Human Herpesviruses

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Contents of Teaching in Medical Virology Lecture:

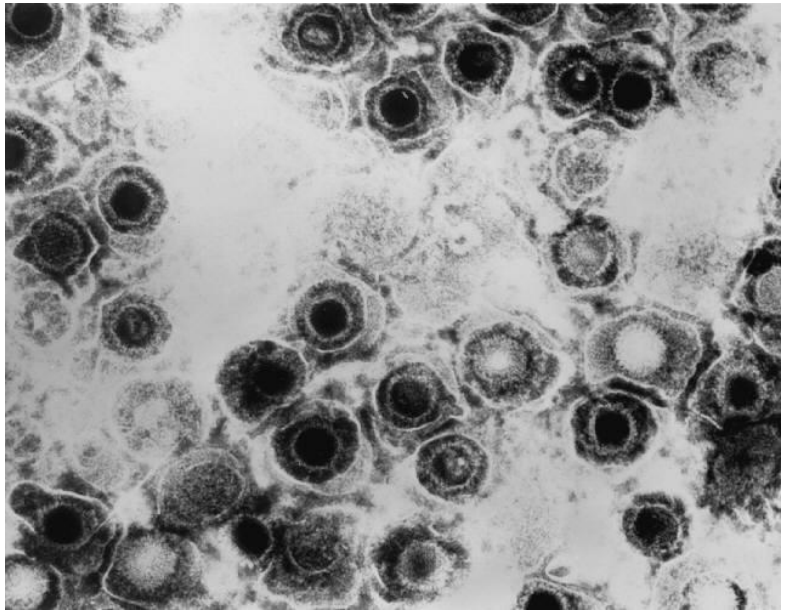
1. Introduction to virology
2. Laboratory diagnosis
3. **Childhood illnesses**
4. **Human herpesviruses**
5. Respiratory infections
6. Gastroenteritis
7. Acute neurological syndromes
8. Hepatitis
9. Human retroviruses
10. Human papillomaviruses

The family of herpesviruses is very large and its members infect most vertebrate species.

There are 8 herpesviruses which are known to infect humans:

Human Herpes Virus

HHV-1	Herpes Simplex Virus 1	(HSV-1)	α
HHV-2	Herpes Simplex Virus 2	(HSV-2)	α
HHV-3	Varicella Zoster Virus	(VZV)	α
HHV-4	Epstein-Barr Virus	(EBV)	γ
HHV-5	Cytomegalo Virus	(CMV)	β
HHV-6	Human Herpes Virus 6	(HHV-6)	β
HHV-7	Human Herpes Virus 7	(HHV-7)	β
HHV-8	Kaposi's Sarcoma-associated Herpes Virus (KSV)		γ



Herpes simplex virus

Structure of the virion

- All herpesviruses are morphologically identical: They have a large **double stranded DNA genome**.
- The virion consists of an icosahedral nucleocapsid which is surrounded by a lipid bilayer **envelope**.
- Between the capsid and the envelope is an amorphous layer of proteins, termed the **tegument**.

