infection to impact older children aged 9 to 11. Varicella in vaccinated individuals, in particular if one dose was administered, is usually mild with fewer than 50 lesions, mostly without vesicles or fever. These cases are only a third as contagious as individuals infected with typical varicella but transmission of the infection has been documented. Frequently, the index case remains unidentified. This situation may result in varicella outbreaks at schools. Mild varicella is also known as modified varicella or breakthrough varicella: it is the most frequent clinical presentation of vaccine failure, even though typical varicella is still possible.^{3,4,7,8}

Burden of the Disease in Latin America

The most conservative estimates indicate that there are 1,420,000 cases worldwide of varicella every year: 4.2 million are severe cases and approximately 4,200 deaths occur.² In 2012, a meta-analysis to estimate the burden of disease in Latin America and the Caribbean was published. Incidence was 42.9 per 1,000 individuals annually (95% CI: 26.9–58.9) in the population aged 5 and younger. The hospitalization rate was 3.5 per 100,000 population in individuals younger than 15 years of age (95% CI: 2.9–4.1) and the hospitalization period averaged 5 to 9 days. The most frequent complications were: skin infection (3% to 61%), respiratory tract infection (0% to 15%), and neurological problems (1% to 5%).^{1,9}

Recently, new data were published on the burden of disease for varicella in Latin America. When analyzing the data consideration should be given to whether the disease is notifiable, and whether the surveillance is passive or through sentinel sites.¹

In Argentina, the National Health Surveillance System recorded between 150,000 and 180,000 annual cases of varicella during 2008–2013; the estimated rate was 250–450 cases/100,000 population. VZV is a notifiable disease but there is significant underreporting amongst outpatients. Children younger than 10 years of age are most affected: the specific incidence per age is higher between 12 and 48 months. During 1997–2012, an estimated 17 deaths per year were reported, and approximately 60% of the deaths were amongst children younger than 10 years of age. Argentina is estimated to have between 350,000 and 400,000 cases per year. In 2015, the National Immunization Program introduced the vaccine to be administered in one dose at 15 months.^{1,5}

In Brazil, varicella is not a notifiable disease, so reporting is passive. There are no consistent data to estimate incidence. During 2000–2013, the number of cases reported by the Ministry of Health was 7,113, with 3,444 hospitalizations, and 1,503 deaths (39% in children aged 1 to 4 years). However, three million cases are estimated to occur every year. In 2013, Brazil introduced the tetravalent vaccine (measles-rubella-mumps-varicella) in the National Immunization Program for children between 15 months and 2 years as long as they had been previously vaccinated (at 12 months) with a dose of the triple viral vaccine (MMR). In 2017, the period to be vaccinated with the viral tetravalent vaccine was extended to 5 years of age.^{10–12} In 2002, the city of Florianópolis implemented vaccination for children younger than 2 years of age in Brazil. A 75% reduction was observed in the incidence of varicella in the 1–4 years age group. In 2015, at the Meeting of the European Society of Pediatric Infectious Diseases, a case-control study performed in Goiânia and São Paulo was presented, with 74% and 78% vaccine coverage, respectively. The group of children infected with varicella had a lower rate of vaccinees (18.8%) as compared to the group that did not acquire the infection (control group) comprising 54% vaccinees. Vaccine efficacy was 86.5% (95% CI: 70.2%–94.1%) for mild/severe cases.¹³

In Chile, there are 21 sentinel sites throughout all regions of the country. During 2008–2012, the average number of reported cases was 2,135, and was 1,661 in 2013. Varicella reached rates of 16 to 39 per 10,000 population during 2007–2013; the rate was 39.4 in 2011. Children between 1 to 9 years of age were the most affected and accounted for 70% of the cases.¹⁴

In Colombia, an incidence of 140/100,000 population was reported during 2005–2009, and increased to 213/100,000 population during 2010–2015. The highest incidence occurred in the 1 to 9 years age group (accounting for 67.4% of the cases). During 2012–2015, 2,126 varicella cases were reported in pregnant women accounting for 0.3% to 0.8% of the cases reported yearly. During 2012–2015, 5,488 hospital admissions (averaging 1,372 cases/year) were reported, accounting for 1% to 2% of the total number of cases; children younger than 5 years of age were most affected, followed by the 15–24 year age group and those older than 60 years. In the same period, there were 114 deaths due to varicella. In July 2015, the varicella vaccine was introduced into the National Immunization Program as part of a two-dose schedule (12 months and 5 years).¹

