ISSN: 3032-3134 (ONLINE)
InaJBCS Indonesian Journal of Biomedicine and Clinical Sciences

Current topics in human varicella infection: Pearls and challenges

Luthvia Annisa[1]*, Mohamad S. Hakim[2], Abu T. Aman[1]

[1]Department of Microbiology, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia, [2]Postgraduate School of Molecular Medicine, Erasmus MC-University Medical Center, Rotterdam, the Netherlands

https://doi.org/10.22146/inajbcs.v56i4.16811

Submitted: 2023-08-02
Accepted : 2024-02-29

ABSTRACT

Varicella zoster virus (VZV), an alphaherpesvirus, is a highly contagious and neurotropic virus infecting the majority of the adult and pediatric population worldwide. Varicella zoster virus is the only human herpesvirus for which a licensed live attenuated vaccine has been developed. It can be considered that additional study on VZV is superfluous given the significant success of the VZV vaccines. This has been the case for other viruses including rubella and measles, for which effective vaccinations are widely available. Contrarily, much regarding VZV, a complex and chronic human disease due to its latency, still needs to be uncovered. Over the past two decades, our understanding of the molecular biology of VZV and its pathogenicity has expanded. In this review, we discussed our recent understanding of VZV biology, pathogenesis as well as its clinical aspect, including diagnosis, clinical management, and vaccine development.

ABSTRAK

Virus varicella zoster (*Varicella zoster virus*/VZV), salah satu anggota *alphaherpesvirus*, merupakan virus neurotropik dan sangat mudah menular. Sebagian besar populasi anak-anak dan dewasa di seluruh dunia telah terinfeksi virus ini. Virus varicella zoster adalah satu-satunya anggota famili herpesviridae yang dapat dicegah dengan pemberian vaksin. Karena keberhasilan vaksin terhadap pencegahan infeksi VZV, muncul asumsi bahwa penelitian lebih lanjut terhadap VZV menjadi tidak diperlukan lagi. Hal yang sama terjadi virus lain yang telah memiliki vaksin yang efektif, seperti virus campak dan rubela. Padahal fakta menunjukkan sebaliknya, masih banyak yang harus kita teliti terkait VZV. Karena kemampuannya dalam berkembang menjadi infeksi laten, infeksi VZV menjadi kompleks dan persisten dalam tubuh manusia. Oleh karena itu, dalam dua dekade terahir, pengetahuan terhadap biologi molekuler dan patogenesis infeksi VZV berkembang dengan pesat. Pada artikel ini, kami membahas pengetahuan terkini tentang aspek biologi dari VZV, patogenesis, dan juga aspek klinis, meliputi diagnosis, manajemen, dan pengembangan vaksin.

Keywords:
clinical manifestation;
diagnosis;
replication;
vaccines;
varicella zoster virus

INTRODUCTION

Herpesviruses have been found in a large variety of vertebrates. Naturally, each herpesvirus is specifically associated with a single host species. Indeed, several herpesviruses have been known to infect humans. This host-specific herpesvirus infection indicates that they are well adapted to their hosts over a long time. Thus, herpesviruses have been recognized as a group of viruses with magnificent evolutionary success.[1]

The economic burden associated with VZV infection is substantially

*corresponding author: luthvia.annisa@ugm.ac.id

high.[2] Varicella zoster virus is highly contagious. It is a neurotropic virus infecting the majority of adult and pediatric populations worldwide.[3] Varicella zoster virus belongs to the *Varicellovirus* genus. Clinically, VZV infection manifests in two distinct forms: primary infection with a widespread vesicular skin rash (chickenpox or varicella) and reactivation of latent infection with a particular dermatomal skin rash [shingles or herpes zoster (HZ)]. Following the primary infection (varicella), VZV establishes a long-term stage of infection (latency) in the sensory ganglia, and in a specific condition, VZV can be reactivated.[4] The incidence of HZ increases with age or in various immunosuppressed conditions.[5]

Many animal models of VZV infection have been developed. Seroconversion without clinical signs has been observed following experimental VZV inoculations in mice and guinea pigs.[6] On the other hand, infection with the closely related simian varicella virus (SVV) in non-human primates (NHP) resulted in varicella.[7] Despite being laborious and expensive, the NHP model has offered vital insights into the neurotropism and pathophysiology of varicella that are not possible with any other models.[8] During the past two decades, understanding of the molecular biology of VZV and its pathogenicity has markedly increased.

In this review, we discussed current developments in the knowledge of both the biological and clinical aspects of human varicella infections, as well as highlight aspects as to why VZV is a complex pathogen to humans.

MATERIALS AND METHODS

We searched two literature databases: MEDLINE and Google Scholar for human varicella infections, using the Boolean search string of 'Varicella OR human varicella OR varicella zoster virus AND (epidemiology OR diagnostic OR management OR complications OR vaccine). After removing duplicates, a total of 61 articles were used and synthesized for a narrative review.

RESULTS AND DISCUSSION

Epidemiology of varicella

Globally, varicella is considered endemic in many populations and sustains whole-year transmission, with epidemics occurring every two to three years. Five viral clades and their corresponding geographic distribution have been found by viral genomic studies: clades 1, 3, and 5 are European in origin; clade 2 comprises Asian strains, including the parental Oka strain from which varicella vaccine was developed; and clade 4 comprises African strains.[9,10] In India, several outbreaks were reported between 2015-2020, but the majority occurred in tribal mountainous areas.[11] In Indonesia, the exact number of prevalence could not be found. There is only one study reporting the seroprevalence of varicella zoster antibodies to be two-thirds of the population at the age of 15 y.o., but this study was conducted over 20 yr ago.[12]

In temperate regions, the incidence of varicella is most common in preschool-aged and early elementary school children, with an annual incidence of over 100 per 1,000 children. In tropical regions, the mean age of contracting varicella is older, with a higher proportion of cases occurring in adults. The differences may be caused by the virus's characteristics, such as its inactivation by heat and/or humidity, or variables that influence the risk of exposure.[9,13]

There is a noticeable seasonal trend to varicella, with peak incidence occurring

in the winter and spring or the cool, dry season.[13] Typically, outbreaks occur in places where children congregate, such as daycares and schools, although they can also happen in other age groups. Recently, in the Bantul district, Special Region of Yogyakarta, Indonesia, an outbreak of varicella was reported in an elementary school affecting eighteen students and is confirmed to have originated from one student, illustrating varicella's high reproduction number.[14] The epidemiology of varicella has undergone significant changes in nations where childhood immunization against the disease is recommended. Within the United States (US) where it has universal varicella vaccination, hospitalizations, and deaths have decreased by almost 95% since the program's introduction in 1995, concluding a herd immunity achieved, and in addition to that, a stoppage of yearly outbreaks.[15-17]