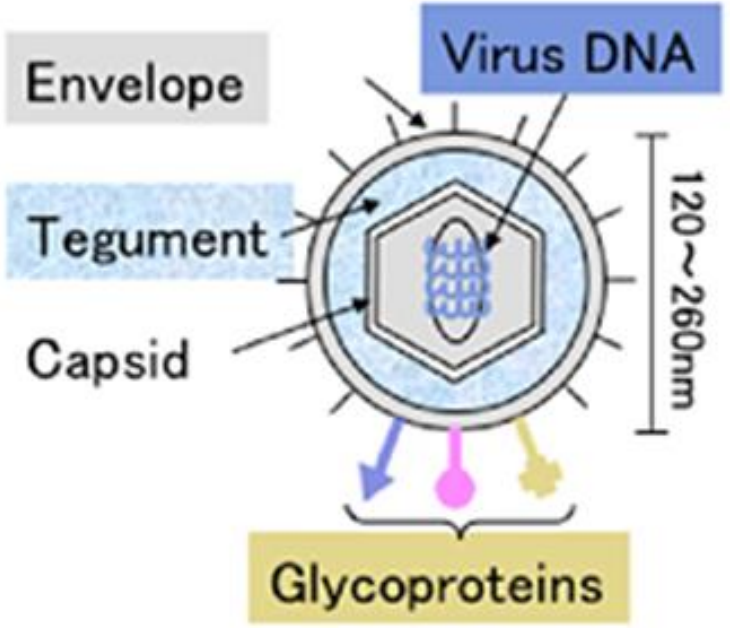


Fig. 1: HSV structure

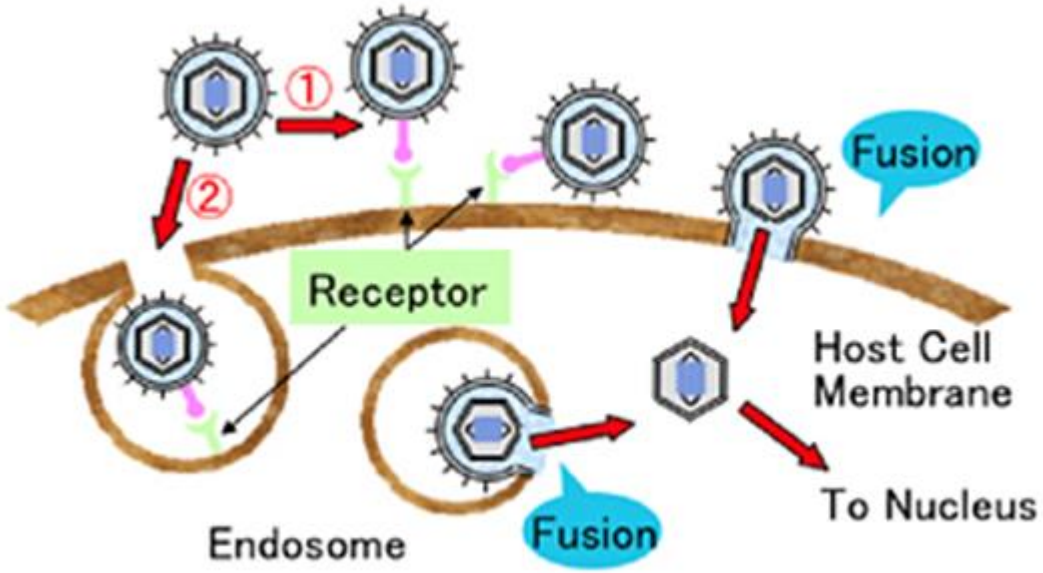


Fig. 2: HSV entry routes

Herpes Simplex 1 and 2

HSV 1-2

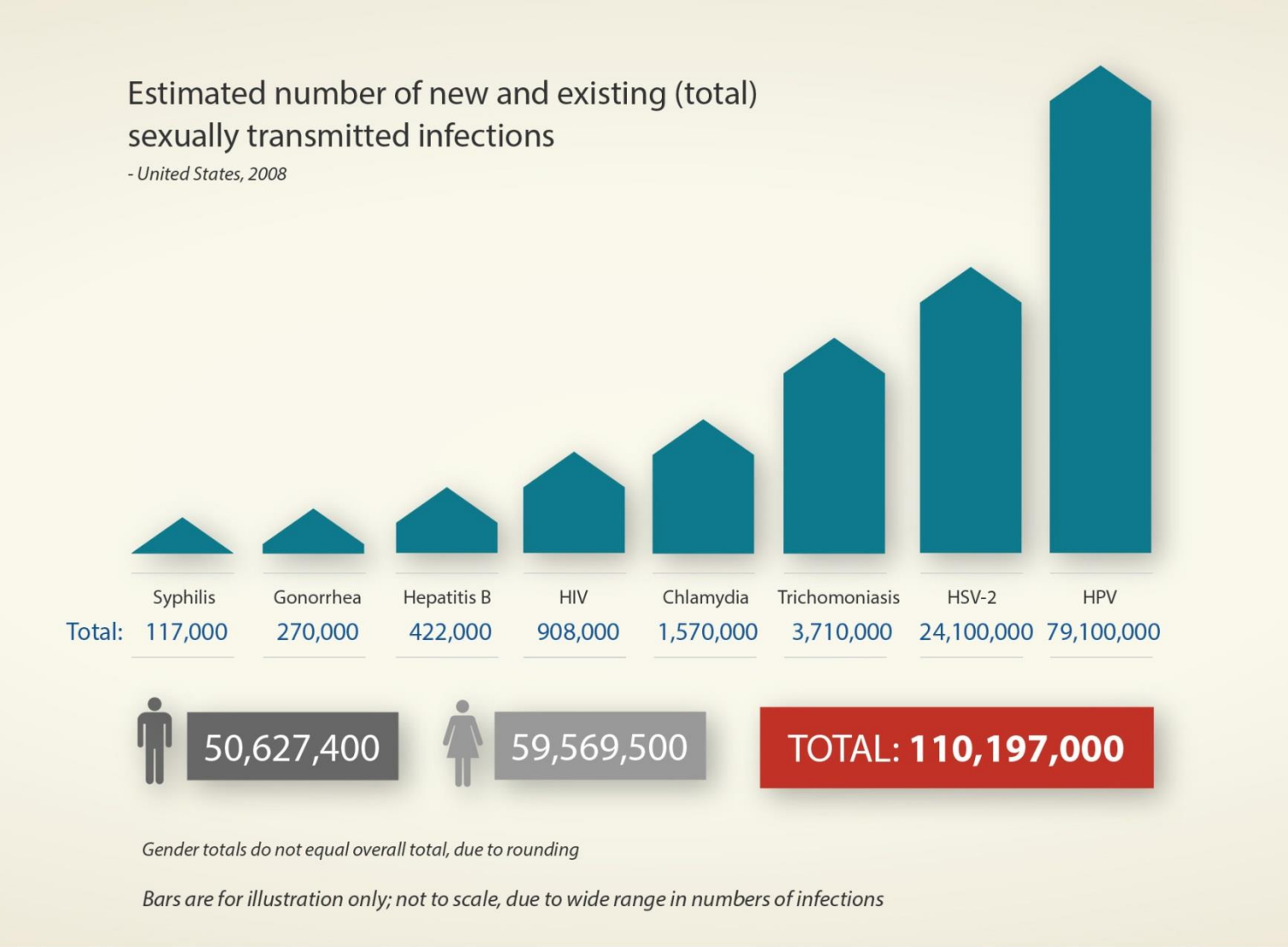
- There are two closely related viruses termed Herpes Simplex 1 and 2. Both cause **painful vesicles** on the skin at the site of inoculation.
- **HSV1** is usually associated with **oro-facial** lesions
- **HSV2** is usually associated with **genital** lesions

Infection with HSV 1 is almost **universal**.

Epidemiology

- Many infections are sub-clinical, virtually **100% of adults have HSV 1-specific antibodies** in their serum.
- Most individuals become infected with HSV1 in the first few years of life. HSV2 is acquired later in adolescence and adulthood (predominantly spread by sexual intercourse) the adult prevalence is lower than for HSV1.
- Approximately 40% of adults have antibodies.
- Virus is shed from the infected area of skin or mucous membrane and spread occurs as a result of **direct contact** with lesions. For example, through **kissing** (HSV1) or sexual **intercourse** (HSV2)
- Both HSV1 and 2 reactivate frequently although lesions are not always clinically apparent. Virus can be shed from clinically inapparent lesions.

HSV-2 infection - genital herpes - is a common diseases.



How many Americans have GENITAL HERPES?

25% OF WOMEN

AND OF MEN, 20%

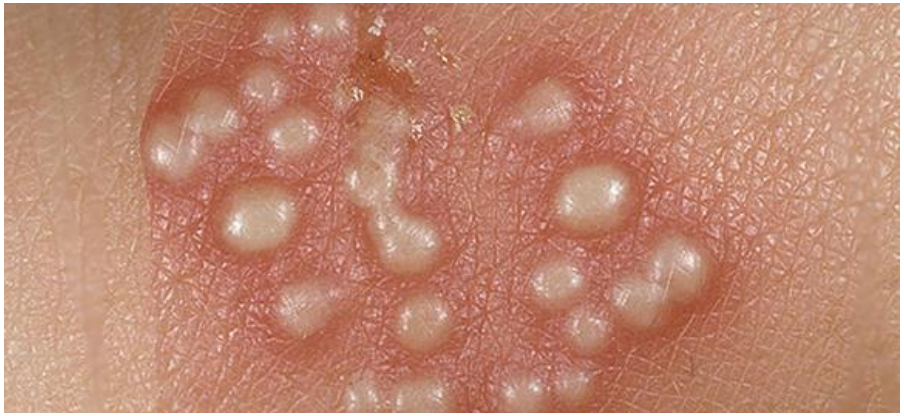
50+ MILLION

85% OF THOSE WHO HAVE IT DON'T KNOW

- There are 2 clinical patterns of disease:
  a) **Primary Infection**
  b) **Recurrent disease**

Primary infection:

- The vast majority of primary infections are **asymptomatic**
- But in clinically apparent cases, the typical presentation is of a painful blistering rash that usually develop 1-3 days post exposure.
- Vesicles usually remain **localised** to the site of inoculation, but spread to other areas of skin and mucous membranes can occur through auto-inoculation.