In Costa Rica, varicella is a notifiable disease. During 1991–2006, the annual rates ranged between 400 and 800 cases/100,000 population. In 2007, the varicella vaccine was included in the National Immunization Program for children aged 15 months. For 8 years during the pre-vaccine period, the Infectious Disease Department of the National Children's Hospital recorded 432 discharges of complicated varicella cases, including 58% amongst children younger than 2 years of age. The average hospital stay was 5 days (ranging from 1 to 44 days) and mortality was 2.8%. Eight years after the introduction of universal varicella vaccination, and upon averaging coverage at 84.3% (ranging from 76% to 95%) in the target population, the reduction of incidence was 73.8% for the total population and 79.1% for children younger than 5 years of age. The reduction of hospitalizations was 85.9% in the general population and 87% in children younger than 5 years of age. These data demonstrate an important herd effect.^{1,15–16}

In Mexico, varicella is a notifiable disease but cases are believed to be underreported. The incidence of varicella is cyclical, peaking every 4 to 5 years. A total incidence that ranged between 2.33 and 3.81/100,000 population, with a 2.98 median was reported during 1995–2010. Most of the infected population was younger than 10 years of age. The National Health Surveillance System reported meningoencephalitis in 4.6% of hospitalized varicella cases, pneumonia in 2.5%, and other complications in 18%. The varicella vaccine is not included in the Mexican National Immunization Program; however, it is indicated for populations at risk: children attending day-care centers, immunocompromised individuals, pediatric cancer patients (following the safety criteria established for application), and staff at day-care centers and assisted-living facilities, who have not acquired the disease or

have seroprotection.¹ In 2017, a publication analyzed data about hospitalization for varicella from the National Information System for Epidemiological Surveillance (SUIVE) from 2000 to 2013. The average number of annual cases of varicella was 296,733, mostly in children under 9 years (57%) and mostly during March to May. From 2004 to 2012, hospital discharge of varicella included 17,398 cases, of which 4.6% had meningoencephalitis, 2.5% had pneumonia and 18% had other complications.¹⁷

In Paraguay, varicella is a notifiable disease. During 2007–2012 before the introduction of the vaccine, the annual average number of cases was 3,500, ranging from 2,000 to 4,200. In 2013, universal varicella vaccination was introduced with one dose at 15 months.⁶

In Peru, varicella was not a notifiable disease until 2016. Before 2016, the Regional Health Directorates (DIREAS) reported a yearly average of 4,000 cases during 2009–2015, and 36,296 medical consultations during 2009–2014. Seventy-nine percent of the individuals who received care were younger than 11 years of age. In 2016, 9,977 cases were reported and outbreaks of severe varicella were recorded.^{1,18,19} A retrospective study conducted amongst 1,073 patients hospitalized for complicated varicella at the National Institute of Children's Health (INSN) observed that 72% developed skin and soft tissue superinfection, and neurological (18%) and ocular complications (8%). Sixty-nine cases (6%) suffered from severe varicella with complications. Most of the cases were in children aged 2 and 5 years (46%). Fatality was 1.2% due to necrotizing varicella and pneumonia. Peru also has data on the health care cost for hospitalized patients.^{20,21}

