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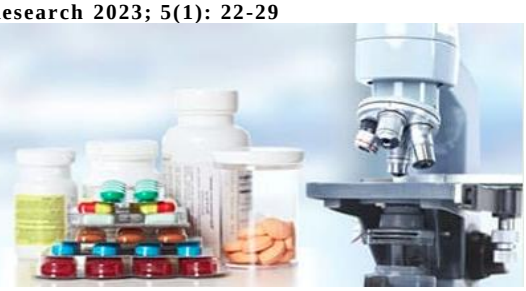

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Yash Srivastav
Department of Pharmacy, Goel Institute of Pharmacy & Sciences (GIPS), Lucknow, Uttar Pradesh, India

Moni Rawat
Department of Pharmacy, Goel Institute of Pharmacy & Sciences (GIPS), Lucknow, Uttar Pradesh, India

Akhandnath Prajapati
Department of Pharmacy, Goel Institute of Pharmacy & Sciences (GIPS), Lucknow, Uttar Pradesh, India

Nisha Bano
Department of Pharmacy, Goel Institute of Pharmacy & Sciences (GIPS), Lucknow, Uttar Pradesh, India

Madhaw Kumar
Department of Pharmacy, Goel Institute of Pharmacy & Sciences (GIPS), Lucknow, Uttar Pradesh, India

Corresponding Author:
Yash Srivastav
Department of Pharmacy, Goel Institute of Pharmacy & Sciences (GIPS), Lucknow, Uttar Pradesh, India

Review of the symptoms, pathogenesis, and available treatments for the Chickenpox

Yash Srivastav, Moni Rawat, Akhandnath Prajapati, Nisha Bano and Madhaw Kumar

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Abstract
The varicella-zoster virus (VZV), which causes chickenpox or varicella, is a contagious illness. The virus is in charge of causing chickenpox. Anywhere in the world, sneezing, coughing, and direct skin contact with lesions can spread the chickenpox virus. It may start to spread one to two days before the rash manifests and continue to do so until all lesions have crusted over. Those who are not immune can contract chickenpox from shingles sufferers through touch with their blisters. The disease is recognized based on the symptoms that are now present, and the diagnosis is then confirmed by polymerase chain reaction (PCR) testing of the blister fluid or scabs. In India, chickenpox is among the most commonly neglected diseases. Chickenpox is more common in children and those with weakened immune systems. There are complications as a result. In 1990, there were recorded 11,200 deaths from chickenpox worldwide, and 6,800 in 2010. The virus may remain dormant in the ganglion and reactivate as a result of ageing, immunity (acquired, inherited, or iatrogenic), and other factors. Falling cellular immunity is one of the main causes of zoster, which can occur for a variety of reasons. In this review study, the pathophysiology, aetiology, symptoms, and combined therapy of chickenpox are discussed.

Keywords: Chickenpox, epidemiology, histology, symptoms, pathophysiology, treatments

Introduction
Varicella, also known as chickenpox, is a highly contagious skin disease that can be transferred through airborne or direct contact between people who have either varicella or herpes zoster (HZ). HZ is caused by the varicella-zoster virus (VZV), which has been latently infecting the dorsal root ganglia. During the vesicular stages of the rash, HZ patients are contagious. Compared to Chicken Pox or disseminated HZ, localized HZ is only around one-fifth as contagious [1]. The herpesvirus family includes the extremely contagious varicella-zoster virus. This family is quite important and has been taken into account in terms of pathology and treatment due to its broad diversity. VZV does not infect any reservoir or animals. The chickenpox virus is a member of the genus Varicello. T-lymphocytes, epithelial cells, and ganglia are its principal targets [2]. This big virus measures 150–200 nm in diameter, and its nucleocapsid, which has 162 capsomeres and icosahedral symmetry, is about 100 nm in size. A lipid-containing envelope that originates from the infected cell's nuclear membrane encircles these capsomeres. The capsid releases eight nanometer-long spikes of glycoprotein, giving the virus its crown-like form [3]. The linear, double-stranded DNA viral genome has a length of between 125 and 240 kbp. At least 100 distinct proteins are encoded by this genome. Of them, the structure of the virion particle involves more than 35 polypeptides [4]. One of the most frequently disregarded illnesses in Assam, India, is chickenpox. Children and people with impaired immune systems are at a higher risk of developing chickenpox. Following chickenpox, there is a chance of developing secondary bacterial infections. Complications result from this. 11,200 deaths from chickenpox were reported worldwide in 1990 and 6,800 in 2010. Age, immunity (acquired, hereditary, or iatrogenic), etc. may cause the virus to remain latent in the ganglion and become reactive again, leading to zoster, where falling cellular immunity is one of the key reasons [5-7]. There is a danger of HIV or AIDS, TB, and other diseases since immune-compromised persons are at a high risk of getting chickenpox. Actually, the virus known as the human