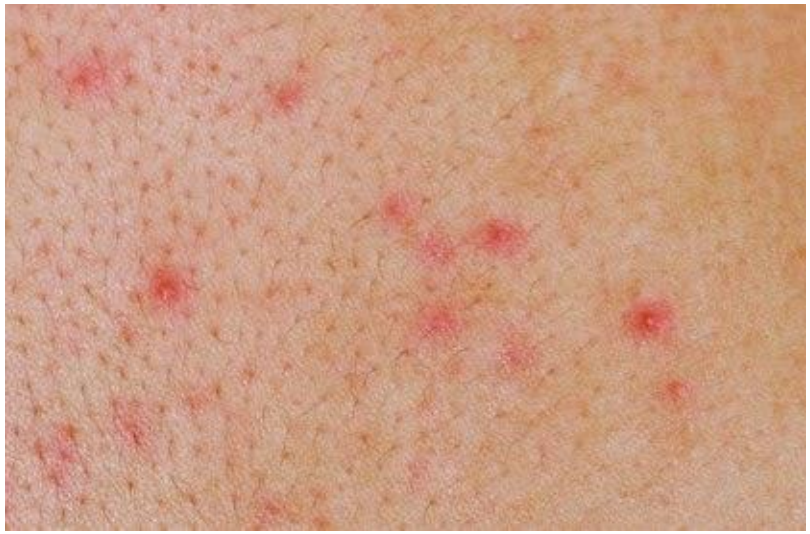


Herpetic vesicles

HSV

Clinicial status in primary infection

- **Gingivo-stomatitis**
  Most common form of primary infection; inoculation is usually through **kissing.**
- **Eczema Herpeticum**
  Super infection of **eczematous** skin with HSV
- **Herpetic Whitlow**
  Inoculation of virus into the **fingers;** an occupational hazard of doctors, nurses and dentists.
- **Conjunctivitis, Keratitis**
  A herpetic lesion on the cornea
- **Genital Herpes**
  Usually due to **HSV 2** but 20-30% of cases are due to type HSV 1; sexually transmitted. Vesicles develop on the genitalia and/or peri-anal area. In females, infection may be confined to the cervix. The primary eruption lasts approximately 14-21 days and may be associated with aseptic meningitis.

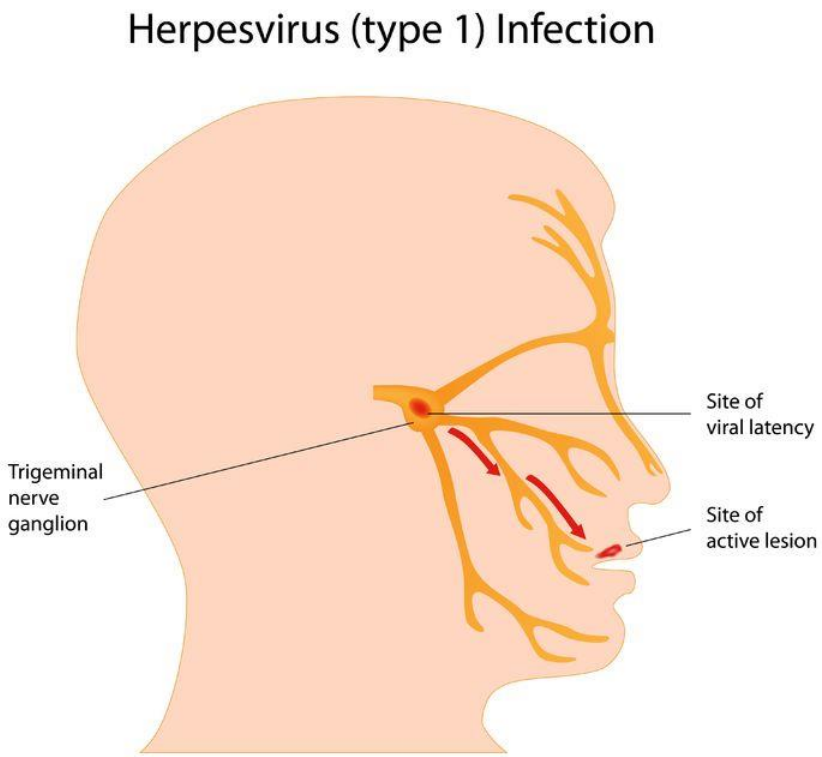


Genital herpes

HSV

Latency

- Following primary infection, the virus enters **sensory nerve** endings at the site of inoculation, travels up the axon and establishes a **latent** infection in the **ganglion** supplying that area of skin.
- **Genital area - sacral ganglia**
- **Oro-facial trigeminal ganglion**
  The viral genome persists in an **episomal** form (plasmid) in the nucleus of the neurone.
  Infection is life long.
- Periodically the virus **reactivates from its latent state**: a cycle of viral replication occurs in the neurone and new virus particles travel down the axon to re-infect the skin or mucous membrane in the area supplied by the nerve.
- Reactivation may be provoked by a number of stimuli: including **sunlight, stress, febrile illnesses, menstruation or immunosuppression.** Reactivation is very common, but often clinically in-apparent.



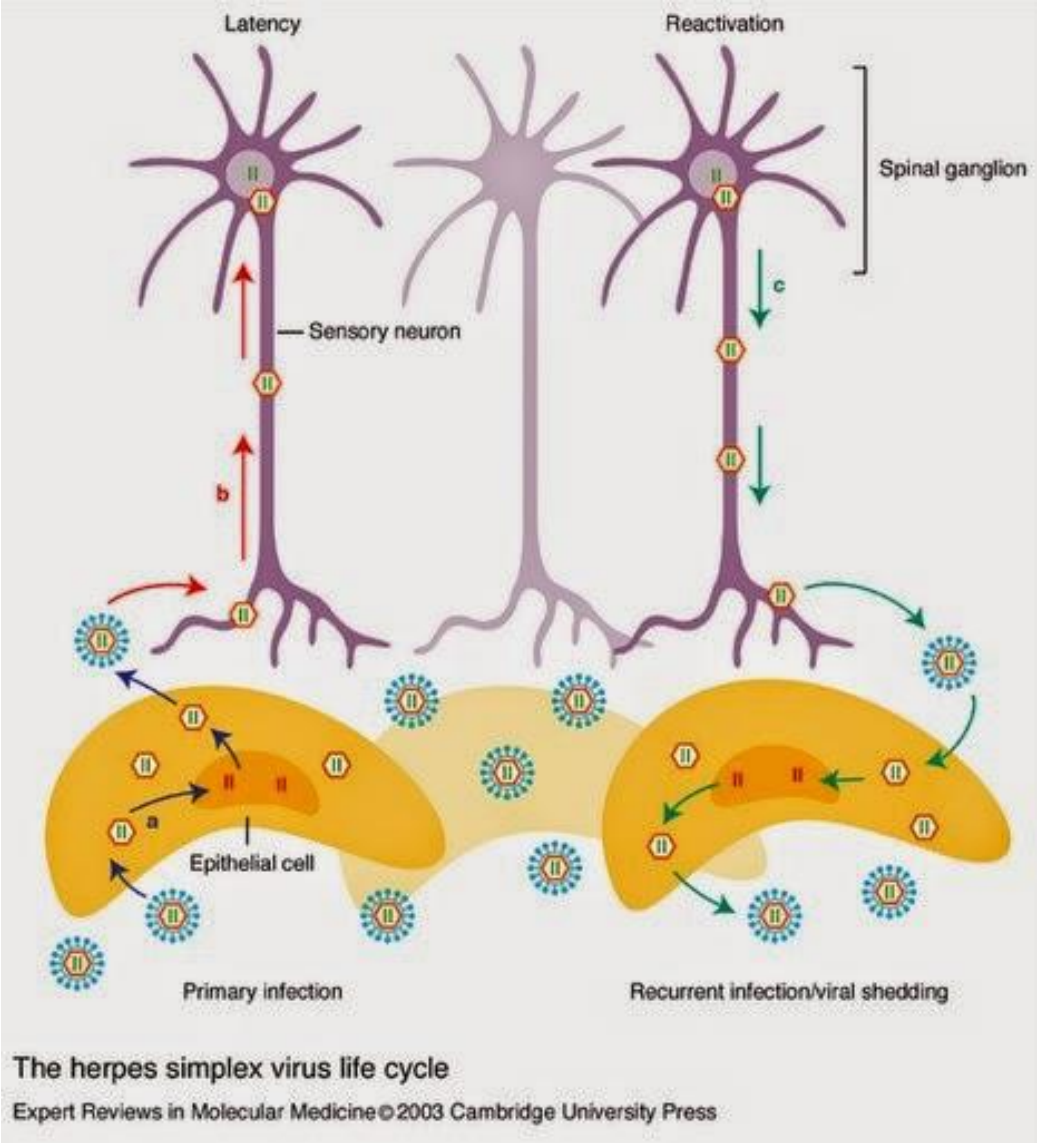
HSV

Clinical manifestations of reactivation:

- **Cold sores** (follows gingivo-stomatitis); vesicles erupt on the muco-cutaneous junctions of the nose or mouth. The lesions are more localized than the primary infection and heal more rapidly (7-10 days). Eruption is often preceded by paraesthesia of the involved area.

