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Course Title : Medical Virology

Course Code : BM59C19MV

Unit-IV

Varicella – Zoster Virus

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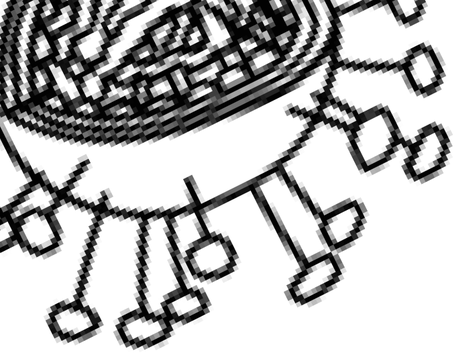

VIROLOGY

VARICELLA - ZOSTER VIRUS

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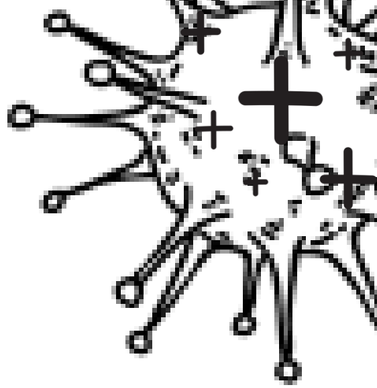
IVth YR BIOMEDICAL SCIENCE

(BMS21604)

BHARATHIDASAN UNIVERSITY

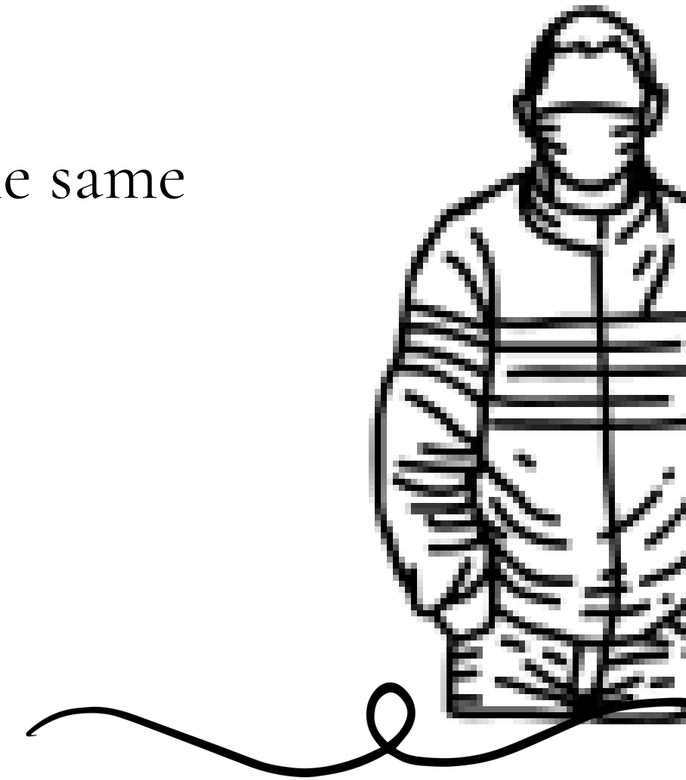
INTRODUCTION



Chickenpox or varicella is a contagious disease caused by the varicella-zoster virus (VZV). The virus is responsible for chickenpox [**Varicella**] (usually primary infection in non-immune hosts) and or shingles [**herpes zoster**] (following reactivation of latent infection).

Varicella-zoster virus (VZV) is an alphaherpesvirus that is in the same subfamily as herpes simplex virus (HSV) 1 and 2.

VZV is a member of the varicellovirus genus.