While the global epidemiology study is well documented for varicella, the same cannot be said about zosters, where the majority of epidemiology studies were reported from developed countries only. The incidence of zosters is higher nowadays than it was decades ago, but it is mainly due to the advances in medicine that result in the growing of the elderly population above anything else.[9,17,18]

The biology of VZV and its pathogenesis

The structure of virion particle

The diameter of the VZV particle (virion) is ~150-200 nm. The virion is composed of three concentric layers (FIGURE 1).[19] The innermost layer is an icosahedral nucleocapsid core containing the VZV genome. The capsid is composed of several proteins that are encoded by *orf20*, *orf21*, and *orf23* genes, among others. The second (middle) layer is a tegument, consisting of various viral- and host-derived proteins surrounding the nucleocapsid. Its precise structure is less understood, yet mainly consists of regulatory proteins, such as the intermediate-early (IE) protein that functions as viral transactivating factors. It is also composed of viral proteins with unknown functions. The outermost layer is a lipid-rich envelope composed of a host-derived lipid bilayer (lipid membrane) with inserted viral glycoproteins, including glycoprotein B (gB)/gH-gL, which form the minimal (core) fusion complex.[19]

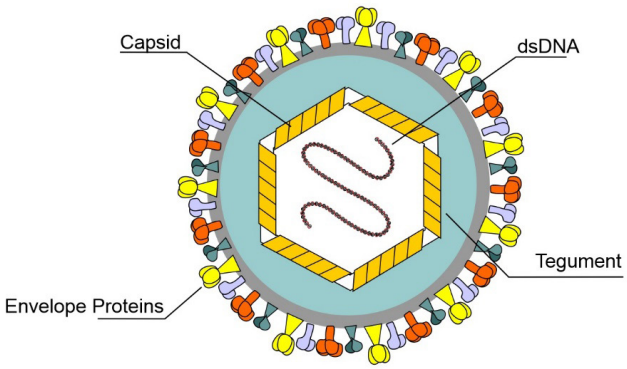

FIGURE 1. Schematic representation of the VZV particle (virion).[19]

The genome of VZV

Varicella zoster virus has a linear double-strand DNA genome, about 125 kbp in length. Its G+C content is about 46%. However, the VZV genome can undergo circularization mediated by unpaired bases at each end. The genome encodes at least 71 unique open reading frames (ORFs). The majority of VZV genes (about two-thirds) are essential for viral replication, as shown in various *in vitro* studies. Most of them belong to the 40 well-characterized genes that are present in all herpesviruses.[20] The genome consists of a unique long (UL) of ~105,000 bp and a unique short (US) region of ~5,232 bp. Additionally, the genome contains internal (IR) and terminal repeat (TR) regions.[19]

VZV entry into target cells

Similar to other viruses, the life cycle of VZV begins with the entry of the virion. Currently, this entry process remains poorly understood. Presumably, it goes via either endocytosis or direct fusion of viral particles with the plasma membrane. The surface glycoproteins, including gB, gH, and gL, play a pivotal role as the core fusion complex. They are suggested to interact with cell surface molecules, including myelin-associated glycoprotein or mannose-8-phosphate receptors.[19] Following entry into a specific target cell, the tegument protein is subsequently released. This release leads to an alteration of the intracellular environment of the infected hosts, thereby inhibiting antiviral responses and importantly, influencing the outcome of the virus life cycle, i.e., lytic or latent infections.[20]

VZV replication within the target cells

The nucleocapsid core goes through primary envelopment, packages newly generated genomic DNA, moves to the inner nuclear membrane, and buds across the nuclear membrane. The nucleocapsid thus experiences de-envelopment during translocation to the cytoplasm. The nucleocapsid enters the cytoplasm, followed by a secondary envelopment in the cisternae of the trans-Golgi network (TGN). The nucleocapsid undergoes secondary envelopment by acquiring viral glycoproteins (that mature in the trans-Golgi region) and the tegument proteins (that assemble in vesicles). Nascent viral particles are then transported out to the cell surfaces, via post-Golgi compartment vesicles, where the freshly assembled virus particles are finally released (FIGURE 2).[8]

The first enveloped progeny of virions is identified nine hours following primary infection. Within twelve hours of infection, numerous virions are found on the cell surfaces. The assembled virions of VZV often maintain a highly cell-associated state, which makes it distinct from other viruses. The same viral glycoproteins thought to facilitate the entrance process are produced on the cell membranes and facilitate the fusion of the infected and uninfected cells. This process results in the formation of syncytia and multinucleated polykaryocytes, which furthers the virus's ability to disseminate throughout the body.[19,20]

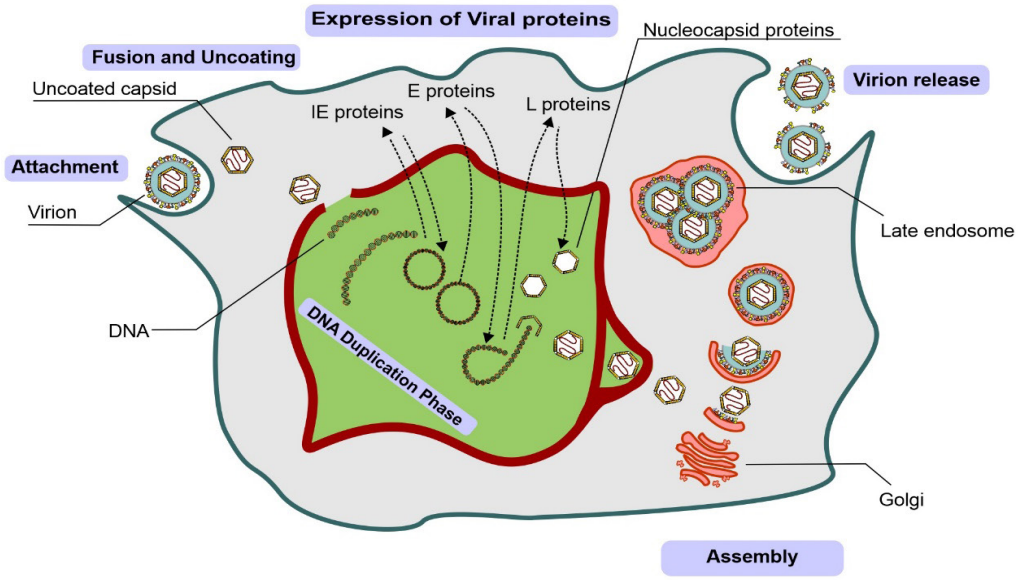

FIGURE 2. VZV life cycle (replication) within the infected cells.[19]