immunodeficiency virus (HIV) assaults immune cells and causes immunosuppression. HIV/AIDS patients are more likely to contract chickenpox infections due to decreased immunity and the disease's transmission mechanisms (air, aerosols, skin contact with lesions). During their studies, many studies found various seropositivities for HIV in chickenpox patients. In individuals with chickenpox, Baghel N *et al*. reported 33.6% HIV positivity. Found 35% HIV positivity. Once more, there is ample evidence that VZV DNA persists in immune cells, whether they are HIV-positive or negative [8, 9]. Shingles (also known as herpes zoster) is a condition that primarily affects elderly or immune-compromised persons and is brought on by the reactivation of a latent virus. However, the condition is more severe in adults, although having a significantly lower incidence rate. Adult infection is linked to consequences such as encephalitis, hepatitis, and pneumonia [10]. The symptoms of varicella, which typically last 4-5 days and is self-limited, include fever, lethargy, and generalized pain. There are commonly 250–500 lesions in the vesicular rash. Varicella typically takes 14 days to incubate, and practically all cases manifest 10–20 days after exposure. On the other hand, reactivation disease (herpes zoster) in immunocompetent people typically affects a small area of the skin that is innervated by one or two nearby dermatomes. Typically generalized zoster with or without visceral involvement, local (classic) zoster, visceral zoster without skin lesions, and disseminated disease with widespread cutaneous and visceral involvement may develop in patients with impaired cell-mediated immunity [11]. In some areas, especially in areas of overpopulation and poverty where there are many unvaccinated youngsters in close proximity, the disease takes on epidemic proportions. Measles generally appears in temperate and tropical climates in late winter and early spring. Chickenpox is regarded as a disease that is extremely contagious, much like measles. Unlike measles, which is caused by the measles virus, varicella zoster is caused by a different virus. Measles and chicken pox are both fairly prevalent paediatric illnesses. Measles and chickenpox viruses spread from person to person through airborne droplets emitted by infected individuals during coughing, sneezing, and laughter. Measles can be transferred through contact with nasal or throat secretions, while chickenpox can be spread through contact with skin blisters. Despite certain fundamental similarities, measles and chickenpox can be distinguished from one another clinically [12]. Chickenpox can be contracted anywhere in the world by sneezing, coughing, and direct skin contact with lesions. One to two days prior to the rash developing, it may begin to spread until all lesions are crusted over. Through blister contact, shingles patients can transmit chickenpox to people who are not immune. Based on the presenting symptoms, the disease is identified, and polymerase chain reaction (PCR) testing of the blister fluid or scabs is used to confirm the diagnosis. To find out if immunity exists, tests for antibodies may be run. Varicella infections can come back, although they normally do not cause symptoms and are considerably less severe than the initial illness [13-15].

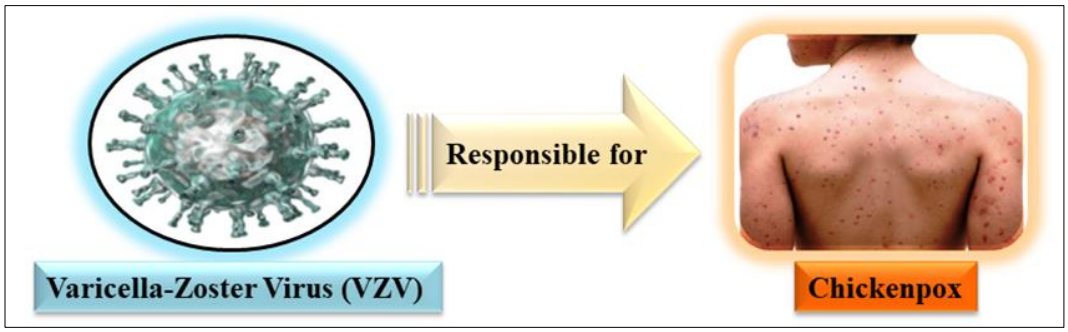

Fig 1: The Varicella-Zoster Virus (VZV) which causes chickenpox

Epidemiology

VZV appears everywhere and is endemic in populations large enough to support year-round transmission, with epidemics taking place every two to three years. Compared to other viral diseases like za, measles, and poliomyelitis, VZV appears to be a disease of low significance [16, 17]. It has been found to occur commonly in adults as well as frequently in children under the age of 10. In temperate regions, it is significantly more social in the winter and spring than in the summer. Although VZV is often not a dangerous illness, it can have devastating consequences for adults and those with impaired immune systems [18].

Histology

VZV was thought to be a strange ultra-filterable virus a century ago. Using a newly developed electron microscope in 1943, German physician Helmut Ruska was able to see the virus but was unsure whether it was varicella or zoster [19]. Vesicular fluid can inoculate VZV onto human foetal diploid kidney or lung cells. Due to the sensitivity of VZV, every effort should be taken to reduce the amount of time spent in specimen transport and storage during the cultivation process. Human foetal diploid kidney or lung cell monolayers can be inoculated with VZV using vesicular fluid. Due to the sensitivity of the virion, VZV is labile, hence every effort should be taken to reduce the amount of time spent in specimen transport and storage during the cultivation process [20]. It is not asymptomatic for VZV to shed. A live infection can be identified by the presence of virions, antigens, and nucleic acids in bodily fluids or tissues (other than sensory ganglia). Histopathology or transmission electron microscopy can be used to see multinucleated giant cells in tissues. This makes it challenging to differentiate between VZV and the herpes simplex virus (HSV) [16].