Classification

(unranked): Virus

Realm: *Duplodnaviria*

Kingdom: *Heunggongvirae*

Phylum: *Peploviricota*

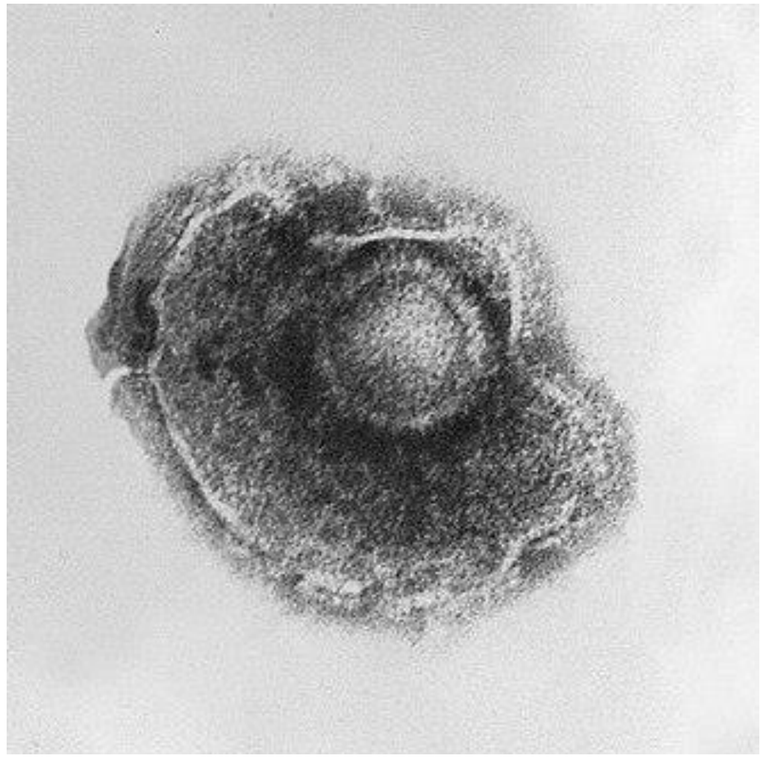
Class: *Herviviricetes*

Order: Herpesvirales

Family: *Orthoherpesviridae*

Genus: *Varicellovirus*

Species: *Human alphaherpesvirus 3*



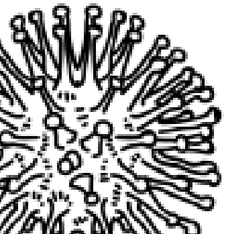
Epidemiology

- Varicella occurs in all countries and is responsible annually for about 7000 deaths.
- Before the widespread use of vaccine, varicella occurred throughout the year but was most prevalent during late winter and spring.
- In temperate countries, it is a common disease in children, with most cases occurring in winter and spring.
- Varicella is one of the classic diseases of childhood, with the highest prevalence occurring in the 4 – 10-year-old age group.
- Varicella has an infection rate of 90%. This means they are highly communicable, with an attack rate of 90% in close contact.

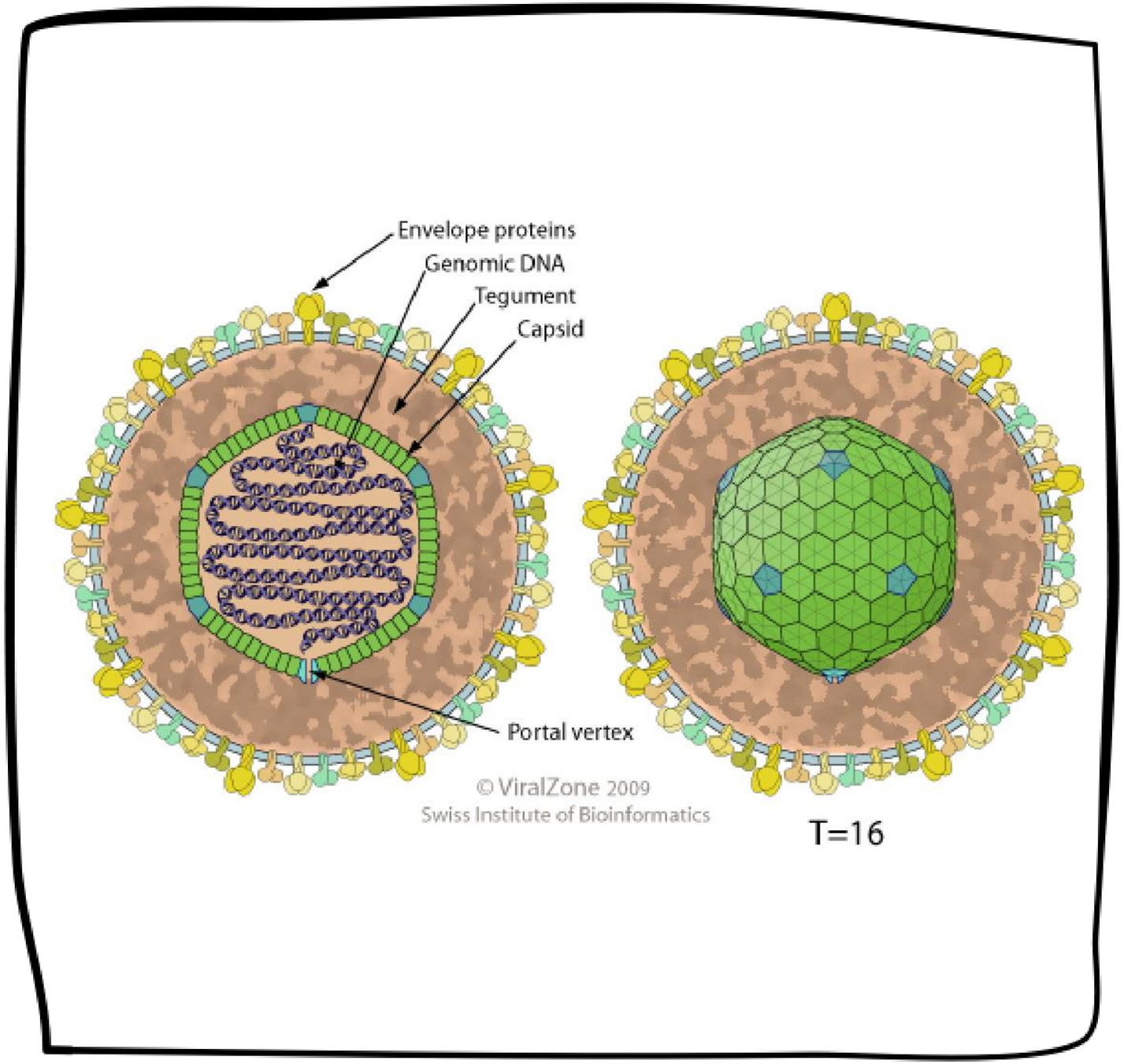
- Chickenpox is a very contagious disease caused by the varicella-zoster virus and spreads easily from people mainly by touching or breathing in the virus particles that come from chickenpox blisters, and possibly through tiny droplets from infected people that get into the air after they breathe or talk.
- Secondary cases in household contacts tend to have more severe disease than primary cases. In the tropics, varicella tends to occur in older people and may cause more serious disease.
- Adults get deep pockmarks and more prominent scars.