Transmission of VZV

Varicella zoster virus is a virus that spreads easily and mostly does so in two ways: 1) by coming into close proximity with skin lesions that haven't completely healed and crusted (contact transmission); or 2) by inhaling viral aerosols from vesicular skin lesions (airborne transmission).[21,22] The period of communicability lasts from one to two days prior to the appearance of the rash until all lesions have crusted.[23] Indeed, in the period of 24 to 48 hr before the first skin eruption, the infected host is highly contagious and spreads the virus through the respiratory route.[23,24] Skin lesions from varicella and zoster both have a lot of infectious viruses in them, which is how they spread to those who are vulnerable. While viral transmission from people with HZ may occur and can result in the development of primary varicella infection in susceptible individuals, HZ is considered to be less infectious than varicella.[25]

Pathophysiology and clinical manifestations of VZV infection

Primary VZV infection

Varicella zoster virus enters the host mainly through the upper respiratory tract but sometimes conjunctiva is also involved. The epithelial cells of the upper respiratory tract mucosa are the first and the main site of viral replication in primary VZV infection.[26,27] Those patients primarily contracted with VZV may experience prodromal symptoms before the development of classic vesicular rash.[28] Subsequently, the virus is disseminated to the tonsils and other local lymphoid tissues. This process contributes to the bloodstream spread of the virus and is mediated by the systemic circulation of the infected T cells to the skin.[29,30] A widely distributed vesicular rash develops after an incubation period of about 10 to 21 d. However, the host is highly contagious and can transmit VZV via the respiratory route even 24 to 48

hr before the initial skin eruption. These rashes are mainly present on the trunk, head, and face (FIGURE 3 and 4).[24,31,32]

Over a few days, the skin lesions commonly progress from papules to vesicles, and then to crusts. The lesions can be found anywhere from a few to several hundreds of vesicles, with approximately 500 lesions. In severe cases, more severe rashes are usually observed and thus, take a more prolonged time to completely heal. Concomitant symptoms experienced by the patients include fever, malaise, and fatigue. The symptoms frequently last about one week.[24,32]

In addition to the discomfort of the primary skin eruption, primary VZV infection can result in severe consequences that increase morbidity and death. These complications include superinfections of bacteria that may lead to necrotizing fasciitis, meningoencephalitis, cerebellar ataxia, and Guillain-Barre syndrome (GBS), as well as pneumonitis and even death.[24,33-35] In a high-risk population group, the clinical symptoms of primary VZV infection might be more severe. Pregnant women, newborns, those who have never been vaccinated or exposed to an infection before, older adolescents, and those with compromised cellular immunity are among the high-risk populations.[24]

After being vaccinated, a person may still get the illness when exposed to the virus. Vaccine recipients who still get varicella infection typically experience milder illnesses with fewer vesicles and side effects compared to the natural infection. The name “breakthrough varicella” refers to this condition, which is less communicable than primary varicella.[36] A one-dose vaccine recipient is far more likely to disseminate the virus to exposed varicella-susceptible individuals than a two-dose vaccine recipient. When a person catches varicella despite receiving two doses of the immunization, the disease is typically extremely mild and may be difficult to recognize as varicella, both in terms of clinical manifestation or by the laboratory profile.[31,37]

Establishment of latent infection and reactivation

After the primary infection resolves, VZV enters the nerve ending and by retrograde axonal transport to the sensory nerve ganglia in the dorsal root ganglion where it stays dormant, this marks the state of VZV latent infection which can happen for decades until it is reactivated. Herpes zoster, which is characterized by a vesicular rash in the dermatome, innervated by the afflicted ganglion, is caused by VZV accessing the skin during reactivation via anterograde axonal transport (FIGURE 3 and 4).[19] HZ, often referred to as “zoster”, is the illness that results from the symptomatic reactivation of VZV. The typical manifestation of zoster is the emergence of a unilateral, dermatomal skin rash that is painful and/or itchy. However, it is currently known that zoster may also occur without a rash.[31]

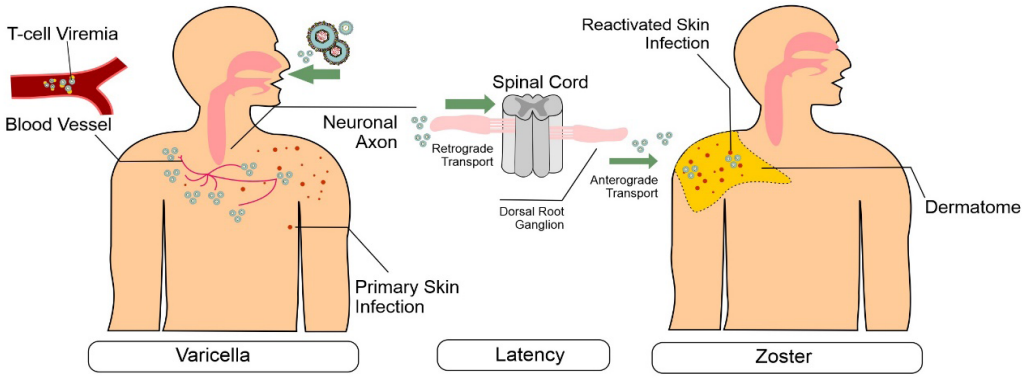

FIGURE 3. Illustration on how VZV causes varicella (primary infection), establishes latency, and then undergoes reactivation.[19]