Symptoms and Causes

Through to the blisters have developed a crust. The virus is easily transmitted through close contact, breathing in contaminated air, direct touching, contact with infected

secretions from the nose, throat, rash, or through the spray from infected people's sneezing and coughing. Contagious chickenpox takes 1-2 days before the rash appears to until the blisters have become visible. The virus is easily transmitted through close physical contact, breathing space sharing, direct tactile contact with contaminated secretions from the nose, throat, rash, or through the spray from infected people's coughing and sneezing. The varicella virus can also be spread by coming into close contact with an infected child, sharing towels, or sleeping on the same pillows [20, 21]. In average, symptoms begin to show up 14 to 16 days after exposure, though they can sometimes arise as early as 10 days or as late as 21 days. Rashes can be used to diagnosis symptoms in these circumstances. Before rash, the first symptoms are malaise and fever. In average, symptoms begin to show up 14 to 16 days after exposure, though they can sometimes arise as early as 10 days or as late as 21 days. Rashes can be used to diagnosis symptoms in these circumstances. Before rash appears, malaise and fever are the first signs [22]. Additionally, the temperature has risen (to 37.7–38.8 °C), which could cause flu-like symptoms. The rash first appears on the trunk, then spreads to the face, limbs, buccal mucosa, and pharyngeal mucosa in the mouth. So that all stages of macules, papules, vesicles, and crusts may be seen at once, fresh vesicles form in crops [23]. The rash initially appears as red spots similar to those that follow insect bites, swells to form translucent water vesicles, then becomes soured and bursts these vesicles to reveal open sores. Additionally, the dry sores develop as brown scales and vanish after a week or two [24]. The itching is getting worse at this point, and a secondary bacterial infection could happen. The death rate is exceedingly low, and complications are uncommon. Rare incidences of encephalitis and varicella pneumonia do exist. Numerous deaths linked to varicella are caused by the typical complications, which mostly affect adults, newborns, and immune-compromised people. Varicella subclinical cases are rare [25, 26].

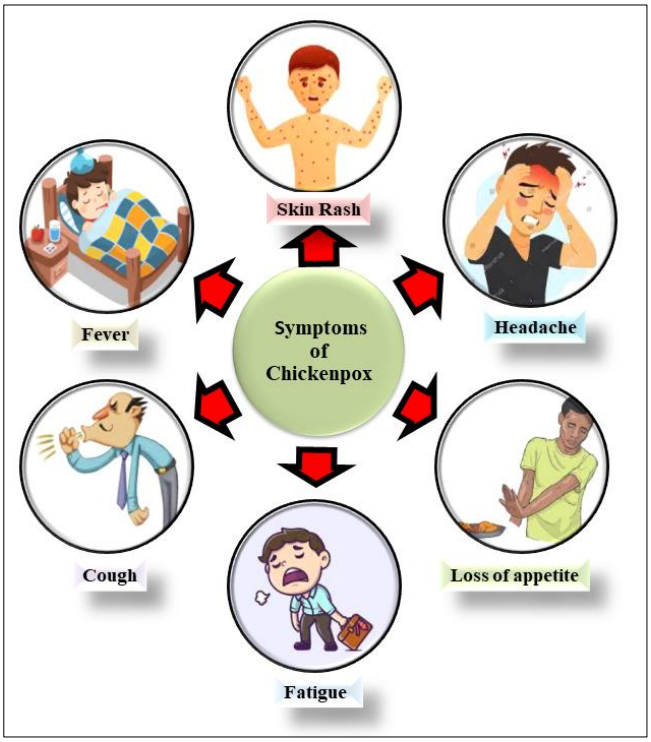

Fig 2: The typical symptoms of chickenpox

Pathophysiology

Production of host immunoglobulins G, M, and A is triggered by exposure. Immunity is provided by IgG antibodies, which last a lifetime. Immune responses that are cell-mediated are crucial for reducing the severity of primary varicella infection. Varicella is believed to spread from the initial infection to mucosal and epidermal lesions that affect nearby sensory neurons. After then, it stays dormant in the sensory nerves' dorsal ganglion cells. The immune system controls the virus, but reactivation can still happen later in life and cause Ramsay Hunt syndrome type II, postherpetic neuralgia, and the clinically different syndrome of herpes zoster (shingles). A stroke may arise from varicella zoster damage to the arteries in the neck and head. To prevent herpes zoster, the Advisory Committee on Immunization Practices of the United States (ACIP) advises vaccination for all persons older than 60. One in five adults who had chickenpox as kids, particularly those with compromised immune systems, develop single cases. Adults over 60 who were diagnosed with chickenpox before the age of one are most likely to develop shingles [27, 28]. Central nervous system (CNS) issues arise following VZV reactivation when virus travels to arteries of the brain and spinal cord in immunocompetent and immune-compromised people. Although VZV encephalitis is the name given to the infection of the CNS by the virus, it is actually a vasculopathy that affects both the big and small cerebral arteries. Elderly immunocompetent persons with large artery infection are more common, and this condition is marked by an abrupt focal impairment that appears weeks or months after a contralateral trigeminal-distribution zoster infection. Usually, only one to three big anterior circulation arteries are affected by the vasculopathy. On the other hand, immune-compromised people are more likely to have VZV infection of the small cerebral blood vessels, which is characterized by headache, fever, altered mental status, and multifocal impairment as seen by neurological examination and brain MRI imaging. Small-vessel VZV disease can appear without zoster rash and is frequently chronic. Cortical, subcortical grey, and white matter exhibit both ischemic and hemorrhagic infarcts [29]. Cerebral spinal fluid (CSF) pleocytosis, typically 100 cells (predominantly mononuclear), oligoclonal bands, and elevated CSF IgG are present in the majority of individuals with VZV vasculopathy. Angiography demonstrates focal constriction and segmental narrowing when big arteries are implicated. Microscopic and virologic analysis of arteries revealed inflammation, multinucleated giant cells, Cowdry A inclusions, herpesvirus particles, and VZV antigen and VZV DNA in damaged vessels - all signs of herpesvirus infection [30, 31].