Structure

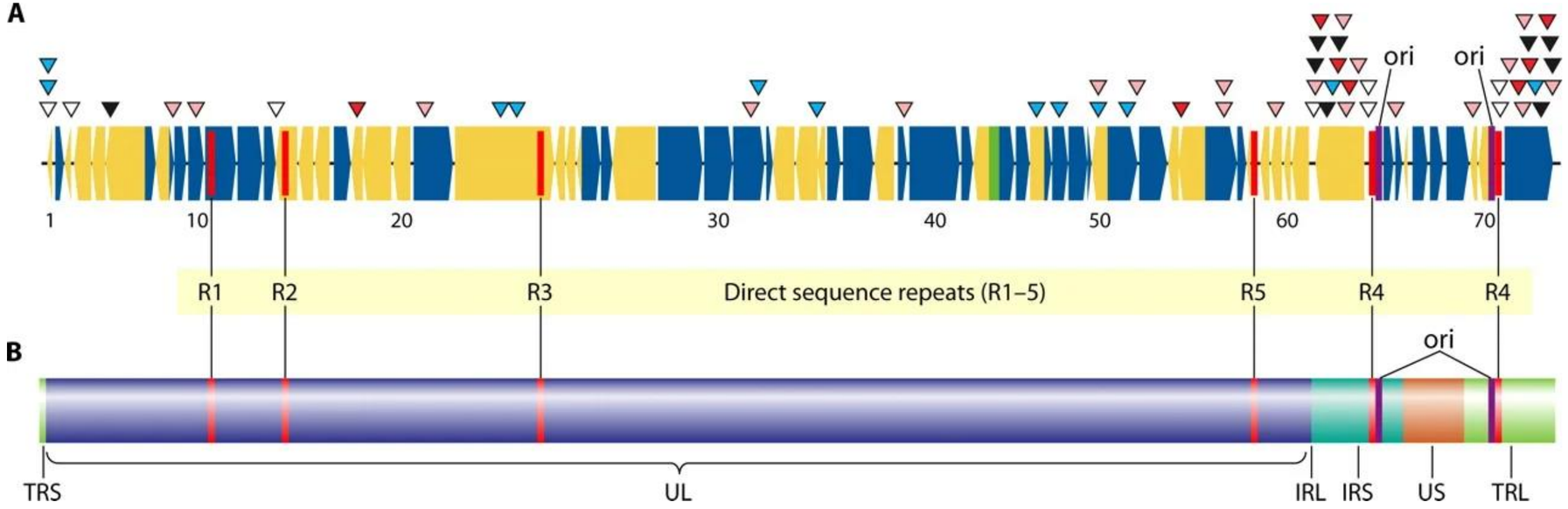
- The virion is spherical in shape with icosahedral symmetry measuring 159-200nm.
- The icosahedral protein capsid with an average diameter of 100 nm consists of 162 hollow hexagonal and pentagonal capsomeres with an electron-dense core containing the double-stranded DNA genome with 125-240 kbp nucleotides together forming the nucleocapsid.
- The nucleocapsid is surrounded by an envelope which is lipoprotein in nature.
- The lipid part is derived from the nuclear membrane of the infected host cell.
- The enveloped particle is pleomorphic to spherical, and 180 to 200 nm in diameter.



- Projecting from the trilaminar lipid host-derived envelope are spikes of viral glycoproteins, 8nm long, which bind to specific host receptor and mediate virus entry.
- gB, gE and gH are proteins abundantly found and mediate primary attachment to host cell surface, glycosaminoglycan and fusion.
- In mature virus particles, outside the capsid is an amorphous proteinaceous layer, the tegument, surrounded by a lipid envelope derived from host cell membranes.
- The tegument consists of enzymes such as VP16 which is responsible for subverting cellular proteins and enzymes to involve in viral nucleic acid replication and VHS (Virion Host Shutoff) protein which shut off the host cell protein synthesis in the cytoplasm.


Envelope proteins
Genomic DNA
Tegument
Capsid
Portal vertex
© ViralZone 2009
Swiss Institute of Bioinformatics
T=16

Genome



- The virus contains a double-stranded DNA genome and is linear measuring 125 kbp in length.
- The genome consists of a unique long region (UL) bounded by terminal long (TRL) and internal long (IRL) repeats, and a unique short region (US) bounded by internal short (IRS), and terminal short (TRS) repeats.

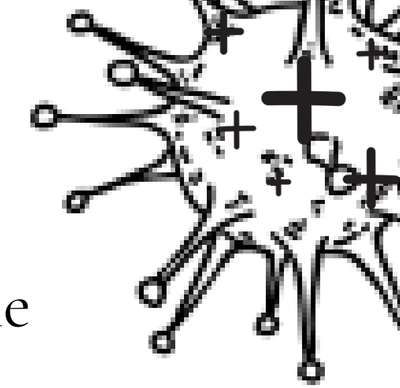
- The varicella-zoster virus (VZV) genome contains at least 70 genes.
- VZV encodes at least 3 immediate-early (IE) proteins that are located in the tegument of virions and regulate virus transcription.
- The VZV genome contains about 41 “core genes” that are conserved with each of the three subfamilies of herpesviruses, alphaherpesvirus, betaherpesvirus, and gammaherpesvirus.
- Core genes include IE4, the VZV DNA polymerase, helicase-primase components, single-stranded DNA-binding protein, ribonucleotide reductase, uracil-DNA glycosylase, dUTPase, DNase, ORF47 protein kinase, major capsid protein, protease, assembly protein, several tegument proteins, gB, gH, gL, gM, and gN.

Etiology

Chickenpox or varicella is caused by the varicella-zoster virus (VZV), a herpes virus with worldwide distribution. It establishes latency after primary infection, a feature unique to most herpes viruses.[4]

Chickenpox is acquired by inhalation of infected aerosolized droplets. This virus is highly contagious and can spread rapidly. The initial infection is in the mucosa of the upper airways. The virus enters the circulation after 2 to 6 days, and another bout of viremia occurs in 10 to 12 days. At this time, the characteristic vesicle appears. Immunoglobulin (Ig)A, IgM, and IgG antibodies are produced, but the IgG antibodies confer lifelong immunity. After the primary infection, varicella localized to sensory nerves and may reactivate later to produce shingles.