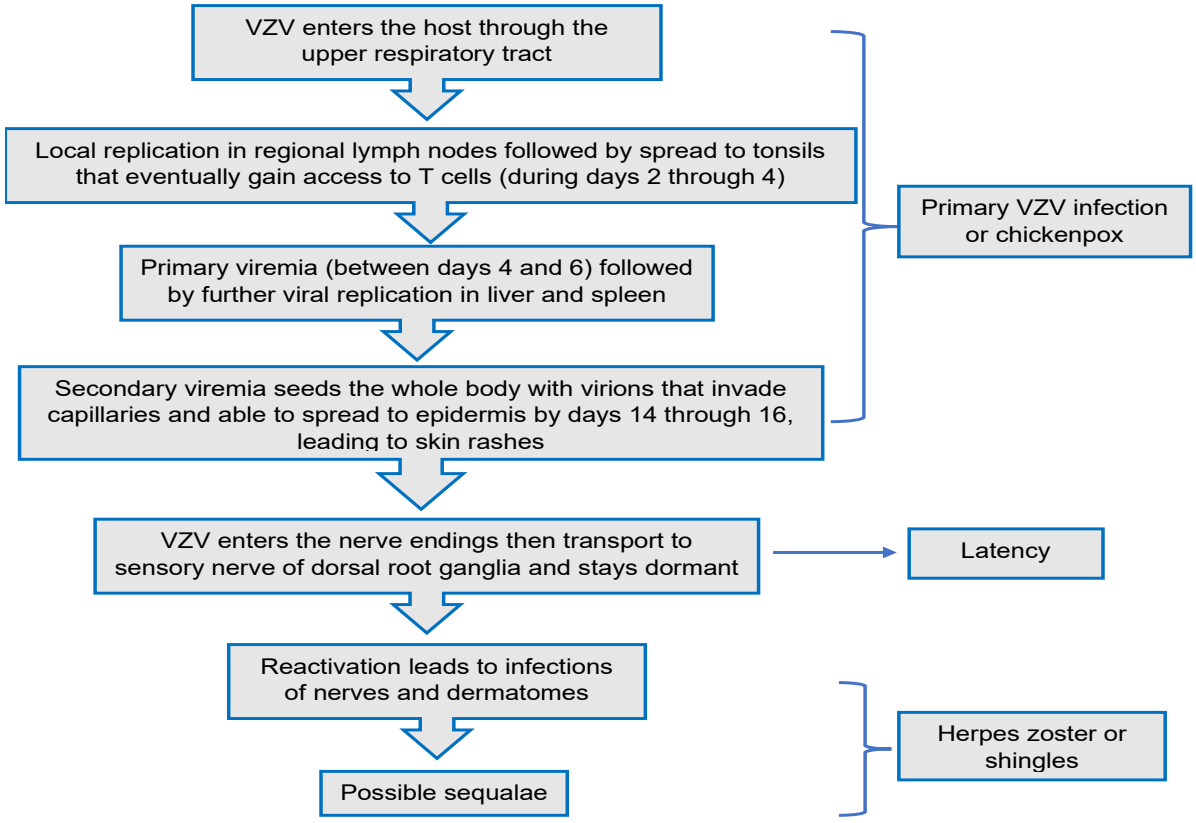

FIGURE 4. Schematic diagram showing the pathophysiology of human VZV infection.[31,32]

Development of HZ is associated with the waning of cellular mediated immunity (CMI) against VZV infection. VZV-specific CMI is essential for suppressing the onset of HZ.[38] This phenomenon is also observed in people with immunocompromised organ transplant recipients and people with HIV/AIDS.[39,40] However, the exact mechanism of viral reactivation following the decrease of the host CMI as well as the role of the humoral immunity remain unclear and thus need further studies.[8,38] Several findings indicate that contact with varicella patients enhances immunity to VZV and the risk of developing HZ.[38]

The zoster incubation period is unknown since the process of reactivation is not well understood. A unilateral vesicular rash on the trunk in one or two adjacent dermatomes is a defining feature of the zoster presentation. Despite it can also occur on the face, head, or extremities, it usually does not cross the body's midline.[31] Although zoster is approximately half as transmissible as varicella, the vesicles are still packed with infectious virions that can spread through the air and infect surrounding varicella-susceptible individuals and cause chickenpox.[21,25] The zoster eruptions may be mild to moderate and resolve quickly, or it can be in a more severe form with larger lesions that may linger for several weeks, and in some cases, a painful complication known as post-herpetic neuralgia (PHN) may develop. Elderly patients and immunocompromised individuals are more prone to experience this complication.[31]

Several different neurological problems are linked to VZV reactivation, as follows: VZV vasculopathy, Giant cell arteritis, segmental weakness and myelopathy, VZV encephalitis, VZV cranial neuropathies, GBS, and zoster sine herpete (ZSH). It is a specific term used when typical dermatomal discomfort associated with VZV develops without the associated rash.[31]

Diagnosis of VZV infection

The most frequent method of diagnosis for varicella and zoster is through clinical examination. When a broad or isolated dermatomal vesicular skin rash manifests, the clinical diagnosis of VZV infection has often been made. The diagnosis can be established by isolation of VZV DNA in the skin lesions by polymerase chain reaction (PCR) in rare instances (such as atypical rashes or rashes probably caused by other causes, including poxviruses, rickettsia, or contact dermatitis). It is also possible to use a culture of VZV from skin lesions, although this method is more costly, takes longer, is less accessible, and is less sensitive than PCR. Viral DNA may be found in cerebrospinal fluid (CSF) and/or saliva in individuals with suspected encephalitis, meningitis, and other VZV-related disorders. Although reliable, VZV-specific antibody measurements in blood samples do not provide quick enough data for clinical application due to the time needed for patients to produce antibodies.[31,32]

Submission of clinical samples

Skin vesicles (submitted as swabs, fluid, or scabs), saliva, tissue, bronchoalveolar lavages (BAL), EDTA blood, amniotic fluids, and CSF are examples of clinical samples used for PCR diagnosis. If neurological symptoms or signs are present, CSF may also be used. The patient's sample must be transported in its primary container together with an outer package made of adsorbing material and packaged in a transport box (cardboard box). Shipping at room temperature is feasible; chilling is only advised if the samples will be used for viral isolation in cell culture. Early, meticulous sample collection and

optimal laboratory transfer are crucial for fruitful viral isolation.[32,41,42] A case of neuroretinitis caused by the VZV was confirmed by PCR testing of the ocular fluid has been reported.[43]

Viral detection

Virus detection provides confirmative evidence that a patient has an acute VZV infection. For the detection of viral genomes in vesicles, tissues, CSF, BAL, EDTA blood, or amniotic fluids, PCR is the method of choice.[44,45] The PCR is particularly significant for evaluating CSF in the event of suspected acute CNS infections as well as for detecting amniotic fluids in the prenatal diagnosis of varicella infection during pregnancy.[46,47]

Only limited cell types, including human embryonic fibroblasts, allow for the isolation of VZV. This process is lengthy, demanding, and lacks clinically applicable sensitivity. It also calls for a high degree of laboratory experience.[44] Noteworthy, only vesicle fluids with a high viral load are appropriate for viral isolation. For effective isolation, samples must be carefully and promptly collected, and they must be transported in the best possible way.[42]

Detection of antibodies

The assessment of antibody status following varicella immunization in healthy children, adolescents, and adults is not required due to the high rates of seroconversion. However, for healthcare professionals and immunodeficient vaccination recipients, immunological status management is advised.[42] Serological VZV diagnosis is important to identify susceptible persons who need active or passive immunoprophylaxis.