Phases of the varicella-zoster virus infection

- **Primary infection phase**

VZV the oral pharynx (tonsils) after entering. When T-cells are infected with VZV, the virus multiplies and is released into the bloodstream, where it spreads to the skin and possibly other organs. Innate immunity regulates the early stages of infections. To promote skin trafficking, VZV alters a variety of T-cell populations. VZV DNA can be found in T-Cells (viraemia) as soon as 10 days before a rash appears, and it can remain for a week after that [17, 32].

- **Latency infection phase**

VZV is dormant in the neurons of the dorsal root ganglia, enteric and autonomic ganglia, and cranial nerve ganglia. To create the zoster virus (shingle), latent cases may reactivate.

Long believed to enter epidermal nerve endings during varicella and travel retrogradely along axons to reach neuronal cell bodies in the ganglia, is how VZV is said to spread [18].

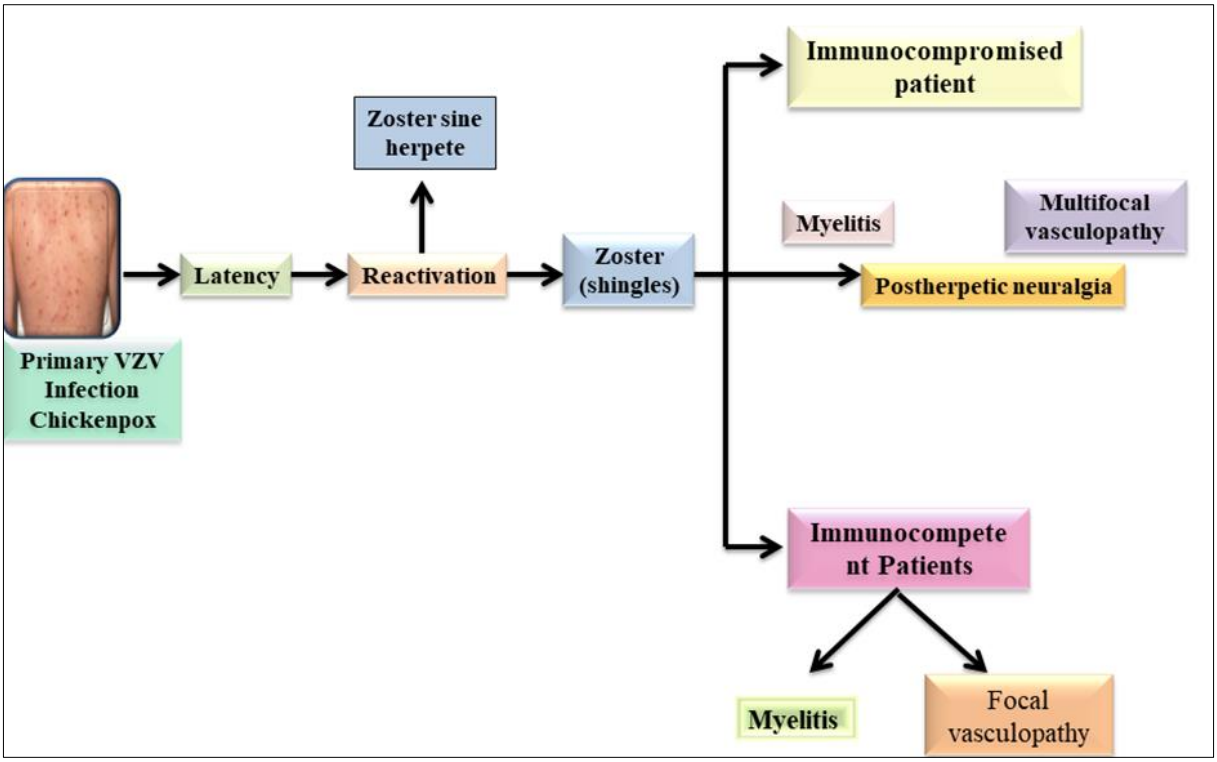

Fig 3: General chickenpox pathophysiology (33).

Evaluation (diagnosis in the lab)

The main criteria for diagnosing varicella infection are the symptoms and indicators. The fluid inside the vesicles can be examined, lesions that haven't crusted can be scraped, and blood can be examined for signs of an acute immune response. The most yielding method is the polymerase chain reaction (PCR), which may be used with non-skin samples including cerebrospinal fluid and bronchoalveolar lavage samples. The Tzanck test has mostly been supplanted by direct fluorescent antibody testing. The yield from vesicular fluid culture is lower than from PCR, but it is still possible. Acute infection responses (IgM), prior infections, and subsequent immunity (IgG) are all detected through blood tests. Ultrasound can be used to diagnose foetal varicella throughout pregnancy, but it's best to wait five weeks after the main maternal infection before doing so. It is possible to screen the amniotic fluid for DNA using PCR, however this comes with a higher risk of spontaneous abortion due to amniocentesis than it does of the foetus getting varicella [34, 35].