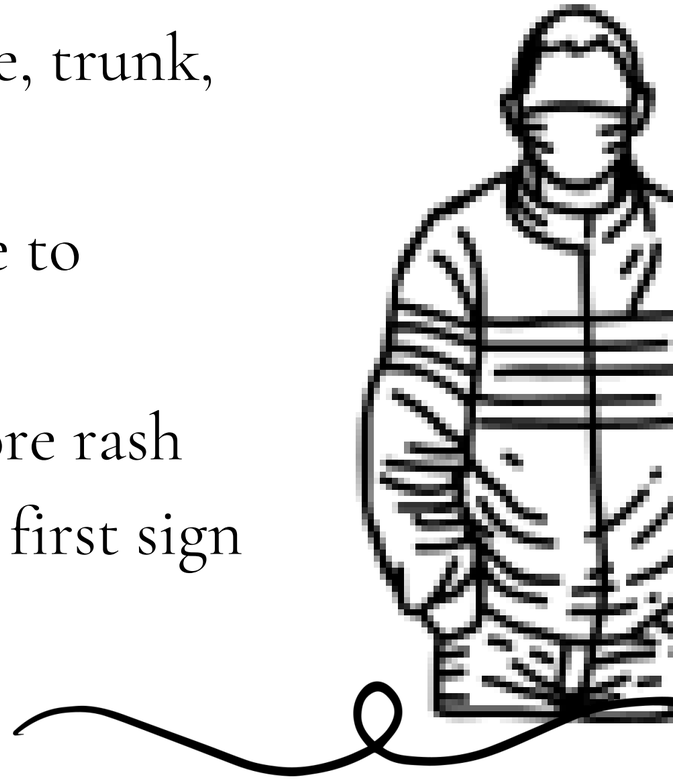
Clinical Features



Varicella-zoster virus (VZV) infection causes two clinically distinct forms of the disease.

Varicella

- Primary infection with VZV results in varicella (chickenpox), characterized by vesicular lesions in different stages of development on the face, trunk, and extremities.
- The incubation period for varicella is 14 to 16 days after exposure to varicella or a herpes zoster rash, with a range of 10 to 21 days.
- A mild prodrome of fever and malaise may occur 1 to 2 days before rash onset, particularly in adults and in children, the rash is often the first sign of disease.



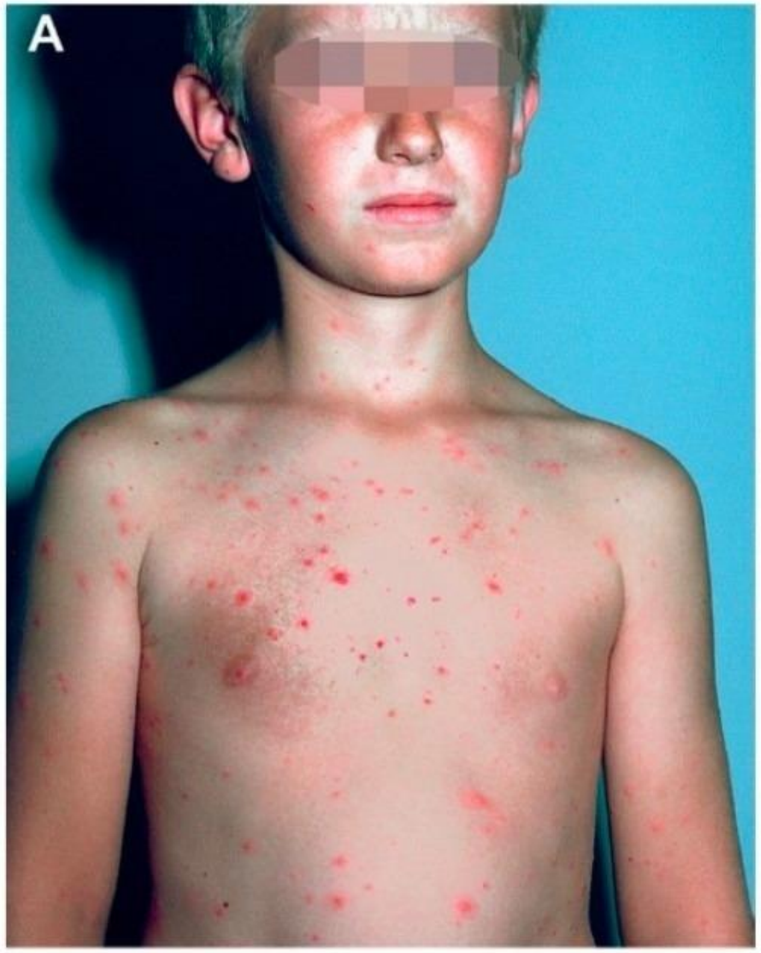
- The rash is generalized and pruritic (itchy).
- It progresses rapidly from macules to papules to vesicular lesions before crusting.
- The rash usually appears first on the head, chest, and back then spreads to the rest of the body.
- In case of children, the signs and symptoms are generally mild with an itchy rash, malaise, and temperature up to 102°F for 2 to 3 days.
- Infants, adults, and immunocompromised people are at risk for more severe disease and have a higher incidence of complications.
- Severe complications caused by varicella include cerebellar ataxia, encephalitis, viral pneumonia, and hemorrhagic conditions.