In Uruguay, varicella is a notifiable disease. It was the first country in Latin America to include varicella vaccination as part of the National Immunization Program in 1999, with a dose at 12 months. As of 2014, two doses are administered (12 months and 5 years). Coverages have ranged between 95% and 97%. In the pre-vaccine period, there were outbreaks every two to three years. Until 2007, those affected were not vaccinated. Starting in 2010, 70% of the cases were reported amongst vaccinated individuals due to the increase of vaccinated cohorts, mostly as outbreaks in schools. During the vaccine period, the majority of infected individuals had fewer than 50 lesions, did not require hospitalization, and no deaths were reported. In the pre-vaccine period, annual reporting reached about 5,000 cases. In 2009, 1,000 cases were reported. During 1989–1998, incidence in the general population averaged 148/100,000 population (95% CI: 136–144), decreased to 39 (95% CI: 36–40) in 2000–2012, accounting for a 73% reduction. The rate continued to decrease to 20/100,000 population in 2009, and remained nearly unchanged in the following years until the rate reached 58/100,000 in 2013. This increase was related to mild varicella outbreaks (breakthrough infections) in vaccinated children during school outbreaks. In 2014, the second dose was added. The rates in 2014 and 2015 were 40 and 41 per 100,000, respectively.^{1,7,22} Hospitalizations (including intensive care) decreased significantly by 81% in children younger than 15 years of age and by 94% in children aged 1 to 4 years. There was a significant reduction in outpatient care (-87%). The association between varicella and severe infections due to *S. pyogenes* or *S. aureus* in vaccinated individuals has not been described during the vaccine period. Vaccination with one dose significantly reduced morbidity, hospitalizations and mortality. The addition of a second dose will contribute to controlling outbreaks and will increase individual protection as well as the herd effect already acquired.^{1,7,8}

In Venezuela, varicella is a notifiable disease. During 2007–2014, 267,282 cases were reported. The highest incidence was in children ranging from 12 months to 14 years of age (59% of the cases). Varicella ranks ninth as the most frequent cause for medical consultation. During 1989–2011, 1,072 deaths were attributed to varicella. In 2014 and 2015, the incidence rate was 146.17/100,000 population (44,153 cases) and 146.69/100,000 population (44,922 cases at week 40), respectively. The annual average number of deaths was 30 throughout all age groups. However, during the years 1994, 2001, and 2008, 90 deaths were reported annually.¹

Outbreaks

In the Latin American countries with universal varicella vaccination, mild outbreaks clearly prevail at schools. In countries without universal varicella vaccination, outbreaks continue to occur every 3 to 4 years with cumulative cases in cities or regions with severe clinical manifestations and fatalities.^{7,8,15,17,18}

Clinical Manifestation

Varicella

The incubation period ranges between 14 and 16 days and is asymptomatic. The typical clinical picture starts with mild fever and malaise over 24 to 48 hours before the onset of exanthema and enanthema. The vesicles appear in successive rashes 6 to 24 hours apart and are significantly pruritic. Initially, the lesions are macules or erythematous papules; within hours they develop a central vesicle and evolve to crusting. The polymorphic exanthema develops from the trunk to the extremities and the scalp. The three types of lesions co-exist in the same area. Unvaccinated individuals present between 250 and 500 vesicles. Seven to 14 days after the onset of the exanthema crusting resolves mostly without scarring. Usually it is a benign and self-limiting disease; occasionally it may leave sequela or turn fatal. Asymptomatic primary infection is very rare. Symptomatic reinfection is infrequent in immunocompetent individuals.¹⁻⁵

The most frequent complication is bacterial superinfection (impetigo or cellulitis). It may evolve into fasciitis, necrotizing cellulitis, myositis, bacterial pneumonia or sepsis. The germs involved are mostly *Streptococcus pyogenes* and *Staphylococcus aureus*. Toxic shock syndrome is a rare but very severe complication. In terms of frequency, it is followed by central nervous system impairment: acute cerebellar ataxia (1/4,000 cases) and encephalitis (1.7/100,000 cases). Ten percent of cases are left with sequela and mortality ranges between 5% and 20%.¹⁻⁴

Other infrequent complications include: aseptic meningitis, Guillain-Barré syndrome, transverse myelitis, thrombocytopenic purpura (generally 1 to 2 weeks after the onset of the disease), Reye's syndrome, arthritis, glomerulonephritis, myocarditis, pericarditis, hepatitis, orchitis, and neutropenia.^{1,2,4,5}

In general, the following persons are at high risk of developing severe symptoms: immunocompromised individuals, susceptible pregnant women, newborns whose mothers acquired varicella in the perinatal period, and healthy adolescents or adults.^{2,4,5}

In immunosuppressed individuals with impaired cellular immunity (persons living with the human immunodeficiency virus/acquired immunodeficiency syndrome [HIV/AIDS], patients with leukemia or solid tumors, solid organ transplants or hematopoietic cell recipients, patients under extended corticosteroid or immunosuppressive treatment), varicella has higher morbidity and mortality rates; with numerous vesicles and persistent fever; visceral dissemination of VZV (pneumonitis, hepatitis, central nervous system impairment); hemorrhagic varicella (vesicles with hemorrhagic content) and recurring herpes zoster are the most frequent. Complications affect 40% of these cases.^{4,5}