To assess the immunity status following varicella vaccination and for vaccine research, highly sensitive procedures such as particular glycoprotein enzyme-linked immunosorbent assays (ELISAs) or the fluorescent antibody to membrane antigen (FAMA) test should be performed.[48] The measurement of VZV IgG seroconversion can be used to provide a laboratory diagnosis of VZV primary infection (varicella). In order to do this, blood samples must be collected sequentially, with the initial sample needing to be anti-VZV IgG-negative. At the earliest, on the fourth day following the beginning of illnesses, anti-VZV IgM will be detected, typically in conjunction with anti-VZV IgG.[42]

In a country with a universal varicella vaccination program, such as the US, serologic testing for varicella can be more challenging to interpret, due to changes in the course of immunity in vaccinated persons. In this case, PCR testing remains the diagnostic test of choice.[49]

Therapy for VZV infection

General approach

In general, children experience a more benign form of varicella compared to adults and adults have a higher incidence of complications.[50] The majority of varicella infections are self-limiting, treatment is more focused on supportive care and alleviating the discomforts, such as itching which can be very frustrating. Histamine lotion and a cool bath can be advised in addition to giving nutritious meals to support the speedy recovery.

In contrast, a severe form of varicella may require hospitalization to monitor the potential complication. Admitted patients should be cared in negative airflow rooms whenever possible.[51] Airborne and contact precautions should be implemented until all lesions are dry and crusted. If no negative airflow room is available, patients suffering from varicella should be kept in closed

rooms isolated from others who have no evidence of immunity. Ideally, only healthcare personnel who have evidence of immunity against varicella can take care of varicella patients.[52]

Antiviral therapy

Antiviral therapy is only recommended for patients with clinically severe infections or those at risk of complications due to advanced age (elderly), immunocompromised conditions, and chronic respiratory or skin diseases.[32] A pathway for determining whether to administer antiviral therapy for primary varicella infection is shown in FIGURE 5.

By administering antiviral therapy, VZV replication in infected cells can be blocked.[53,54] Early treatment, particularly for zoster, may lessen tissue damage and, as a result, the loss of damaged ganglion cells may be slowed down or even be avoided. For antiviral therapy, the acyclic nucleoside analogs acyclovir, including its prodrug (valaciclovir), famciclovir (prodrug of penciclovir), and the cyclic nucleoside analog brivudin [(E)-5-(2-bromovinyl)-2′-deoxyuridine, BVDU], are primarily used.[42]

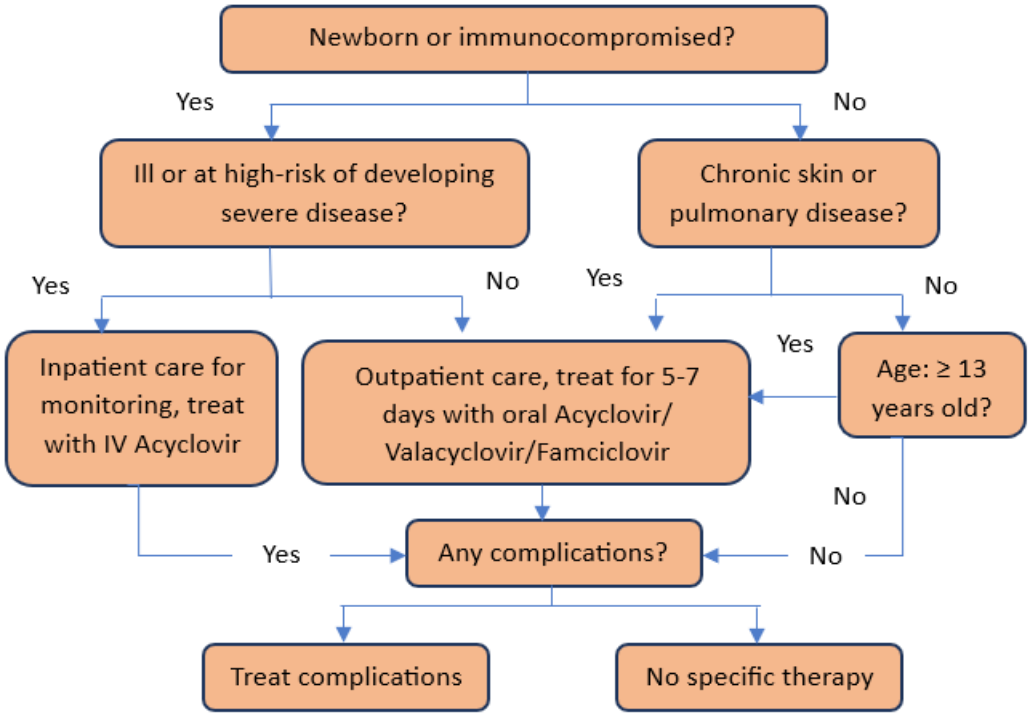

FIGURE 5. Therapeutic approach for primary varicella infection.[32]

Antiviral prophylaxis for specific populations

Varicella can be extremely serious and even fatal in specific populations, such as immunocompromised people, expectant mothers, and newborns with no evidence of varicella immunity. In this case, a post-exposure prophylaxis (PEP) approach is advised to reduce the illness severity and lower the risk of having complications including pneumonitis, rather than to prevent them from contracting the infections. Previously, a Varicella Zoster Immunoglobulin (VZIG) was recommended routinely to the populations who were concerned about experiencing the severe form of the disease. However, several considerations were put forth afterward, mainly due to the scarcity of VZIG supply, another factor is the evidence of the safety and efficacy of using antivirals for this purpose. Currently, the United Kingdom Health Security Agency (UKHSA) recommends antivirals be given as PEP to all at-risk groups with the exception of vulnerable newborns exposed within one week of delivery (either in utero or post-delivery), while VZIG is given when antivirals are contraindicated only. The recommended antiviral is acyclovir with a dose of 10 mg/kg body weight (up to a maximum of 800 mg) four times daily, given from days 7 to 14 after significant exposure to varicella or zoster during the infectious period.[55]

The development of VZV vaccine

VZV is the only human herpesvirus for which a licensed live attenuated vaccine has been developed. This vaccine is based on attenuation of the Oka strain.[56] This vaccine possesses high safety and effectiveness profiles. It significantly reduces the burden of VZV-related diseases worldwide, although it is far from eradication. The World Health Organization (WHO) recommends universal vaccination program in countries where varicella become a significant health problem.[57]

After a single dose of varicella vaccines, this vaccine effectively protects against all forms of diseases in 76% to 85% of vaccinees and reaches up to 100% after two doses. It also prevents hospitalization in more than 95% of the vaccines.[57] In the US, with a low vaccination coverage (currently ~34%), the vaccine annually prevents >120,000 cases of severe cases of HZ.[58]

Among important factors associated with vaccine effectivity is the waning of the immune system with increasing age.[59,60] This phenomenon of immunosenescence reduces the strength and longevity of vaccine-induced immunological responses. Overall, 51% of vaccinees ≥60 years of age are protected against HZ. However, for individuals aged 70 to 79, it drops to 41%, and older vaccinees have even greater declines.[58]