Available chickenpox treatments

Medical treatment

Symptomatic alleviation is the only kind of treatment. Those who are ill typically have to stay at home while they are contagious as a precaution. Wearing gloves and keeping nails short can help minimize scratching and lower the risk of subsequent infections [15, 36, 37]. Calamine lotion applied topically could reduce itching. Warm water washing on a daily basis will aid in preventing subsequent bacterial illness. Fever can be reduced with paracetamol. Aspirin should be avoided as it may trigger Reye syndrome. Intramuscular varicella-zoster immune globulin, a treatment with high titers of varicella-zoster virus antibodies, may be administered to people at risk of complications and who have experienced extensive exposure to help avoid the disease [38]. Acyclovir reduces symptoms in children by one day if administered within 24 hours of the onset of the rash, but it has little impact on complication rates and is not advised for those with healthy immune systems. When treating adults, antiviral medications (acyclovir or valacyclovir) are indicated if they can be started within 24 to 48 hours of the commencement of the rash because the infection tends to be more severe in adults. An key component of the management is supportive care, which includes things like drinking more water and taking antipyretics and antihistamines. Antivirals are usually recommended for adults, including pregnant women, as they are more likely to experience problems. Although oral therapy is typically favoured, immune-compromised patients may benefit from injectable antivirals [39]. In healthy youngsters, VZV is a minor, self-limiting illness. In children in good health, VZV is mild, self-limiting, and simple. The length of the sickness can be shortened with antiviral medication. Acetaminophen (paracetamol) is frequently the only treatment option for children with uncomplicated varicella [40]. The medication acyclovir is very well accepted and safe. Extravasation works best if it is administered as early as feasible within the first day of beginning after the rash begins, as local inflammation and phlebitis may follow. The medication acyclovir is very well accepted and safe. Acyclovir administered intravenously may cause local irritation and phlebitis. Viral DNA polymerase is only mildly inhibited by penciclovir triphosphate, which prevents viral DNA from being synthesized. The pyrophosphate binding site is activated by the pyrophosphate analogue foscarnet. Antihistamines are additionally used to treat itching. However, the illness is typically permitted to

progress naturally. When a bacterial infection occurs, the attending physician will prescribe antibiotics for treatment, as a blocker of viral DNA polymerase as an inhibitor [40, 41].

Vaccination

The vaccine for chickenpox is quite safe and very successful at preventing the illness. The varicella vaccine protects against chickenpox. If a person who has had the vaccination develops chickenpox, the symptoms are typically milder, with fewer or no blisters (may only have red spots), and a low-grade fever. In the 1970s and 1980s, a live attenuated VZV (Oka strain) vaccine was created and clinically tested. In 1984, Sweden and Germany issued the first licences for it [18, 42]. In the US, varicella annually resulted in 4 million infections, 11,000 hospital admissions, and 100 fatalities. Varicella disease incidence has steadily decreased since the introduction of the vaccination. Due to some children's lack of vaccination, varicella outbreaks continue to affect schoolchildren. 80% to 85% of people can benefit from attenuated vaccines. Chickenpox can be stopped from spreading by isolating those who have it. Infection spreads by direct contact with lesions or exposure to respiratory droplets between 3–4 days prior to the rash's start and 4 days after it appears. Disinfectants like sodium hypochlorite (chlorine bleach) can kill the chickenpox virus. VZV is vulnerable to desiccation, heat, and detergents like all enveloped viruses [18, 43].

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Conclusion and Future direction

Our review articles provide a basic overview of chickenpox, including its symptoms and causes, origins, pathophysiology, and combined therapy, including drug and vaccination options. Our research shows that while pharmaceuticals and vaccinations yield acceptable results, take some time to take effect, and have no negative side effects, medicine offers some symptom relief but does not totally cure the patient and requires time. More randomised controlled studies are required to improve chickenpox treatment. Future research on chickenpox is something we intend to pursue. Future research on counselling will be conducted in our nation and state with the assistance of our colleagues with the aim of evaluating patients' physical and mental health and creating more exact data on chickenpox and its enhanced therapy.