- **Recurrent genital herpes:** . Lesions are less extensive and heal more rapidly than the primary infection. Recurrence with HSV 2 infections is more common than with HSV1.

- Rarely, patients may develop **aseptic meningitis** (Mollaret's syndrome) associated with reactivation of HSV2.
  Keratitis: This follows a primary herpes infection of the eye. After reactivation, the virus reaches the cornea via the ophthalmic branch of the trigeminal nerve. The clinical lesion is termed a dendritic ulcer. It heals more rapidly than the primary infection



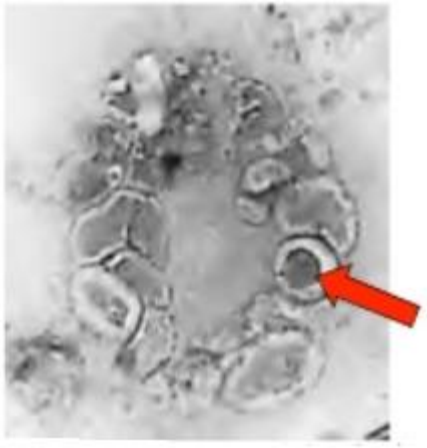
The herpes simplex virus life cycle

HSV

Laboratory diagnosis:

- **Direct detection**- Electron microscopy - herpesvirus particles in vesicle fluid
  Immunofluorescence - viral antigen in smears from vesicles
- **Cell culture** - Clinical material from skin lesions may be inoculated onto cell mono layers which are monitored for the development of characteristic cytopathic effect.

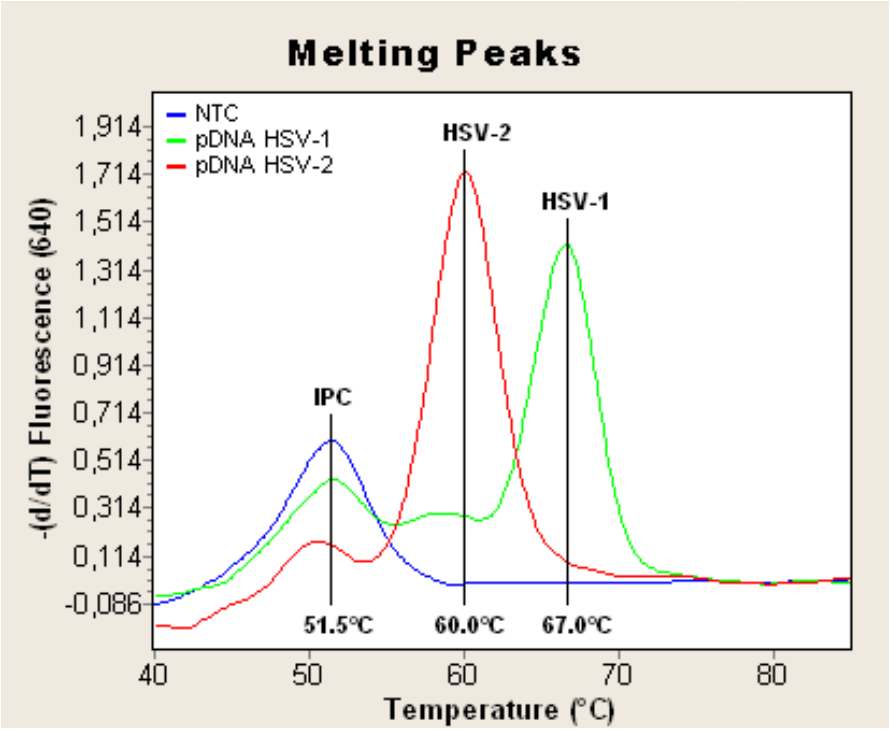
- **Serologies not helpful -** IgG indicates immunity (past exposure)
  IgM marker of primary or recurrent infection, but is not a reliable marker.



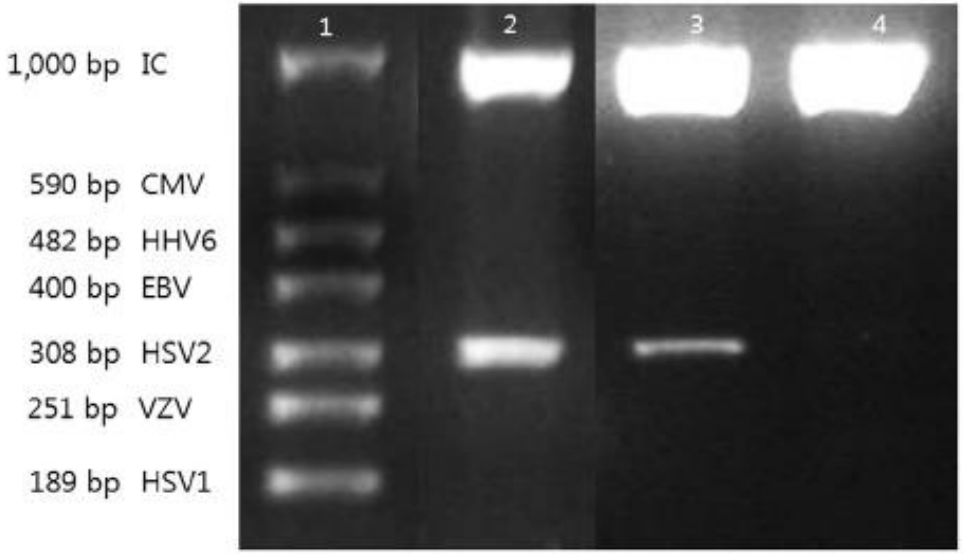
Multinucleated giant cell with intranuclear inclusions

Laboratory diagnosis:

- **PCR** - Detects viral genome in clinical material. HSV PCR on CSF is the test of choice for confirming the diagnosis of HSV encephalitis.



Fig; Amplification of a fragment of the polymerase gene, for the differentiation between HSV-1 and 2.



Fig; HSV-2 DNA PCR in agarose gel electroforesis.