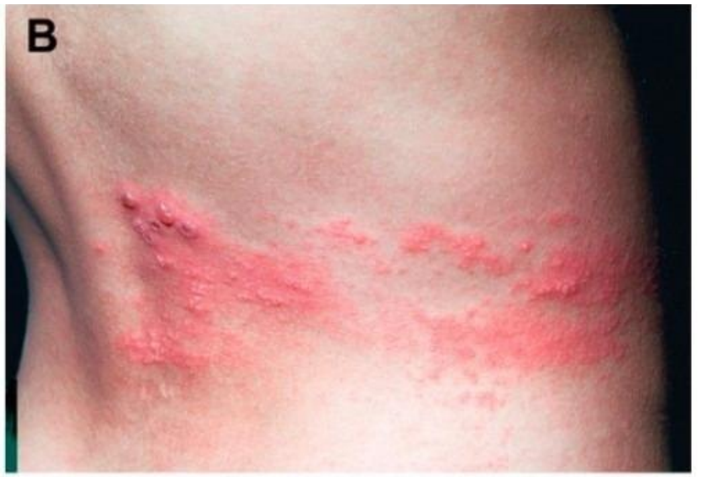
- Other complications include septicemia, toxic shock syndrome, necrotizing fasciitis, osteomyelitis, bacterial pneumonia, and septic arthritis.
- Several discreet neurologic syndromes have been attributed to VZV infection.
- Acute cerebellar ataxia is a complication of primary varicella infection and does not occur with viral reactivation.
- Patients with acute cerebellar ataxia develop acute gait ataxia, nystagmus, vomiting, tremor, and headache, although they usually have intact cognition.
- Symptoms typically begin in the 10 days following cutaneous eruption; however, rarely there may be up to three-week latency between rash and onset of cerebellar symptoms.
- Full recovery generally occurs within weeks to months.
- Another neurologic syndrome suggestive of VZV is CNS vasculitis of either large or small blood vessels.

Herpes- zoster

- Herpes zoster, also known as shingles, results from reactivation of endogenous latent VZV infection within the sensory ganglia.
- People with herpes zoster most commonly have a rash in one or two adjacent dermatomes (localized zoster).
- The rash most commonly appears on the trunk along a thoracic dermatome.
- Less commonly, the rash can be more widespread and affect three or more dermatomes.
- The rash is usually painful, itchy or tingly.
- These symptoms may precede rash onset by days to weeks and some people may also have a headache, photophobia (sensitivity to bright light), and malaise in the prodromal phase.

- The rash develops into clusters of vesicles.
- New vesicles continue to form over three to five days and progressively dry and crust over and they usually heal in two to four weeks.
- There may be permanent pigmentation changes and scarring on the skin.
- Complications in herpes zoster infection include Postherpetic neuralgia (PHN), ophthalmic involvement with acute or chronic ocular sequelae (herpes zoster ophthalmicus), bacterial superinfection of the lesions, cranial and peripheral nerve palsies and visceral involvement, such as meningoencephalitis, pneumonitis, hepatitis, and acute retinal necrosis.


A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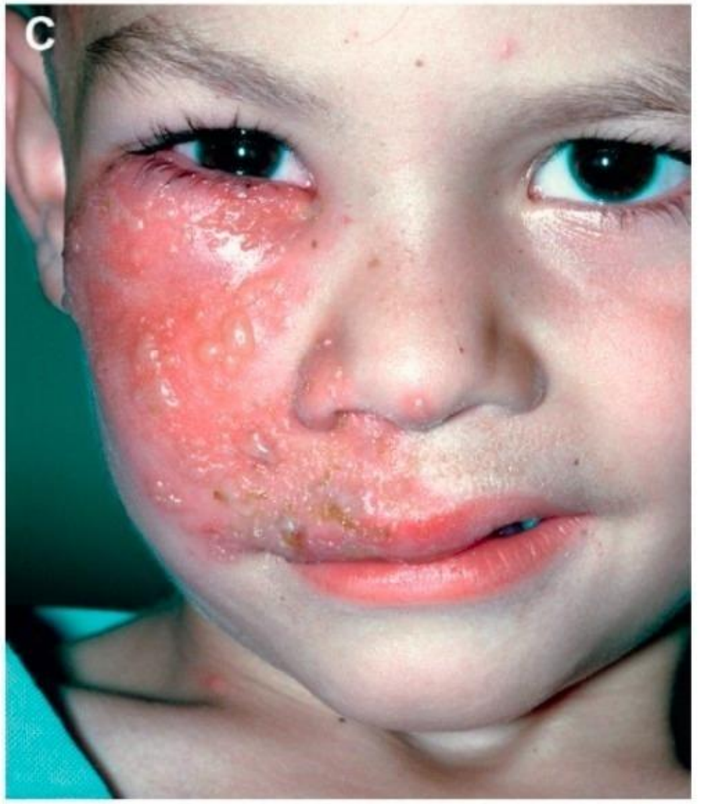
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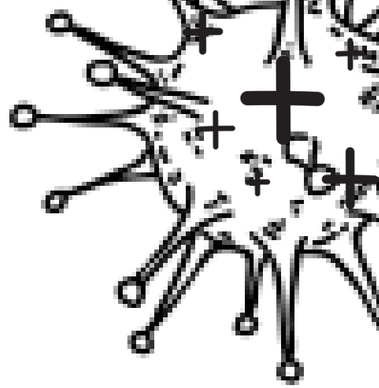
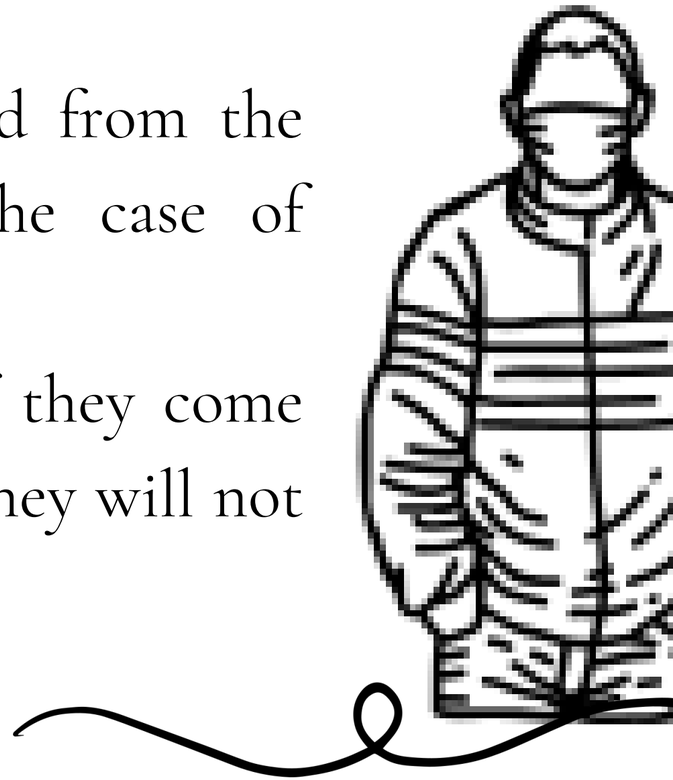
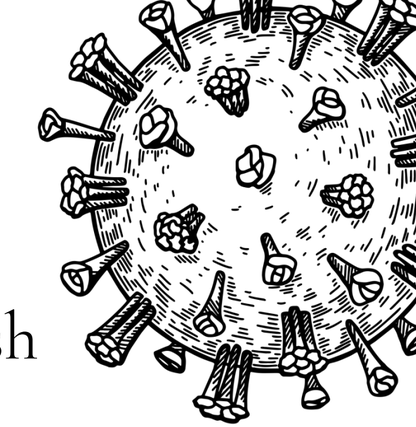
Transmission