Table 1: Current status of clinical trials on Chickenpox

Drug	Mode of administration	Disease	Enrolment	Allocation/Intervention model/Masking	Official Title of the study	Status	Clinical trial	Year
NA	Observational	Chickenpox	32	NA	MMR and Varicella Vaccine Responses in Extremely Premature Infants	NA	NCT00156559	2015
Varilrix HSA-free/ Varilrix	Interventional	Chickenpox	1236	Randomized/ parallel assignment/quadruple (participant care provider investigator outcomes assessor)	Safety and Immunogenicity Study of 2 Formulations of GSK Biologicals' Varicella Vaccines Given as a 2-dose Course in the Second Year of Life.	Phase-3	NCT02570126	2019
Varicella-1/ varicella-3/ varicella-5	Interventional	Chickenpox	716	Non-randomized/ parallel assignment/ none (open label)	A Study to Evaluate the Immunogenicity and Safety of 2 Doses of Live Attenuated Varicella Vaccine	Phase-4	NCT02173899	2014
VarilrixTM	Interventional	Chickenpox	45	Non-randomized/ single group assignment/ none (open label)	A Phase III, Open-label, Multi-centre Study to Assess the Immunogenicity and Safety of GlaxoSmithKline Biologicals' Live Attenuated Varicella Vaccine (VarilrixTM), Given as a Primary Vaccination at 4.5 Months and 6.5 Months Post-transplantation, in Autologous Stem Cell/ Bone Marrow Transplant Recipients Aged 18 Years and Older.	Phase-2	NCT00792623	2018
Tai chi chih	Interventional	Chickenpox	70	Na	Tai Chi Chih and Varicella Zoster Immunity	Phase-2	NCT00029484	2006
NBP608/ Varivax	Interventional	Chickenpox	152	Randomized/ Parallel Assignment/Quadruple (participantcare providerinvestigatoroutcomes Assessor)	Randomized, Double-blinded, Parallel-group, Exploratory Study to Assess The Immunogenicity and Safety of NBP608 and Varivax in Healthy Children	Phase-2	NCT03114982	2017
NBP608/ Varivax	Interventional	Chickenpox	516	Randomized/ Parallel Assignment/Quadruple (participantcare providerinvestigatoroutcomes Assessor)	A Multi-national, Multi-center, Randomized, Double Blinded, Parallel-group Study to Assess the Immunogenicity and Safety of NBP608 Compared to Varivax in Healthy Children 12 Months to 12 Years of Age	Phase-3	NCT03114943	2019
VARIVAX	Interventional	Chickenpox	150	N/a/ single group assignment/ none (open label)	An Open-Label, Multicenter, Single-arm Study to Evaluate the Immunogenicity of VARIVAX™ in Healthy Russian Individuals 12 Months of Age and Older	Phase-3	NCT03843632	2021
VARIVAX PE34 Process/ VARIVAX 2016 Commercial Process/ M-M-R II	Interventional	Chickenpox	600	Randomized/ Parallel Assignment/Triple (participantcare providerinvestigator)	A Phase 3, Double-Blind, Randomized, Multicenter, Controlled Study to Evaluate the Immunogenicity, Safety, and Tolerability of VARIVAX™ Passage Extension 34 (PE34) Process Administered Concomitantly With M-M-R™ II	Phase-3	NCT03239873	2021
VARIVAX	Observational	Chickenpox	754	Na	Re-examination Study for General Vaccine Use to Assess the Safety Profile of Varivax in Usual Practice	NA	NCT01062061	2015

Varicella Virus Vaccine Live (2007 Process) (Oka/Merck)/ Comparator: Varicella Virus Vaccine Live (1999 Process) (Oka/Merck)/ Measles, Mumps, and Rubella Virus Vaccine Live (MMR)	Interventional	Chickenpox	598	Randomized/ Parallel Assignment/Triple (participantinvestigatoroutcomes Assessor)	Safety, Tolerability, and Immunogenicity of VARIVAX (2007 Commercial VZV Bulk Process) Administered Concomitantly With M-M-R II in Healthy Children 12-to-23 Months of Age	Phase-3	NCT00822237	2017
Varicella Virus Vaccine Live (Oka-Merck)	Interventional	Chickenpox	100	Non-randomized/ single group assignment/ none (open label)	Evaluation of Safety,Tolerability and Immunogenicity of Vaccination With VARIVAX (V210)in Healthy Indian Children	Phase-3	NCT00496327	2019
VAQTA/ ProQuad	Interventional	Chickenpox	1800	Randomized/ parallel assignment/ none (open label)	An Open, Multicenter Study of the Safety and Tolerability of VAQTA(TM) and ProQuad(TM) in Healthy Children 12 to 23 Months of Age	Phase-4	NCT00326183	2019
Zostavax/ Normal Saline	Interventional	Chickenpox	100	Randomized/ Parallel Assignment/ Double (participantinvestigator)	Efficacy and Safety of a Novel Intradermal Live-attenuated Varicella Zoster Vaccine in Hematopoietic Stem Cell Transplantation Donors: a Randomized Double Blind Placebo-controlled Trial	Phase-2&3	NCT02329457	2019
JE-CV Vaccine/ Varicella Vaccine	Interventional	Chickenpox	454	Randomized/ parallel assignment/ none (open label)	Assessment of the Memory Immune Response, Safety of Japanese Encephalitis Chimeric Virus Vaccine (JE-CV) in Children Previously Immunized With a Single Dose of JE-CV and Long-Term Follow-Up	Phase-3	NCT01190228	2022
M-M-R™II manufactured with recombinant Human Albumin (rHA) and VARIVAX	Interventional	Chickenpox	752	Randomized/ parallel assignment/ none (open label)	An Open, Randomised, Comparative, Multicentre Study of the Immunogenicity and Safety of M-M-R™II Manufactured With Recombinant Human Albumin (rHA) and VARIVAX® When Administered Concomitantly by Intramuscular (IM) Route or Subcutaneous (SC) Route at Two Separate Injection Sites in Healthy Subjects 12 to 18 Months of Age	Phase-3	NCT00432523	2021
Recombinant subunit Herpes zoster vaccine	Interventional	Chickenpox	23	N/a / single group assignment/none (open label)	Safety and Immunogenicity of Non-live, Recombinant Subunit Herpes Zoster Vaccine in VZV-seronegative Solid Organ Transplant Recipients	Phase-3	NCT03685682	2020
Zoster Vaccine, Live, (Oka-Merck)	Interventional	Chickenpox	150	Non-randomized/ single group assignment/ none (open label)	A Phase III Clinical Trial to Study the Safety, Tolerability, and Immunogenicity of ZOSTAVAX(R) in Healthy Adults in Taiwan	Phase-3	NCT00444860	2015
Measles, Mumps, Rubella and Chickenpox (live vaccine)	Interventional	Chickenpox	1439	Randomized/ parallel assignment/ double	Blinded, Randomised Study to Assess the Immunogenicity and Safety of GlaxoSmithKline (GSK) Biologicals' Live Attenuated Measles-mumps-rubella-varicella Candidate Vaccine When Given to Healthy Children in Their Second Year of Life	Phase-4	NCT00126997	2016
Measles, Mumps, Rubella and Chickenpox (live vaccine)	Interventional	Chickenpox	944	Randomized/ parallel assignment/ double	Blinded, Randomised, Controlled Study to Evaluate the Immunogenicity and Safety of GlaxoSmithKline Biologicals' Combined Measles-mumps-rubella-varicella Candidate Vaccine Given to Healthy Children in Their Second Year of Life	Phase-3	NCT00127023	2016
Measles, Mumps, Rubella and Chickenpox (live vaccine)	Interventional	Chickenpox	NA	Randomized/ parallel assignment/none (open label)	Blinded, Randomized Study to Evaluate the Immunogenicity and Safety of GlaxoSmithKline Biologicals' Measles-mumps-rubella-varicella Candidate Vaccine Given to Healthy Children During the Second Year of Life	Phase-3	NCT00127010	2016
Live Attenuated Varicella Virus Vaccine	Interventional	Chickenpox	122	N/A / single group assignment/ none (open label)	Safety of a Second Dose of Biken's Varicella Vaccine Administered at 4 to 6 Years of Age in Healthy Children in Argentina	Phase-4	NCT00830648	2013