The development of the new vaccine is achieved by designing a subunit vaccine (HZ/su) composed of the AS01B adjuvant and recombinant VZV gE. The adjuvant functions to direct the type of immunological response and strengthen it. The AS01B is made up of liposomes containing the saponin QS21 (a pure extract from the tree Quillaja saponaria) and an agonist of Toll-like receptor 4 (TLR4), the monophosphoryl lipid A (MPL). In animal models, the combination of gE and ASO1B stimulates both robust CD4+ T cells and antibody responses.[58]

Special consideration regarding viral reactivation

Despite a significant decrease in primary varicella prevalence due to the successful vaccination program, the nature of reactivation in varicella infection is another major concern.[61] Indeed, some hypotheses are put forth that circulating VZV and periodic

outbreaks of varicella are needed to maintain the community levels of immunity to suppress the incidence of zoster in the adult population who have previously been infected.[57,62] However, this belief is proven to be not factual. Varicella vaccination has been confirmed to induce herd immunity, which protects those who cannot be vaccinated, such as newborns.[63] In addition, zoster incidence also declined significantly among vaccinated children and adolescents, probably as a result of the vaccine strain's lower reactivation rates compared to the wild-type VZV.[62]

Due to the debilitating impact of zoster, especially on the older age groups, immunization has been strongly advised as a preventive measure. Previously, a live-attenuated vaccine (Zostavax®) was approved by the US Food and Drug Administration (US FDA), but later to be discontinued in 2020 due to the high side effects compared to its effectiveness. Recently, a recombinant subunit vaccine, Shingrix®, with an overall vaccine efficacy of 97.2% among participants 50 y.o. or older was approved by the US FDA in 2017 and is now recommended by the U.S. Centers for Disease Control and Prevention (the US CDC) as zoster prophylaxis in elderly.[64]

CONCLUSION

Though human VZV infection is often a minor and self-limiting condition, serious consequences can happen. For this consideration, in 1988, WHO advised the national varicella vaccine for nations where varicella poses a serious threat to public health. To date, VZV is the only human herpesvirus in which an effective vaccine is available. A successful vaccination story of varicella in the US showed the importance of both individual and herd immunity to combat VZV infection. A long-lasting immunity to either natural or vaccine-derived varicella develops, however, it does not confer protection to the host from virus reactivation.

Due to the combination of the benign nature of the primary infection and the successful vaccination, a VZV infection is often overlooked. One would believe that more investigation into the VZV virus is superfluous given the vaccines' significant level of effectiveness. Contrarily, there is still much to learn about VZV, a complex and chronic human infection due to its latency.

Surveillance study is needed to fully understand the global health burden associated with varicella, especially in areas where HIV incidence is high. Reactivation of VZV in the elderly and immunocompromised people following spontaneous infection or immunization is a global concern and results in a debilitating disease that may impair the quality of life. Since the sequelae are difficult to manage, thus preventing it through vaccination is crucial. Continued monitoring of the effectiveness and safety of the newly approved zoster subunit vaccine is mandatory, along with better epidemiology surveillance for zoster to assist in informing key health policymakers and later facilitate the implementation of zoster vaccination in a country.

ACKNOWLEDGMENTS

The authors would like to thank Fatah Manohara for his assistance in preparing the figures.

REFERENCES

1. Davison AJ. Evolution of the herpesviruses. Vet Microbiol 2002; 86(1-2): 69-88. https://doi.org/10.1016/s0378-1135(01)00492-8
2. Pawaskar M, Meroc E, Samant S, Flem E, Bencina G, Riera-Montes M, *et al*. Economic burden of varicella in Europe in the absence of universal

varicella vaccination. BMC Public Health 2021; 21(1):2312. https://doi.org/10.1186/s12889-021-12343-x
3. Huang J, Wu Y, Wang M, Jiang J, Zhu Y, Kumar R, *et al*. The global disease burden of varicella-zoster virus infection from 1990 to 2019. J Med Virol 2022; 94(6):2736-46. https://doi.org/10.1002/jmv.27538
4. Laing KJ, Ouwendijk WJD, Koelle DM, Verjans G. Immunobiology of varicella-zoster virus infection. J Infect Dis 2018; 218(suppl_2): S68-S74. https://doi.org/10.1093/infdis/jiy403
5. Arvin AM. Varicella-zoster virus. Clin Microbiol Rev 1996; 9(3):361-81. https://doi.org/10.1128/CMR.9.3.361
6. Walz-Cicconi MA, Rose RM, Dammin GJ, Weller TH. Inoculation of guinea pigs with varicella-zoster virus via the respiratory route. Arch Virol 1986; 88(3-4):265-77. https://doi.org/10.1007/BF01310880
7. Meyer C, Kerns A, Barron A, Kreklywich C, Streblow DN, Messaoudi I. Simian varicella virus gene expression during acute and latent infection of rhesus macaques. J Neurovirol 2011; 17(6):600-12. https://doi.org/10.1007/s13365-011-0057-y
8. Mahalingam R, Gershon A, Gershon M, Cohen JI, Arvin A, Zerboni L, *et al*. Current in vivo models of varicella-zoster virus neurotropism. Viruses 2019; 11(6):502. https://doi.org/10.3390/v11060502
9. Gershon A, Takahashi M, Seward J. In: Plotkin S, Orenstein W, Offit P, eds. Vaccines: Saunders Elsevier; 2011: 915-58.
10. Breuer J, Grose C, Norberg P, Tipples G, Schmid DS. A proposal for a common nomenclature for viral clades that form the species varicella-zoster virus: summary of VZV Nomenclature Meeting 2008, Barts and the London School of Medicine and Dentistry, 24-25 July 2008. J Gen Virol 2010; 91(Pt 4):821-8. https://doi.org/10.1099/vir.0.017814-0
11. Kujur A, Kiran KA, Kujur M. An epidemiological study of outbreak investigation of chickenpox in remote hamlets of a tribal state in India. Cureus 2022; 14(6):e26454. https://doi.org/10.7759/cureus.26454
12. Juffrie M, Graham RR, Tan RI, Widjaja S, Mulyadi S, Weil J, *et al*. Seroprevalence of hepatitis A virus and varicella zoster antibodies in a Javanese community (Yogyakarta, Indonesia). Southeast Asian J Trop Med Public Health 2000; 31(1):21-4.
13. Lolekha S, Tanthiphabha W, Sornchai P, Kosuwan P, Sutra S, Warachit B, Chup Upprakarn S, *et al*. Effect of climatic factors and population density on varicella zoster virus epidemiology within a tropical country. Am J Trop Med Hyg 2001; 64(3-4):131-6. https://doi.org/10.4269/ajtmh.2001.64.131
14. Dinkes ungkap penyebab belasan siswa SD di Bantul terkena cacar air October 2023. https://rejogja.republika.co.id/berita/s2f3bv399/dinkes-ungkap-penyebab-belasan-siswa-sd-di-bantul-terkena-cacar-air.
15. Marin M, Seward JF, Gershon AA. 25 years of varicella vaccination in the United States. J Infect Dis 2022; 226(Suppl 4):S375-9. https://doi.org/10.1093/infdis/jiac251
16. Elam-Evans LD, Valier MR, Fredua B, Zell E, Murthu BP, Sterrett N, *et al*. Celebrating 25 years of varicella vaccination coverage for children and adolescents in the United States: a success story. J Infect Dis 2022; 226(Suppl 4):S416-24. https://doi.org/10.1093/infdis/jiac337
17. Dooling K, Marin M, Gershon AA. Clinical manifestations of varicella: disease is largely forgotten, but it's not gone. J Infect Dis 2022; 226(Suppl 4):S380-4. https://doi.org/10.1093/infdis/jiac390