1. **Primary Mode of Transmission:**
   - **Airborne**: VZV is highly contagious and primarily spreads through the respiratory route. The virus is transmitted via droplets from coughs or sneezes of an infected person.
2. **Direct Contact:**
   - VZV can also spread through direct contact with the fluid from the vesicles (blisters) of an infected person (especially in the case of chickenpox).
   - Shingles (Herpes Zoster): People can acquire chickenpox if they come into direct contact with the fluid from shingles lesions, but they will not get shingles directly.





3. **Highly Contagious Period:**
   - Individuals are most contagious 1-2 days before the onset of the rash (chickenpox) until the lesions crust over.
4. **Secondary Transmission:**
   - VZV can also spread through indirect contact with surfaces contaminated by vesicular fluid, although this is less common.
5. **At-Risk Populations:**
   - Children, adolescents, and immunocompromised individuals are particularly susceptible.
   - Those who haven't had chickenpox or the vaccine are at a higher risk of infection.

6. Reactivation:

- After the primary infection (chickenpox), VZV remains dormant in nerve cells and can reactivate later in life to cause shingles, which are less contagious but still transmittable through direct contact with lesions.

Pathogenesis

VZV infection and replication

Primary infection

Following transmission to susceptible hosts, VZV proliferates in the oral pharynx (tonsils), infects T cells that enter the circulation and disseminate the virus to the skin and possibly other organs; infection is at first controlled by innate immunity

VZV can remodel diverse T cell populations to facilitate skin trafficking.

VZV DNA can be detected in T cells (viraemia) as early as 10 days prior to the occurrence of a rash and can persist for a week afterwards.

Initially, innate immunity delays viral multiplication in the skin, which provides time for adaptive immunity to develop.

Eventually, cutaneous innate immune responses are overcome by the virus, and there is substantial viral replication in the skin (and sometimes the viscera), resulting in the characteristic rash of varicella.