HSV treatment and prevention

- **Available drugs**
  - Acyclovir, valacylovir, famciclovir
- **Target groups**
  - Neonatal HSV infections
  - Immunosuppressed patients (localized or systemic)
  - CNS disease
  - Genital HSV lesions
- **Prophylaxis**
  - Immunosuppressed patients
  - Genital recurrences
- **No vaccine available**

Varicella zoster virus (VZV)

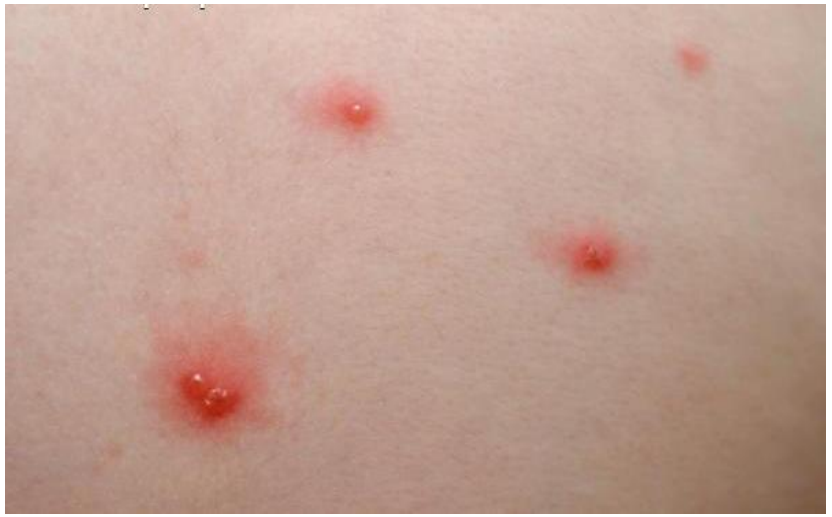
- **Alphaherpesvirus**
- **Aerosol/respiratory transmission**
  - Highly contagious
  - Direct inoculation unusual
- **Epidemiology**
  - >90% of adults seropositive
  - Vaccination program may change epidemiology

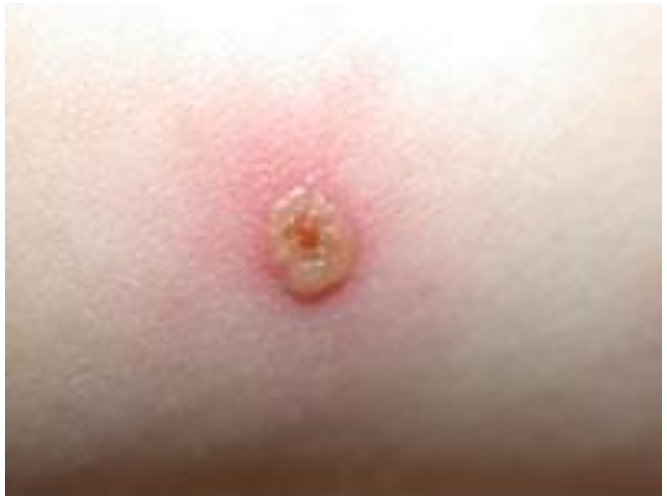
There are two clinical entities:

- (1) **varicella** - chicken pox
- (2) **zoster** - shingles

Varicella

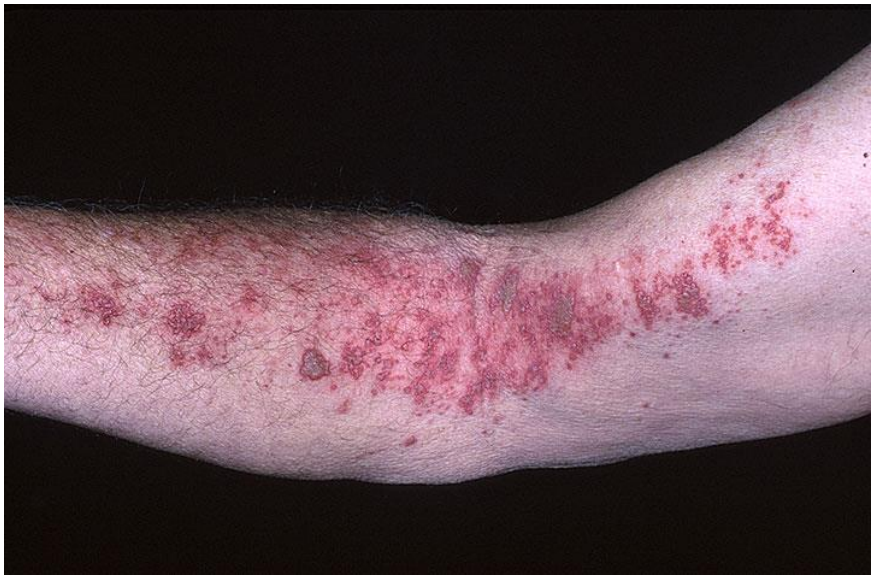
- This is a common childhood infection that presents as a **mild febrile illness** associated with a **generalized vesicular rash**. After a prodromal period, vesicles erupt in successive "**crops**" so that lesions of different ages are present at the same time. The lesions progress from **macule papul**e **vesicle pustule scab.** In **children** the disease is usually **trivial** and complications are rare. If infection is delayed until **adulthood** the disease may be more **severe** and complications such as pneumonia, are more frequent.
  The **incubation period** is long, about **21 days**.
  Infection is transmitted either by **respiratory droplets** or by direct contact with **skin lesions**
  Primary infection is followed by **long lasting immunity**.

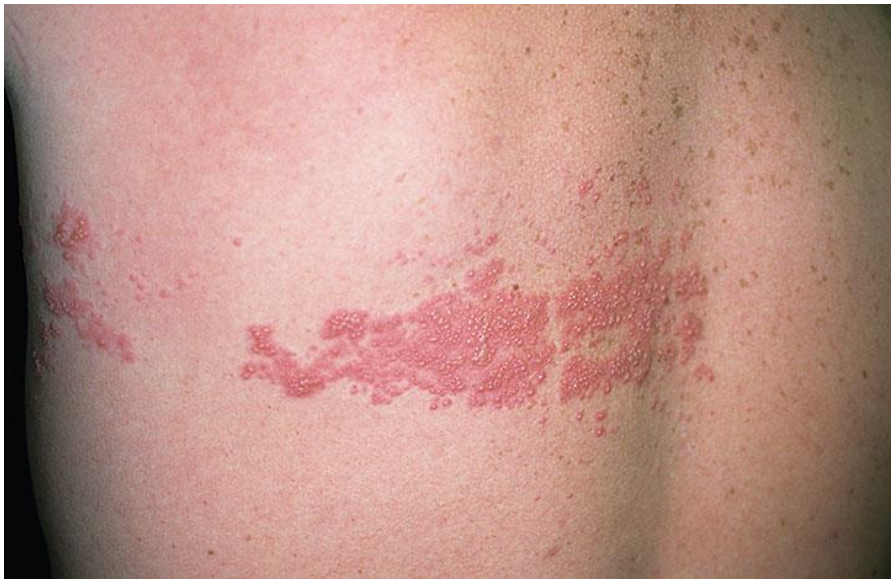




Shingles (Zoster)
Reactivation lesion of VZV

- Like HSV, VZV establishes a **latent** infection in **sensory ganglia**. Reactivation usually occurs many years after primary infection and is often associated with **immunosuppresion** of the host. After a cycle of infection in the ganglion, virus particles travel down the axon to re-infect the dermatome supplied by the sensory ganglion. This gives rise to **painful vesicles on the skin**. Common sites include **the thoracic dermatomes** and those supplied by the **trigeminal nerve**. **Post herpetic neuralgia** is a common complication especially in the elderly.
  Ramsay Hunt syndrome: Zoster involving one of the branches of the trigeminal nerve. Patients present with uni-lateral facial nerve palsy, ear pain and vesicles in the external auditory meatus.