18. Goh AEN, Choi EH, Chokephaibulkit K, Choudhury J, Kuter B, Lee PI, *et al*. Burden of varicella in the Asia-Pacific region: a systematic literature review. Expert Rev Vaccines 2019; 18(5):475-93. https://doi.org/10.1080/14760584.2019.1594781
19. Zerboni L, Sen N, Oliver SL, Arvin AM. Molecular mechanisms of varicella zoster virus pathogenesis. Nat Rev Microbiol 2014; 12(3):197-210. https://doi.org/10.1038/nrmicro3215
20. Depledge DP, Sadaoka T, Ouwendijk WJD. Molecular aspects of varicella-zoster virus latency. Viruses 2018; 10(7):349. https://doi.org/10.3390/v10070349
21. Hatsushika Y, Nii I, Taniguchi T. Varicella caused by airborne transmission of a localised herpes zoster infection in a family. BMJ Case Rep 2021; 14(9):e243217. https://doi.org/10.1136/bcr-2021-243217
22. Marziano V, Poletti P, Beraud G, Boelle PY, Merler S, Colizza V. Modeling the impact of changes in day-care contact patterns on the dynamics of varicella transmission in France between 1991 and 2015. PLoS Comput Biol 2018; 14(8):e1006334. https://doi.org/10.1371/journal.pcbi.1006334
23. Lachiewicz AM, Srinivas ML. Varicella-zoster virus post-exposure management and prophylaxis: A review. Prev Med Rep 2019; 16:101016. https://doi.org/10.1016/j.pmedr.2019.101016
24. Newman AM, Jhaveri R. Myths and misconceptions: Varicella-zoster virus exposure, infection risks, complications, and treatments. Clin Ther 2019; 41(9):1816-22. https://doi.org/10.1016/j.clinthera.2019.06.009
25. Viner K, Perella D, Lopez A, Bialek S, Newbern C, Pierre R, *et al*. Transmission of varicella zoster virus from individuals with herpes zoster or varicella in school and day care settings. J Infect Dis 2012; 205(9):1336-41. https://doi.org/10.1093/infdis/jis207
26. Sawyer MH, Wu YN, Chamberlin CJ, Burgos C, Brodine SK, Bowler WA, *et al*. Detection of varicella-zoster virus DNA in the oropharynx and blood of patients with varicella. J Infect Dis 1992; 166(4):885-8. https://doi.org/10.1093/infdis/166.4.885
27. Haberthur K, Meyer C, Arnold N, Engelmann F, Jeske DR, Messaoudi I. Intrabronchial infection of rhesus macaques with simian varicella virus results in a robust immune response in the lungs. J Virol 2014; 88(21):12777-92. https://doi.org/10.1128/JVI.01814-14
28. Ma H, Fontaine R. Varicella outbreak among primary school students--Beijing, China, 2004. MMWR Suppl 2006; 55(1):39-43.
29. Jones D, Como CN, Jing L, Blackmon A, Neff CP, Krueger O, *et al*. Varicella zoster virus productively infects human peripheral blood mononuclear cells to modulate expression of immunoinhibitory proteins and blocking PD-L1 enhances virus-specific CD8+ T cell effector function. PLoS Pathog 2019; 15(3):e1007650. https://doi.org/10.1371/journal.ppat.1007650
30. Ku CC, Zerboni L, Ito H, Graham BS, Wallace M, Arvin AM. Varicella-zoster virus transfer to skin by T Cells and modulation of viral replication by epidermal cell interferon-alpha. J Exp Med 2004; 200(7):917-25. https://doi.org/10.1084/jem.20040634
31. Kennedy PGE, Gershon AA. Clinical features of varicella-zoster virus infection. Viruses 2018; 10(11):609. https://doi.org/10.3390/v10110609
32. Gershon AA, Breuer J, Cohen JI, Cohrs RJ, Gershon MD, Gilden D, *et al*. Varicella zoster virus infection. Nat Rev Dis Primers 2015; 1:15016. https://doi.org/10.1038/nrdp.2015.16