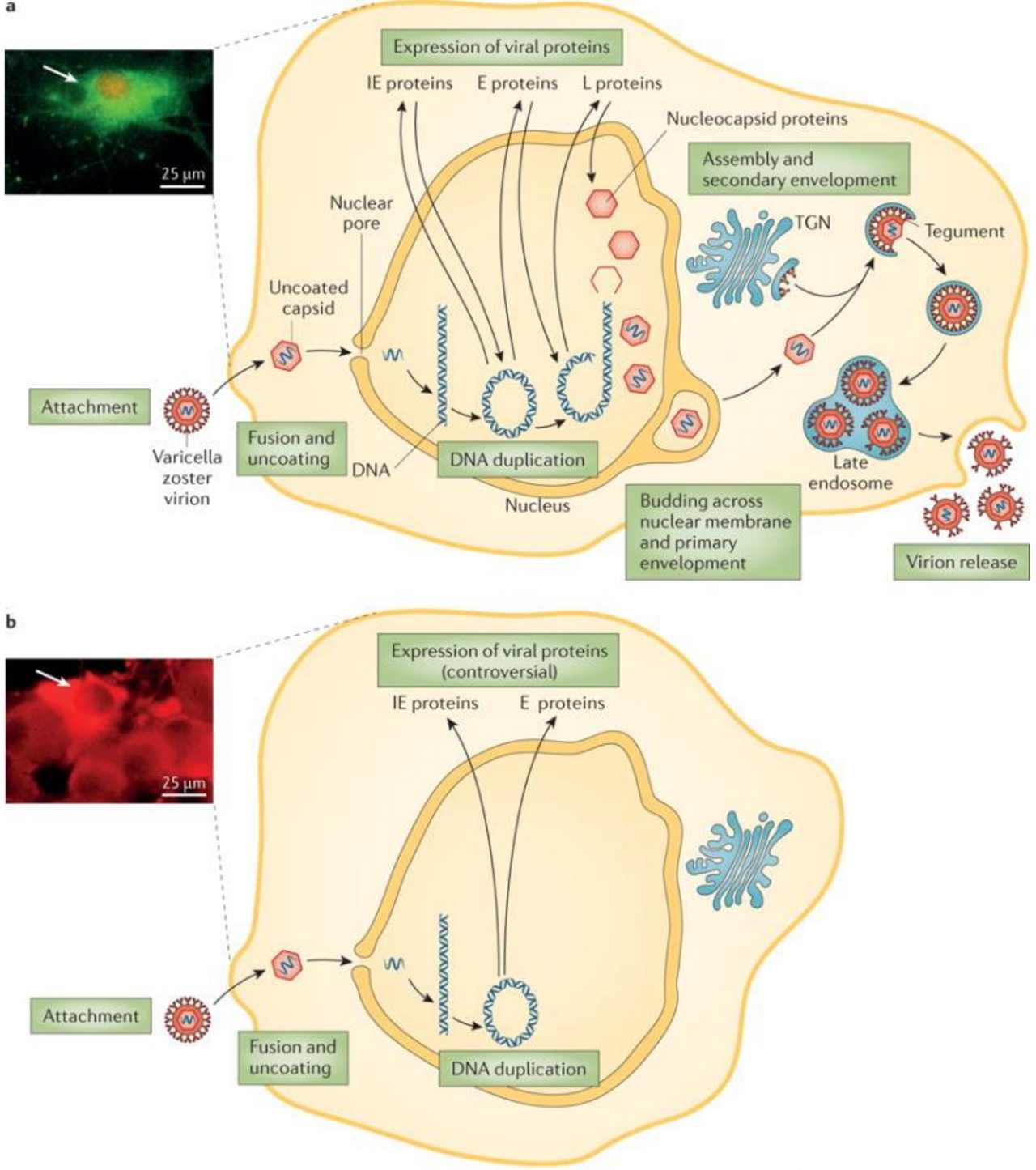
High titres of cell-free VZV develop in skin vesicles and transmit VZV to others.

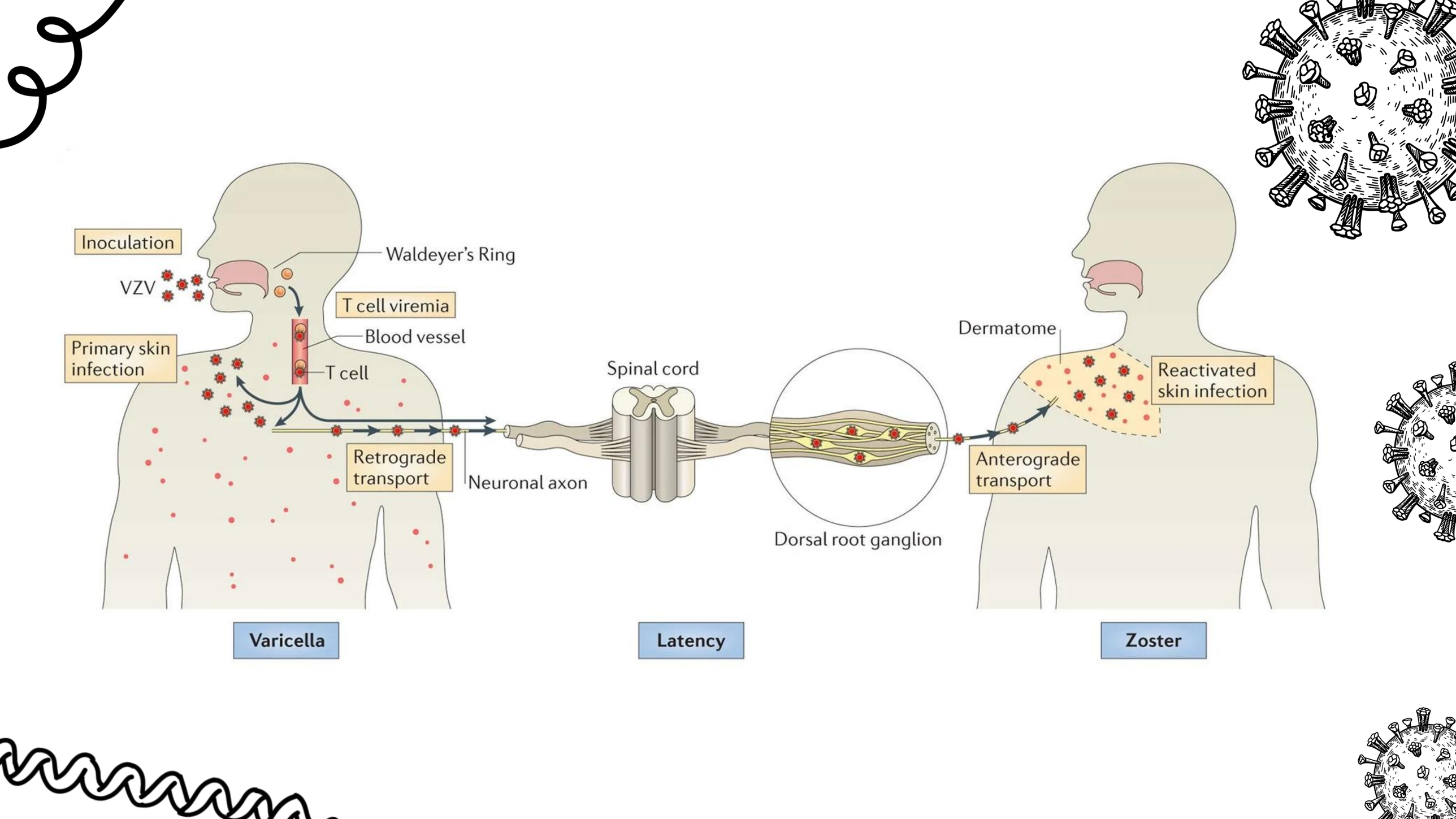
Important and unpredictable complications of varicella in previously healthy children include encephalitis, haemorrhagic manifestations, and bacterial superinfections involving skin, blood, bones and lungs.