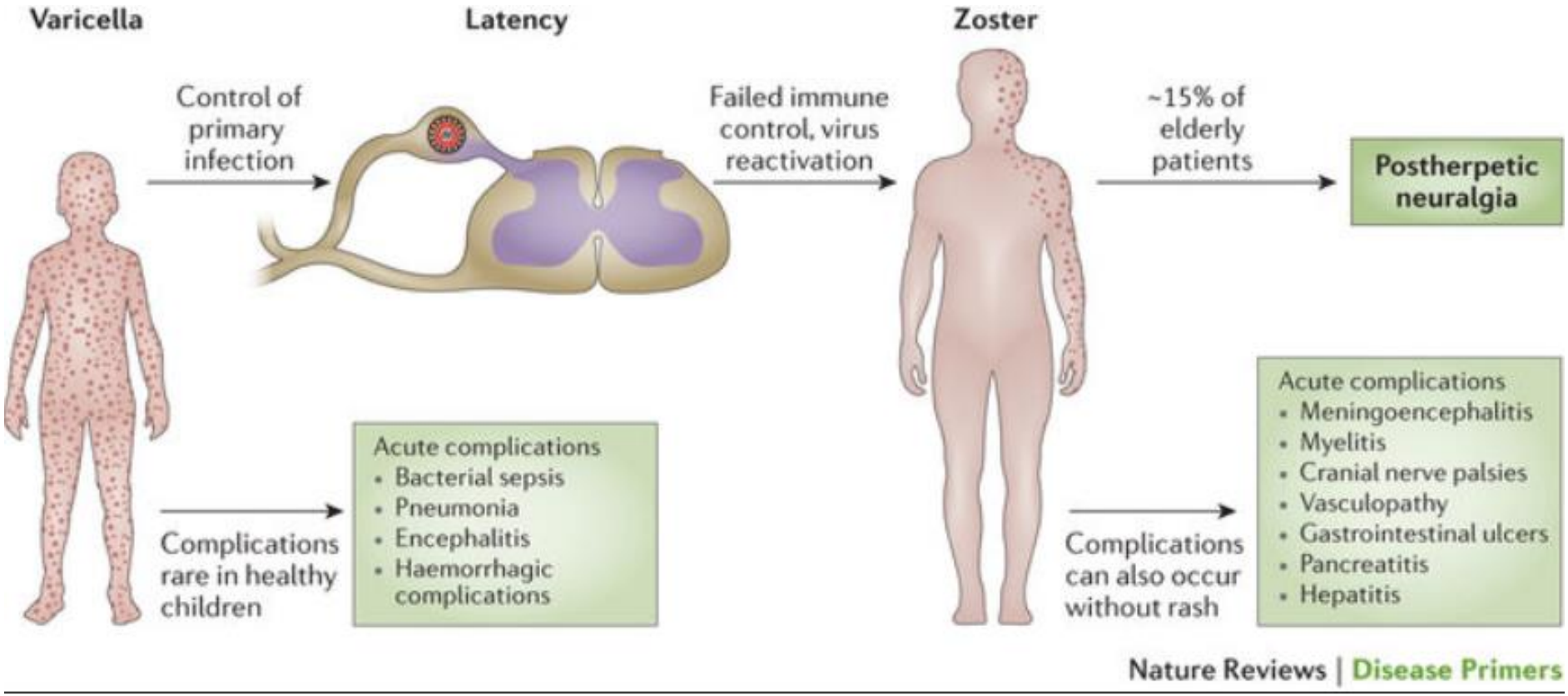


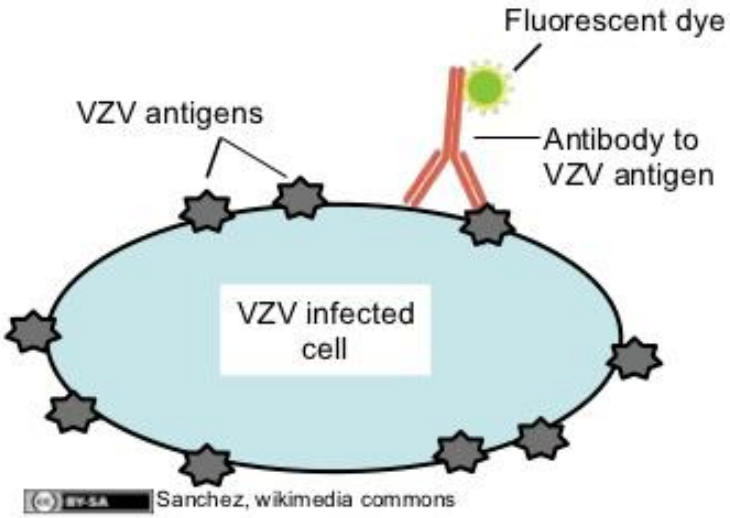
Figure: Different phases of varicella zoster virus infection.

Chickenpox vs. Shingles

	Varicella zoster virus	Herpes zoster virus
Transmission	Through respiratory secretions, vesicular fluid	By reactivation of latent VZV
Signs and symptoms	Malaise, fever, rash	Neuralgia, dermatomal rash, weakness of affected nerve
Distribution of rash	Trunk initially; progressing to face, extremities, mucosa or a combination	Primarily (50%) thoracic; remainder cranial, cervical, lumbar
Character of rash	Non-grouped, itchy vesicles	Grouped, markedly erythematous, painful vesicles

VZV diagnosis

- **Clinical syndrome**
  - Simultaneous lesions at all stages
- **Virus detection**
  - Direct fluorescent antibody test (DFA)
  - PCR
  - Culture
- **Serologies helpful to determine exposure risk**



VZV

Treatment:

- Uncomplicated chicken pox normally resolves without specific treatment.
- Acyclovir is the drug of choice for severe varicella zoster virus infections.
- Patients at risk for varicella complications (adults, immuno-compromised children) should receive acyclovir.
- Therapy should be started as soon as possible (within 48 hours) of disease onset.

VZV prevention

- **Effective vaccine available**
  - Live, attenuated virus
- **Target populations**
  - Routine childhood vaccination (VARIVAX®, ProQuad®)
  - Persons > 60 yo *regardless* of previous shingles history
  - Healthy adolescents and adults without evidence of immunity
    - High risk for VZV transmission (healthcare workers, teachers, childcare employees, chronic care facilities)
    - Non-pregnant women of childbearing age
  - Household contacts of immunocompromised persons
- **Contraindications**
  - Immunosuppression
  - Pregnancy

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5604a1.htm

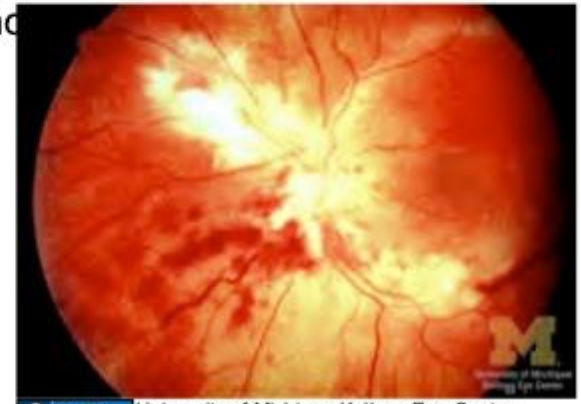
Cytomegalovirus

- Most individuals are infected by human cytomegalovirus (HCMV) in the first few years of life and by **adulthood 70-90%** of people **have IgG antibodies**.
- HCMV **rarely causes disease** in healthy people, particularly when infection occurs in **childhood**.
- When primary infection occurs in **adulthood**, patients may develop an i**nfectious mononucleosis-like illness** associated with, fever, sore throat and lymphadenopathy.
- Like other herpesviruses, following primary infection, the virus becomes **latent** and may **reactivate** at any stage.