33. Islam B, Islam Z, GeurtsvanKessel CH, Jahan I, Endtz HP, Mohammad QD, *et al*. Guillain-Barre syndrome following varicella-zoster virus infection. Eur J Clin Microbiol Infect Dis 2018; 37(3):511-8. https://doi.org/10.1007/s10096-018-3199-5
34. Yan Y, Yuan Y, Wang J, Zhang Y, Liu H, Zhang Z. Meningitis/meningoencephalitis caused by varicella zoster virus reactivation: a retrospective single-center case series study. Am J Transl Res 2022; 14(1):491-500.
35. Masih I, Boyle R, Donnelly A, Soye A, Kidney J. Varicella pneumonitis in an immunocompetent patient. BMJ Case Rep 2011; 201:(bcr0820103259. https://doi.org/10.1136/bcr.08.2010.3259
36. Leung J, Broder KR, Marin M. Severe varicella in persons vaccinated with varicella vaccine (breakthrough varicella): a systematic literature review. Expert Rev Vaccines 2017; 16(4):391-400. https://doi.org/10.1080/14760584.2017.1294069
37. Gershon M, Gershon A. Varicella-zoster virus and the enteric nervous system. J Infect Dis 2018; 218(suppl_2):S113-9. https://doi.org/ 10.1093/infdis/jiy407
38. Asada H. VZV-specific cell-mediated immunity, but not humoral immunity, correlates inversely with the incidence of herpes zoster and the severity of skin symptoms and zoster-associated pain: The SHEZ study. Vaccine 2019; 37(44):6776-81. https://doi.org/10.1016/j.vaccine.2019.09.031
39. Kwon DE, Lee HS, Lee KH, La Y, Han SH, Song YG. Incidence of herpes zoster in adult solid organ transplant recipients: A meta-analysis and comprehensive review. Transpl Infect Dis 2021; 23(4):e13674. https://doi.org/10.1111/tid.13674
40. McKay SL, Guo A, Pergam SA, Dooling K. Herpes zoster risk in immunocompromised adults in the United States: A systematic review. Clin Infect Dis 2020; 71(7):e125-e34. https://doi.org/10.1093/cid/ciz1090
41. Sauerbrei A. Varicella-zoster virus infections - antiviral therapy and diagnosis. GMS Infect Dis 2016; 4:Doc01. https://doi.org/10.3205/id000019
42. Sauerbrei A. Diagnosis, antiviral therapy, and prophylaxis of varicella-zoster virus infections. Eur J Clin Microbiol Infect Dis 2016; 35(5):723-34. https://doi.org/10.1007/s10096-016-2605-0
43. Choi RY, Lauer A, Rosenbaum JT. Molecular diagnosis and ocular imaging of varicella zoster virus associated neuroretinitis. Am J Ophthalmol Case Rep 2018; 11:146-8. https://doi.org/10.1016/j.ajoc.2018.07.002
44. Wilson DA, Yen-Lieberman B, Schindler S, Asamoto K, Schold JD, Procop GW. Should varicella-zoster virus culture be eliminated? A comparison of direct immunofluorescence antigen detection, culture, and PCR, with a historical review. J Clin Microbiol 2012; 50(12):4120-2. https://doi.org/10.1128/JCM.06753-11
45. Schmutzhard J, Merete Riedel H, Zweygberg Wirgart B, Grillner L. Detection of herpes simplex virus type 1, herpes simplex virus type 2 and varicella-zoster virus in skin lesions. Comparison of real-time PCR, nested PCR and virus isolation. J Clin Virol 2004; 29(2):120-6. https://doi.org/10.1016/s1386-6532(03)00113-6
46. Wong AA, Pabbaraju K, Wong S, Tellier R. Development of a multiplex real-time PCR for the simultaneous detection of herpes simplex and varicella zoster viruses in cerebrospinal fluid and lesion swab specimens. J Virol Methods 2016; 229:16-23. https://doi.org/10.1016/j.jviromet.2015.12.009
47. Meyberg-Solomayer GC, Fehm T, Muller-Hansen I, Enders G, Poets

C, Wallwiener D, *et al*. Prenatal ultrasound diagnosis, follow-up, and outcome of congenital varicella syndrome. Fetal Diagn Ther 2006; 21(3):296-301. https://doi.org/10.1159/000091360
48. Liu J, Ye X, Jia J, Zhu R, Wang L, Chen C, *et al*. Serological evaluation of immunity to the varicella-zoster virus based on a novel competitive enzyme-linked immunosorbent asay. Sci Rep 2016; 6:20577. https://doi.org/10.1038/srep20577
49. Dollard S, Chen MH, Lindstrom S, Marin M, Rota PA. Diagnostic and immunologic testing for varicella in the era of high-impact varicella vaccination: An evolving problem. J Infect Dis 2022; 226(Suppl 4):S450-5. https://doi.org/10.1093/infdis/jiac363
50. Gershon AA, Gershon MD. Pathogenesis and current approaches to control of varicella-zoster virus infections. Clin Microbiol Rev 2013; 26(4):728-43. https://doi.org/10.1128/CMR.00052-13
51. Chickenpox (Varicella), For health care professionals. 2022. https://www.cdc.gov/chickenpox/hcp/index.html
52. Indonesia Ministry of Health. Peraturan Menteri Kesehatan Nomor 27 Tahun 2017 tentang Pedoman Pencegahan dan Pengendalian Infeksi di Fasilitas Pelayanan Kesehatan 2017.
53. Kim JE, Song YJ. Anti-varicella-zoster virus activity of cephalotaxine esters in vitro. J Microbiol 2019; 57(1):74-9. https://doi.org/10.1007/s12275-019-8514-z
54. Park S, Kim NE, Park BJ, Kwon HC, Song YJ. Kaempferol interferes with varicella-zoster virus replication in human foreskin fibroblasts. Pharmaceuticals (Basel) 2022; 15(12):1582. https://doi.org/10.3390/ph15121582
55. Agency UHS. Guidelines on post exposure prophylaxis (PEP) for varicella or shingles (January 2023). 2023.
56. Yamanishi K. Molecular analysis of the Oka vaccine strain of varicella-zoster virus. J Infect Dis 2008; 197 Suppl 2:S45-8. https://doi.org/10.1086/522122
57. Varela FH, Pinto LA, Scotta MC. Global impact of varicella vaccination programs. Hum Vaccin Immunother 2019; 15(3):645-57. https://doi.org/10.1080/21645515.2018.1546525
58. Cunningham AL, Levin MJ. Herpes zoster vaccines. J Infect Dis 2018; 218(suppl_2):S127-33. https://doi.org/10.1093/infdis/jiy382
59. Hong K, Sohn S, Choe YJ, Rhie K, Lee JK, Ham MS, *et al*. Waning effectiveness of one-dose universal varicella vaccination in Korea, 2011-2018: a propensity score matched national population cohort. J Korean Med Sci 2021; 36(36):e222. https://doi.org/10.3346/jkms.2021.36.e222
60. Levin MJ. Immune senescence and vaccines to prevent herpes zoster in older persons. Curr Opin Immunol 2012; 24(4):494-500. https://doi.org/10.1016/j.coi.2012.06.002
61. Hertel M, Heiland M, Nahles S, Laffert MV, Mura C, Bourne PE, *et al*. Real-world evidence from over one million COVID-19 vaccinations is consistent with reactivation of the varicella-zoster virus. J Eur Acad Dermatol Venereol 2022; 36(8):1342-8. https://doi.org/10.1111/jdv.18184
62. Gershon AA, Gershon MD, Shapiro ED. Live attenuated varicella vaccine: Prevention of varicella and of zoster. J Infect Dis 2021; 224(12 Suppl 2):S387-97. https://doi.org/10.1093/infdis/jiaa573
63. Waye A, Jacobs P, Tan B. The impact of the universal infant varicella immunization strategy on Canadian varicella-related hospitalization rates. Vaccine 2013; 31(42):4744-8. https://doi.org/10.1016/j.vaccine.2013.08.022
64. Shah RA, Limmer AL, Nwannunu CE, Patel RR, Mui UN, Tyring SK. Shingrix for herpes zoster: A review. Skin Therapy Lett 2019; 24(4):5-7.