Congenital varicella syndrome (CVS) and perinatal varicella are potentially extremely severe. The incidence of CVS in pregnant women is approximately 1–5/10,000 pregnancies based on the risk of exposure. The risk of fetal infection is about 25%; 1% to 2% of infected individuals during the first 20 weeks of the pregnancy may suffer from congenital malformations. This is the highest risk period. CVS is characterized by low birth weight, hypoplasia/aplasia, and paresis in the extremities, rudimentary fingers and skin scars. Neurosensory features include: microcephaly, cortical and cerebellar atrophy, psychomotor retardation, seizures, chorioretinitis, optic atrophy, blindness, cataracts, nystagmus, and microphthalmia, and hearing loss. These extremely severe cases may result in high incidence of zoster during childhood, as well as fetal and child mortality.^{1,2,4,5}

Regarding perinatal varicella, when the maternal disease occurs between 5 and 21 days before delivery, the neonatal infection manifests in the first 4 days of life; prognosis is generally good with transplacental transmission of antibodies. When the diagnosis of maternal varicella occurs within 5 days before and up to 48 hours after delivery, the newborn is at high risk of suffering from severe varicella with pneumonitis, hepatitis or encephalitis; due to the lack of passage of antibodies to the newborn and immunological immaturity. Mortality may reach 30%.^{1,2,4,5}

Varicella in adolescents and adults may result in higher fever, greater general impairment and higher number of lesions. About 10% of such cases are left with scars or severe complications, including pneumonia. Their risk for hospitalization is nine times higher and the risk to suffer from encephalitis is seven times higher than in children. Fatality rates in healthy adults are 30 times higher than in children. Susceptible pregnant women have an even higher risk of severe disease and complications.^{1,4,5}

Herpes Zoster

Ten to thirty percent of individuals who have acquired varicella may suffer from herpes zoster at about 50 years of age. Infected individuals have painful erythematous vesicular exanthema with grouped lesions, following sensory dermatomes. VZV is transmitted through direct contact with the vesicles and may cause varicella in susceptible contacts. About 15% of the patients experience pain or paresthesia in the affected dermatome for several weeks or months (post-herpes neuralgia). Herpes zoster in children is usually milder than in adults; it is more frequent in patients with HIV/AIDS. In immunocompromised individuals, it may affect several dermatomes, spread to the skin beyond the primary dermatomes (the pancreas, lungs, liver, and the central nervous system) and may be fatal.^{2,4} In México from 2000 to 2013, 7,042 discharges due to herpes zoster were notified, mainly in patients 65 years or older, in a female-male ratio of 1.3:1. The most frequent complications were: neuralgia (11%), eye involvement (7%), meningoencephalitis (5.4%) and disseminated disease (2.8%).^{1,7}

Diagnosis

Diagnosis is clinical and difficult to establish in vaccinated or immunocompromised individuals. The presence of the virus may be confirmed in vesicle, tissue or body fluid samples through polymerase chain reaction (PCR) techniques that detect the DNA or viral culture. The PCR may differentiate the natural virus from the vaccine virus; as it is highly sensitive. The viral culture is less sensitive but it may differentiate the VZV from the herpes simplex virus; yet it is costly and the result takes weeks. Viral antigens may be detected in material from lesions through direct immunofluorescence (marked antibodies). The observation of multinucleated giant cells (inclusion bodies) is a less sensitive method than antigen detection and it is not VZV specific.^{1–4}

The detection of IgG serum in the acute and convalescent phase is a specific method with low sensitivity. The detection of IgM in the acute stage is a specific method but it is not the most reliable to either confirm or rule out infection.^{3,4}

The serology to assess past infection or response to vaccination is difficult to interpret. Absence of antibodies does not imply susceptibility since cellular immunity controls viral replication. About 20% of individuals older than 55–65 years of age do not demonstrate measurable cellular immunity, despite having antibodies and a history of varicella.^{3–5}