CMV clinical disease

- **Primary exposure**
  - Usually asymptomatic
  - Can produce "mono-like" syndrome (non-specific symptoms)

- **Complications**
  - Congenital CMV
    - CNS involvement (encephalomalacia, hydrocephalus, retinitis)
  - End-organ damage in immunc
    - Ocular (retinitis)
    - CNS (encephalitis)
    - Respiratory
    - Gastrointestinal
    - Bone marrow



CMV

Infection in immunosuppressed patients:

- **Transplant patients** and patients with **AIDS**, may develop life threatening disease following either primary infection with HCMV or reactivation. Common syndromes include:
  Interstitial pneumonia
  Retinitis
  Enteritis
  Disseminated infection
  CMV pneumonia (following primary CMV infection in the first months of life) is a common cause of death in HIV infected infants in this country.

CMV diagnosis

- **Clinical syndrome *non-specific***
- **Virus detection**
  - PCR (quantitative)
  - Histopathology (“owl eye”)
  - Direct fluorescent antibody (DFA) test
  - Culture
- **Serologies helpful**
  - Assess risk for reactivation if immunosuppression anticipated

Large nuclear inclusion
With peripheral clear zone

CMV

Treatment and Control.

- Ganciclovir,
  in Retinitis, esophagitis, colitis,

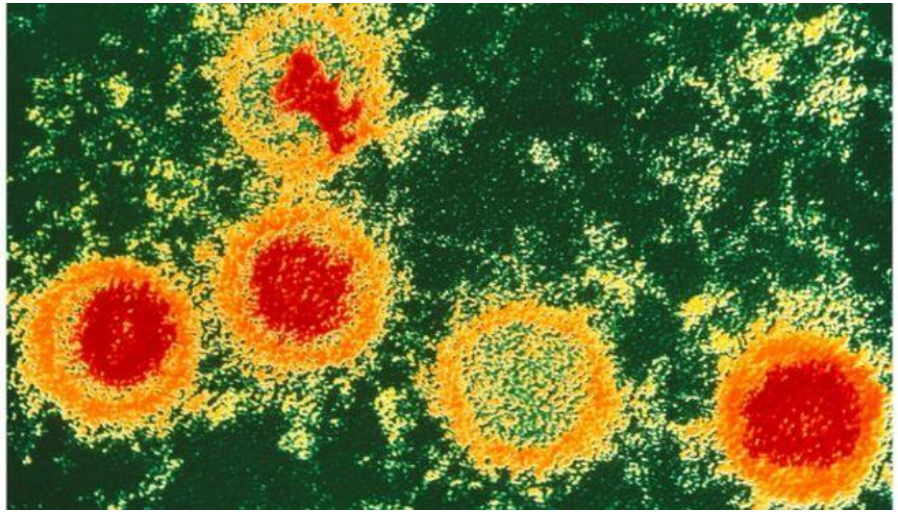
Other Drugs,
  Acyclovir, Valaciclovir
Screening of Blood, and organ donors,
Passive Immunization with CMV hyper immune globulin,

- The nucleoside anologue ganciclovir has activity against actively replicating CMV.
- It has toxic side effects and is expensive.

Epstein-Barr Virus

Anthony **Epstein** and Yvonne **Barr**

- EBV was discovered in 1964.
- Infection is widespread.
- Most people have been infected by the time they reach adulthood.
- Following primary infection, the virus persists in a latent form in the B lymphocytes of the host.
- Periodic reactivation of the virus is associated with shedding of virus in saliva.
- Transmission is by close contact, especially kissing.

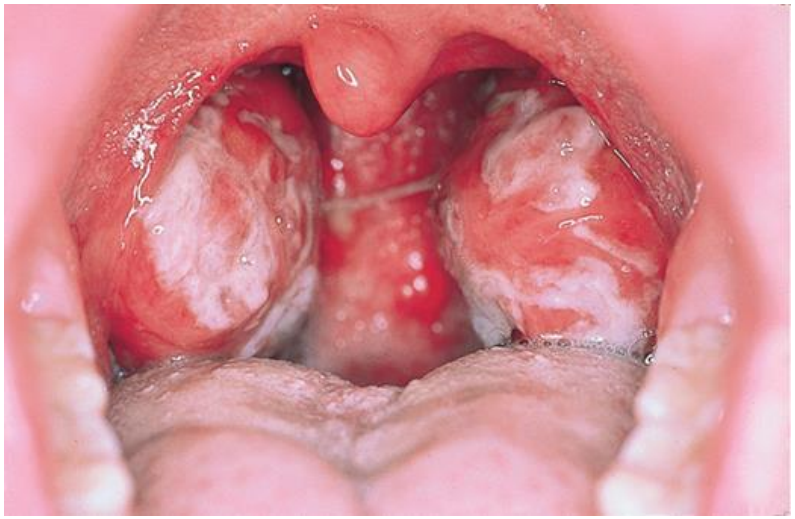


Electron micrograph of the Epstein Barr virus
DR GOPAL MURTI/SCIENCE PHOTO LIBRARY

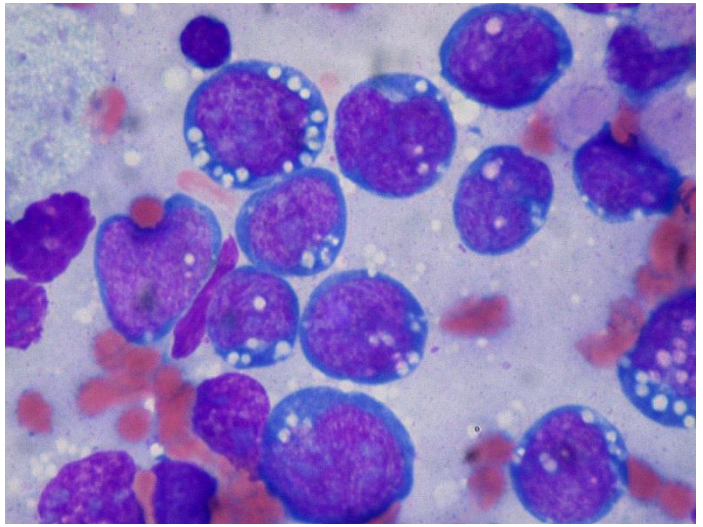
EBV

Clinical Syndromes associated with EBV infection:

- 1) Infectious Mononucleosis (primary infection syndrome)
  2) Lympho-proliferative disorders in immunocompromised patients
  3) Burkitts Lymphoma and other Non Hogkins lymphomas
  4) Naso-pharyngeal Carcinoma
  5) Other tumours e.g. certain forms of Hodgkins disease
  6) Oral hairy leuko-plakia



Infectious Mononucleosis

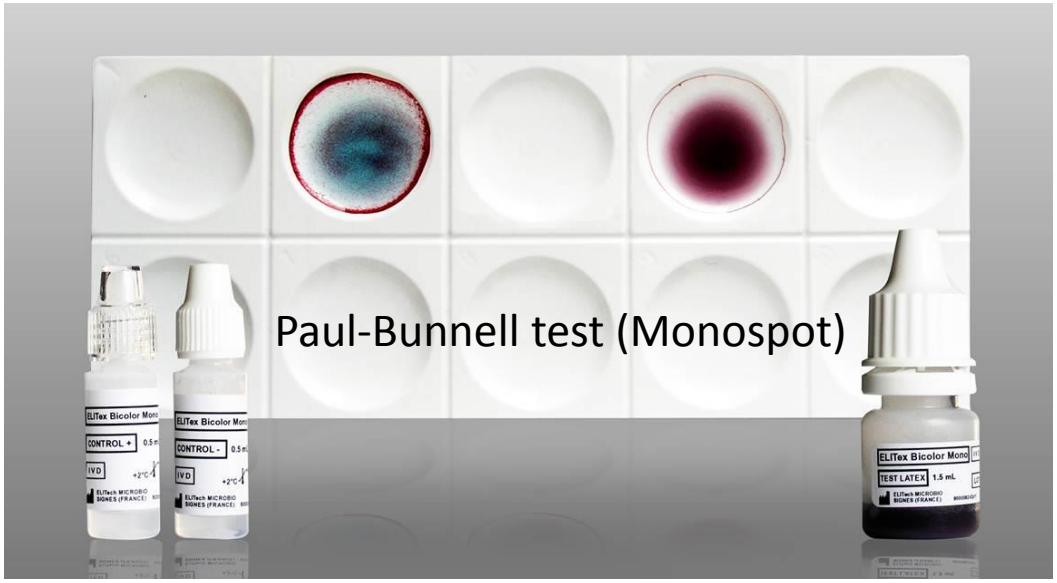


Burkitts Lymphoma

Infectious Mononucleosis (IM)

Laboratory Diagnosis

- **Heterophile antibody** - Paul-Bunnell test (Monospot): Screening test for acute IM; 70-80% of patients with acute IM develop IgM antibodies that agglutinate sheep red blood cells.



Paul-Bunnell test (Monospot)

Specific serological tests:

- Antibody to the viral **capsid** and **nuclear** antigens are useful for confirming the diagnosis of acute IM:
  IgG and **IgM** to **Viral capsid antigen** (VCA): detectable early during the acute phase
  VCA IgM: only present during acute phase
  IgG to **EBV nuclear antigens** (EBNA): detectable late in convalescence (> 6 months post infection)

EBV

B cell and Latency

- EBV infects **B cells** and establishes a latent infection.
- The viral genome enters the nucleus and persists in an episomal form.
- Six viral genes, termed **EBNA 1-6** are expressed during this (latent) stage.
- They **transform** the B cell into an **immortal**, continuously dividing cell. Everyone who has been infected with EBV in the past has some EBV transformed cells in their circulation. Their numbers are controlled by the host's immune response.

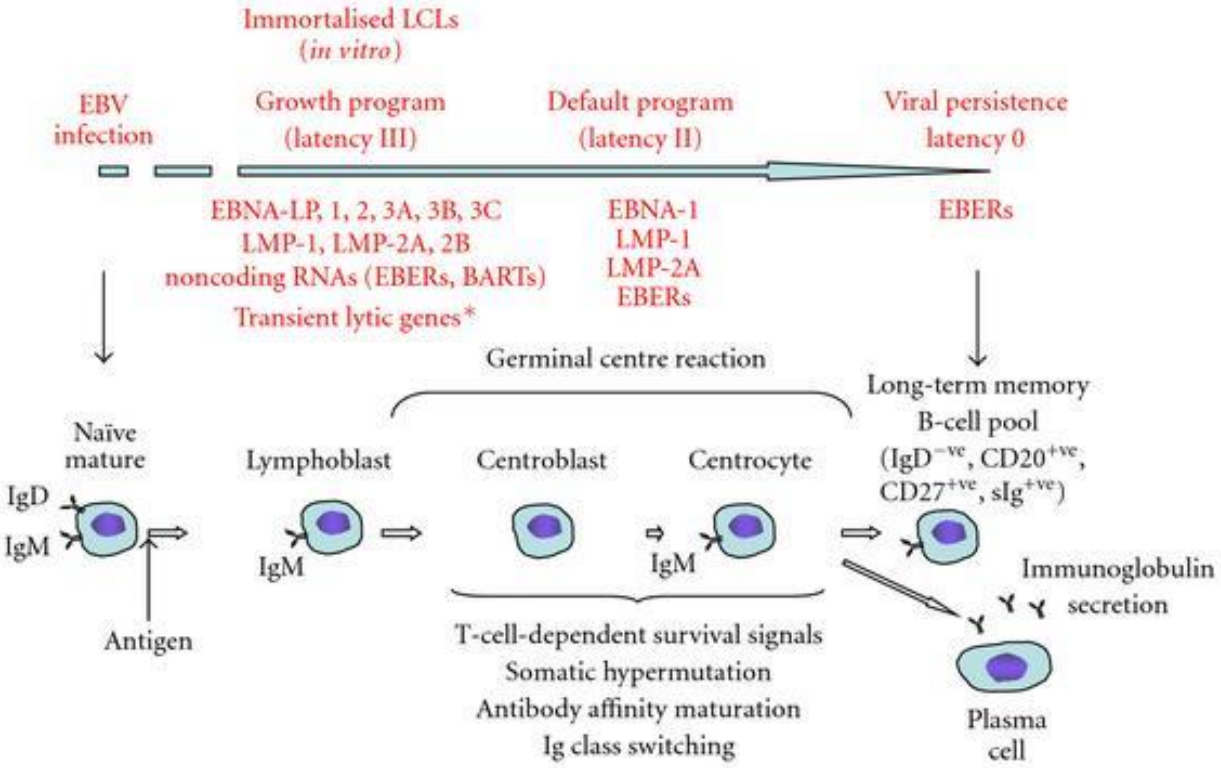


Figure : Model of establishment of EBV latency in B cells.

Summary

Herpes viruses

	Subfamily	Transmission	Clinical Syndromes	Latency site	Diagnosis	Antiviral Rx	Vaccine
HSV	Alpha	Cutaneous	Cutaneous - localized (oral, genital) CNS	Neurons	Clinical PCR Culture/DFA	Acyclovir	No
VZV	Alpha	Respiratory	Cutaneous - disseminated and localized	Neurons	Clinical PCR Culture/DFA	Acyclovir	Yes
CMV	Beta	Secretions (oral, urogenital)	Systemic Ocular, GI, hematopoietic, respiratory	Monocytes, macrophages	Serology PCR Culture/DFA	Ganciclovir	No
EBV	Gamma	Secretions (oral)	Systemic Lymphoma	B cells	Serology, PCR Culture/DFA	None	No