In this process of lytic infection (FIG. 4a), VZV expresses its 71 annotated genes and possibly additional genes that have not yet been identified. As described for other herpesviruses, gene expression is thought to proceed in an orderly cascade, beginning with immediate early genes, then early genes, followed by late genes.

In latency, however, gene expression is restricted and possibly blocked (FIG. 4b).

In reactivation, all VZV genes are expressed, again resulting in lytic infection.


a
25 µm
Expression of viral proteins
IE proteins
E proteins
L proteins
Nucleocapsid proteins
Assembly and secondary envelopment
Nuclear pore
TGN
Tegument
Uncoated capsid
Attachment
Varicella zoster virion
Fusion and uncoating
DNA
DNA duplication
Nucleus
Late endosome
Budding across nuclear membrane and primary envelopment
Virion release
b
25 µm
Expression of viral proteins (controversial)
IE proteins
E proteins
Attachment
Fusion and uncoating
DNA duplication


Inoculation
VZV
Waldeyer's Ring
T cell viremia
Blood vessel
T cell
Primary skin infection
Retrograde transport
Neuronal axon
Spinal cord
Dorsal root ganglion
Dermatome
Reactivated skin infection
Anterograde transport
Varicella
Latency
Zoster

Diagnosis

Microscopy Techniques

Direct detection methods include:

- **Cytology**– smears of scrapings of the base of the lesions will reveal characteristic multinucleate giant cells, also known as Tzanck cells.
- **Electron microscopy**– herpesvirus particles can be seen in fluid taken from the early vesicles of either varicella or zoster.
- Cytology and electron microscopy, however, cannot differentiate between HSV and VZV.
- **Immunofluorescence cytology**– smears of the base of lesions can be examined by immunofluorescence cytology, as in the case of HSV.
- This technique is more sensitive than EM but is more labour-intensive and requires greater technical expertise.

Molecular Methods

- PCR has the highest yield and can be used for non-skin samples such as bronchoalveolar lavage and cerebrospinal fluid.
- PCR assays for VZV are available and have been reported to be of use in the diagnosis of VZV meningoencephalitis from CSF specimens.

Serology

- Serological diagnosis of primary varicella infection can be reliably carried out using paired acute and convalescent sera.
- Detection of VZV-specific IgM can be determined by IF (Immunofluorescence) and capture RIA or EIA.
- Other tests include the Complement fixation test (CFT) and latex agglutination.
- Direct fluorescent antibody testing has largely replaced the Tzanck test. The vesicular fluid can also be cultured, but the yield is low compared to PCR.

Treatment

Treatment is symptomatic relief of symptoms. As a protective measure, those infected are usually required to stay home while infectious. Keeping nails short and wearing gloves may prevent scratching and reduce the risk of secondary infections.

Topical calamine lotion may relieve pruritus. Daily cleansing with warm water helps avoid secondary bacterial infection. Acetaminophen may be used to reduce fever. Avoid aspirin as it may cause Reye syndrome. People at risk of developing complications and who have had significant exposure may be given intramuscular varicella-zoster immune globulin, a preparation containing high titers of antibodies to the varicella-zoster virus, to help prevent the disease.

- **In children:** Acyclovir decreases symptoms by 1 day if taken within 24 hours of the start of the rash. Still, it does not affect complication rates and is not recommended for individuals with normal immune function.
- **In adults,** infection tends to be more severe, and treatment with antiviral drugs (acyclovir or valacyclovir) is advised if they can be started within 24 to 48 hours of rash onset. Supportive care, such as increasing water intake and using antipyretics and antihistamines, is important to management. Antivirals are typically indicated in adults, including pregnant women, because this group is more prone to complications. The preferred treatment is usually oral therapy, but intravenous antivirals are indicated for immunocompromised patients.

Prevention

- Dr. Michiaki Takahashi developed the first chickenpox vaccine.
- Preventing varicella in healthcare settings is done by following standard precautions plus airborne precautions (negative air-flow rooms) and contact precautions until lesions are dry and crusted.
- The best preventive measure for chickenpox is the chickenpox vaccine.
- The vaccine is a live attenuated vaccine and administered subcutaneously.
- Two doses of the vaccine are about 90% effective at preventing chickenpox.

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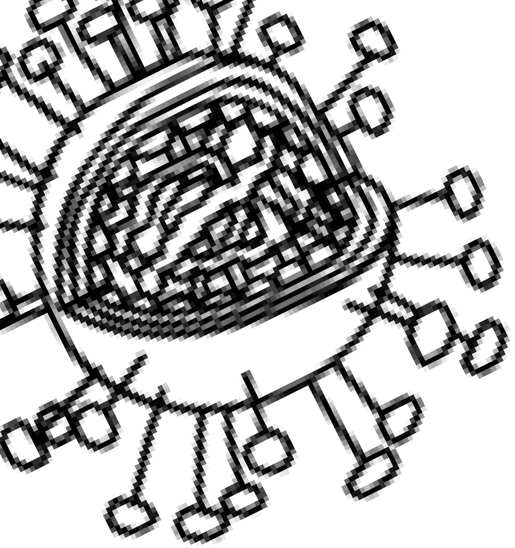

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