Treatment

The treatment of varicella with acyclovir or valacyclovir (administered orally) reduces the duration and severity of cutaneous and systemic manifestations. It is not recommended for healthy children. It is indicated during the first 24 hours of the disease (72 hours maximum) in: individuals older than 12 years of age, carriers of mucocutaneous and chronic pulmonary diseases, immunocompromised individuals under treatment with corticosteroids for extended periods (chronically or intermittently), and individuals under acetyl salicylic acid (ASA) treatment. Some experts recommend treatment of secondary intrafamilial cases. Intravenous therapy is indicated in immunosuppressed individuals. Valacyclovir is approved for the treatment of varicella in individuals between 2 and 17 years of age. Treatment of herpes zoster (orally) should be initiated promptly (before 72 hours) in immunocompetent individuals. Immunocompromised individuals or patients requiring hospitalization should be treated intravenously with acyclovir.^{2–4}

Prevention

Primary prevention of VZV infection may be active through vaccination or passive through the administration of specific anti-VZV antibodies (immunogenicity).

Varicella Vaccine

The live attenuated vaccine is prepared with natural Oka strain, disseminated in cellular cultures and attenuated. In 1970, it was developed in Japan by Professor Michiaki Takahashi. It contains gelatin and residual amounts of neomycin. The monovalent vaccine is approved in immunocompetent individuals aged 12 months and older. The tetravalent vaccine (MMR) was approved more than 10 years ago in children between 12 months and 12 years of age. According to the Latin American Society for Pediatric Infectious Diseases (SLIPE), in some Latin American countries this vaccine is approved for administration as of 9 months.

As of 2016, vaccine availability in Latin America includes: Varivax (Merck & co.), Varilrix (GSK), Priorix Tetra (GSK), Varicella Vaccine (Biken) with Oka strain, and Sudovax (Green Cross) with Corea MAV/06 strain. The WHO does not specify the minimum number of plaque-forming units (PFU) required. The licensed varicella vaccines guarantee a PFU content range between 1,000 and 17,000 PFU. In several randomized studies, the efficacy of

one vaccine dose has been shown to range between 90% to 100% with 10,000 and 17,000 PFU. The vaccines are administered subcutaneously. Upon reconstitution of the freeze-dried solution, vaccine administration should occur within 30 minutes. The freeze-dried vaccine is stored refrigerated (2–8°C) and protected from light, to ensure stability for the two years of its shelf life.^{1,23,24}

Immunogenicity

Between 76% and 85% of healthy children vaccinated with one dose develop a humoral immune response to VZV at levels considered protective: ≥ 5 units/ml in glycoprotein-based enzyme-linked immunosorbent assays (gpELISA) or fluorescent antibodies to membrane antigen (FAMA) $\geq 1:4$. The individuals who were administered two doses reached significantly higher seroprotection levels (close to 100% for ≥ 5 units/ml gpELISA). The cell-mediated immune response is higher in individuals receiving two doses.^{3,4}

The efficacy of the one-dose schedule ranges between 70% and 90% for infections of any type and it reaches 95% for severe disease. Effectiveness, upon certification, to prevent any type of infection is around 85% for the Oka strains vaccines, with few studies showing lower or higher values. One vaccine dose has 97% effectiveness or higher for the prevention of severe varicella. In a case-control study, the effectiveness of a single dose of universal varicella vaccine in South Korea, where the most common vaccine contains the Korea MAV/06 strain, was 54%.²⁵

The two-dose schedule is 3.3 times less likely to result in varicella due to secondary vaccination failure (breakthrough varicella), as compared to the one-dose schedule during the first ten years after vaccination. This schedule demonstrated 98% effectiveness for all types of infection and disease severity.^{1–3}

The vaccine may be administered simultaneously with other childhood vaccines. If not administered simultaneously, the interval between the MMR and varicella vaccines is 28 days. The vaccine virus is susceptible to acyclovir, valacyclovir, or famcyclovir, therefore the administration of these products should be avoided between 1 and 21 days following vaccination.³

The vaccine is properly tolerated and safe. Adverse events are usually mild and occur in 5% to 35% of healthy children and in 20% to 30% of adults. The most common side effects are local erythema, swelling, and pain, within 3 days post vaccination.