References

1. Sharma S, Sharma S, Chhina D, Chhina RS. Chicken pox outbreak in the Intensive Care Unit of a tertiary care hospital: Lessons learnt the hard way. Indian J Crit Care Med. 2015;19(12):723–5.
2. Straus SE, Aulakh HS, Ruyechan WT, Hay J, Casey TA, Vande Woude GF, *et al*. Structure of varicella-zoster virus DNA. J Virol. 1981;40(2):516–25.
3. Marin M, Güris D, Chaves SS, Schmid S, Seward JF. Prevention of varicella: recommendations of the

Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2007;56(RR-4):1–40.
4. Gershon AA, Breuer J, Cohen JI, Cohrs RJ, Gershon MD, Gilden D, *et al*. Varicella zoster virus infection. Nat Rev Dis Prim [Internet]. 2015;1(July):1–19. Available from: http://dx.doi.org/10.1038/nrdp.2015.16
5. Jovanović J, Cvjetković D, Pobor M, Brkić S. [Primary infection with varicella-zoster virus in risk groups]. Med Pregl [Internet]. 1998;51(3–4):151-154. Available from: http://europepmc.org/abstract/MED/9611959
6. Quinlivan M, Hawrami K, Barrett-Muir W, Aaby P, Arvin A, Chow VT, *et al*. The molecular epidemiology of varicella-zoster virus: Evidence for geographic segregation. J Infect Dis. 2002;186(7):888–94.
7. Sharma, J. and MKB. "Incidence of suspected measles and chickenpox cases in Dhemaji district, Assam. J Zool Biosci Res 13 25-27. 2014;3:2014.
8. Malakar M, Choudhury M, Jaiswal G, Gupta S, Kalita P. Chickenpox, Traditional Inhibition and Treatment Neglecting - a Study in Assam, India. Int Res J Pharm. 2019;10(5):112–4.
9. Vossen MTM, Gent MR, Peters KMC, Wertheim-Van Dillen PME, Dolman KM, Van Breda A, *et al*. Persistent detection of varicella-zoster virus DNA in a previously healthy child after severe chickenpox. J Clin Microbiol. 2005;43(11):5614–21.
10. Abro AH, Ustadi AM, Das K, Saleh Abdou AM, Hussaini HS, Chandra FS. Chickenpox: Presentation and complications in adults. J Pak Med Assoc. 2009;59(12):828–31.
11. Chowdhury MK, Siddique AA, Haque MM, Ali S, Biswas S, Biswas PK, *et al*. Life threatening complications of chicken pox in a young adult. J Med. 2014;15(1):55–7.
12. Profile SEE. Incidence of suspected measles and chickenpox cases in Dhemaji district,. 2015;(July 2014).
13. Pereira L. Congenital viral infection: Traversing the uterine-placental interface. Annu Rev Virol. 2018;5:273–99.
14. Kasabwala K, Wise GJ, Kasabwala K, Varicella-zoster WGJ. a case-based review. 2018;9301–6.
15. Shrim A, Koren G, Yudin MH, Farine D. No. 274-Management of Varicella Infection (Chickenpox) in Pregnancy. J Obstet Gynaecol Canada [Internet]. 2018;40(8):e652–7. Available from: https://doi.org/10.1016/j.jogc.2018.05.034
16. Arvin A, Campadelli-Fiume G, Mocarski E, Moore PS, Roizman B, Whitley R, *et al*. (Eds.). Human herpesviruses: biology, therapy, and immunoprophylaxis; c2007.
17. Vleck SE, Oliver SL, Brady JJ, Blau HM, Rajamani J, Sommer MH, *et al*. Structure-function analysis of varicella-zoster virus glycoprotein H identifies domain-specific roles for fusion and skin tropism. Proc Natl Acad Sci U S A. 2011;108(45):18412-7.
18. WHO. Varicella and herpes zoster vaccines : WHO position paper, June 2014 Vaccins contre la varicelle et le zona: note de synthèse de l'OMS, juin 2014. 2014;(June).
19. Yih WK, Brooks DR, Lett SM, Jumaan AO, Zhang Z, Clements KM, *et al*. The incidence of varicella and herpes zoster in Massachusetts as measured by the Behavioral Risk Factor Surveillance System (BRFSS) during a period of increasing varicella vaccine coverage, 1998-2003. BMC Public Health. 2005;5:1–9.
20. Hew K, Dahlroth SL, Veerappan S, Pan LX, Cornvik T, Nordlund P. Structure of the Varicella Zoster Virus Thymidylate Synthase Establishes Functional and Structural Similarities as the Human Enzyme and Potentiates Itself as a Target of Brivudine. PLoS One. 2015;10(12):1-16.
21. Russell ML, Dover DC, Simmonds KA, Svenson LW. Shingles in Alberta: Before and after publicly funded varicella vaccination. Vaccine [Internet]. 2014;32(47):6319–24. Available from: http://dx.doi.org/10.1016/j.vaccine.2013.09.018
22. Kruger DH, Mertens T. Classic paper: Are the chickenpox virus and the zoster virus identical? HELMUT RUSKA. Rev Med Virol. 2018;28(3):1–4.
23. McDonald J. Vaccines for postexposure prophylaxis against varicella (chickenpox) in children and adults. Paediatr Child Heal. 2016;21(2):91–2.
24. Weinmann S, Chun C, Schmid DS, Roberts M, Vandermeer M, Riedlinger K, *et al*. Incidence and clinical characteristics of herpes zoster among children in the varicella vaccine era, 2005-2009. J Infect Dis. 2013;208(11):1859–68.
25. Masters NB, Mathis AD, Leung J, Raines K, Clemmons NS. Public Health Actions to Control Measles among Afghan Evacuees during Operation Allies Welcome - United States, September - November 2021. 2022;71(17):592–6.
26. Peter K, Christopher, Murtaugh M. The New England Journal of Medicine Downloaded from nejm.org on January 12, 2022. For personal use only. No other uses without permission. Copyright © 1991 Massachusetts Medical Society. All rights reserved. 1999;
27. Freer G, Pistello M. Varicella-zoster virus infection: Natural history, clinical manifestations, immunity and current and future vaccination strategies. New Microbiol. 2018;41(2):95–105.
28. Dayan RR, Peleg R. Herpes zoster–typical and atypical presentations. Postgrad Med [Internet]. 2017;129(6):567–71. Available from: http://dx.doi.org/10.1080/00325481.2017.1335574
29. Amlie-Lefond C, Kleinschmidt-Demasters BK, Mahalingam R, Davis LE, Gilden DH. The vasculopathy of varicella-zoster virus encephalitis. Ann Neurol. 1995;37(6):784–90.
30. Dickinson J. Brief Communications. Psychiatry (New York). 1953;16(2):193–6.
31. Gilden DH, Kleinschmidt-DeMasters BK, Wellish M, Hedley Whyte ET, Rentier B, Mahalingam R. Varicella zoster virus, a cause of waxing and waning vasculitis. Neurology. 1996;47(6):1441–6.
32. Thomas SL, Hall AJ. What does epidemiology tell us about risk factors for herpes zoster? Lancet Infect Dis. 2004;4(1):26–33.
33. Seidi O. Intrathecal Immune Response against Axonal Cytoskeltal Proteins in MS a prognostic study. 2014;(April 2002).
34. Onyango CO, Loparev V, Lidechi S, Bhullar V, Schmid DS, Radford K, *et al*. Evaluation of a TaqMan array card for detection of central nervous system infections. J Clin Microbiol. 2017;55(7):2035–44.
35. Inata K, Miyazaki D, Uotani R, Shimizu D, Miyake A, Shimizu Y, *et al*. Effectiveness of real-time PCR for