Between 1 and 3% of vaccinated individuals develop localized vesicles during the first week after vaccination, and from 3% to 5% develop varicelliform rash with few lesions between 7 and 28 days after vaccination. The vaccine virus is transmitted only if the vaccinee develops exanthema. It should be noted that a measles-like rash occurs in 2% to 3% of the vaccinees who were administered the MMRV or the monovalent vaccine + MMR vaccine. Fever occurs in 22% of children aged 12–23 months after one dose of the tetravalent MMRV vaccine and in 15% of the individuals receiving the varicella + MMR vaccines separately. A fever and a rash occur within 5 to 12 days post-vaccination. They are usually short-lived and leave no sequela. There is a slightly higher risk of febrile seizures and higher likelihood of experiencing fever after the first dose of the MMRV vaccine, as compared to MMR + monovalent varicella vaccine. After one dose of the MMRV vaccine, an additional febrile seizure is expected in every 2,300 to 2,600 vaccinated young children, as compared to the MMR + monovalent varicella vaccine. When administering the second dose to children older than 4–6 years of age, there was no difference in the incidence of fever, rash or febrile seizures amongst MMRV and MMR + varicella vaccinees.^{1–3}

In immunocompromised individuals, the adverse reactions may be more severe; 20% to 40% may develop a varicelliform rash. Visceral dissemination of the attenuated virus is unusual.¹⁻³

Post-certification surveillance shows that healthy vaccinated children have a lower risk than unvaccinated children to develop herpes zoster.²⁻⁴

Herpes Zoster Vaccine

In 2006, a vaccine against herpes zoster was licensed and prepared with the Oka strain with 19,400 PFU for administration in individuals aged ≥ 50 in a one dose schedule.^{2,4}

Contraindications

The varicella vaccine should not be routinely administered to children who suffer from congenital or acquired T-cell immunodeficiency, including individuals with leukemia, lymphoma, and other malignancies affecting the bone marrow or the lymph system, as well as children under long-term immunosuppressive medication. Exceptions include certain children infected by HIV (children with no evidence of earlier disease and with 15% or higher CD4 T cell count). It is contraindicated in pregnant women and pregnancies should be avoided one month after vaccination.^{3,4}

Monovalent vaccines do not contain egg proteins. The measles and mumps vaccines included in MMRV are produced in chicken embryo cultures. The amount of egg protein for cross reactions are negligible. Children with an egg allergy may receive the MMRV vaccine without prior skin testing.^{3,4}

Other Strategies to Control Outbreaks and Avoid Disease in Exposed Individuals

Avoiding Infection in Susceptible Individuals Exposed to VZV

- Only vaccination ensures long-term protection; vaccinate ≥ 12 months over the first 3 days and no later than 5 days post-exposure. A second dose is recommended (minimum 3 month interval).
- Administration of anti-VZV antibodies (purified immunoglobulin from human plasma, with a high content of VZV specific antibodies), during the first 96 hours post-exposure. Standard immunoglobulin is an alternative option to consider.
- Administration of acyclovir orally, within the first 7 days post-exposure, may be useful to prevent or attenuate the disease in healthy individuals.

Educational or Residential Institutions Where Children, Adolescents, and Adults Coexist

- Individuals affected by varicella should stop attending school or individual isolation shall be established at the institution where they reside. They will be assisted by individuals who are not susceptible. They will be reintegrated once the exanthema is in the crusting phase.
- The same recommendation applies for herpes zoster.

Protecting Patients, Health Workers and Visitors from Hospital Exposure to Varicella

- Vaccinate individuals who did not acquire varicella or did not receive two doses of the vaccine. If one dose was administered (common situation in Latin America), administer the second dose (if the previous dose was administered at least three months ago). Prophylaxis should not be delayed to perform serological studies intended to confirm vaccine-based immunity or natural infection (to be performed if easily accessible).
- Discharge any susceptible individuals who were exposed as soon as possible upon performing active or passive prevention, or with antiviral drugs, as the case may be.
- Susceptible cases that cannot be discharged must be isolated from the eighth day of exposure (after the incubation period) until 21 days post-exposure.^{3,4}

Conclusions

VZV infection is prevalent in children and it is potentially severe in some groups with special clinical situations. There are treatment and prevention strategies for varicella that have changed the epidemiology and clinical aspect of this disease, and they must be taken into consideration to take health actions at the population and individual level.

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