diagnosis and prognosis of varicella-zoster virus keratitis. Jpn J Ophthalmol [Internet]. 2018;62(4):425–31. Available from: https://doi.org/10.1007/s10384-018-0604-7
36. Poole CL, James SH. Antiviral Therapies for Herpesviruses: Current Agents and New Directions. Clin Ther. 2018;40(8):1282–98.
37. Harrington D, Haque T. Varicella Zoster Immunoglobulin G (VZIG-Do current guidelines advocate overuse? J Clin Virol [Internet]. 2018;103:25-6. Available from: https://doi.org/10.1016/j.jcv.2018.03.007
38. Hayward K, Cline A, Stephens A, Street L. Management of herpes zoster (shingles) during pregnancy. J Obstet Gynaecol (Lahore) [Internet]. 2018;38(7):887–94. Available from: https://doi.org/10.1080/01443615.2018.1446419
39. Ayoade F, Kumar S. Varicella-Zoster Virus (Chickenpox) [Updated 2022 Oct 15]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448191/. 2023;448191.
40. Siedler A, Arndt U. Impact of the routine varicella vaccination programme on varicella epidemiology in Germany. Eurosurveillance [Internet]. 2010;15(13):14-20. Available from: http://dx.doi.org/10.2807/ese.15.13.19530-en
41. Stephanie R Bialek, Dana Perella, John Zhang, Laurene Mascola, Kendra Viner, *et al*. Impact of a Routine Two-Dose Varicella Vaccination Program on Varicella Epidemiology. HHS Public Access Author Manuscr Pediatr Author manuscript; available PMC 2015 Oct 26. 2018;176(5):139–48.
42. Flatt A, Breuer J. Varicella vaccines. Br Med Bull. 2012;103(1):115–27.
43. Brogden RN, Peters DH. Erratum to Teicoplanin: A reappraisal of its antimicrobial activity, pharmacokinetic properties and therapeutic efficacy. Drugs. 1994;48(6):929–929.