Exanthematic viruses

Petr Hubáček

Dept. of Medical Microbiology and Paediatric Haematology and Oncology

2nd Medical Faculty of Charles University and Motol University Hospital

FN MOTOL

HSCT UNIT - PEDIATRICS PRAGUE CZECH REPUBLIC

Viral exanthematic diseases

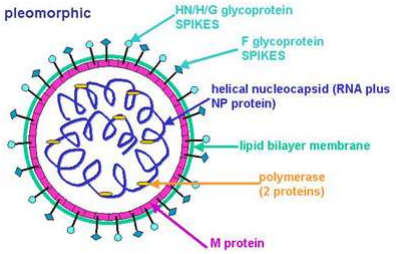
Childhood exanthema diseases

Classical name	„systematic exant. name“	Pathogen
Measles (rubeola)	1st childhood disease	morbillivirus
Scarlet fever	2nd childhood disease	*Streptococcus pyogenes*
Rubella (German measles)	3rd childhood disease	Rubivirus
Filatov-Duke‘s disease (pseudoscarlantina)	4th childhood disease	Coxackie and Echoviruses
Erythema infectiosum	5th childhood disease	Parvovirus B19
Exanthema subitum – Roseola infantum	6th childhood disease	HHV-6 and HHV-7
Hand, Foot and Mouth disease	7th childhood disease	Coxackie A-16

Herpes simplex, Chicken pox - VZV

Paramyxoviridae

Members of the Paramyxovirus Family			
SUB-FAMILY	**GENUS**	**MEMBERS**	**GLYCOPROTEINS**
Paramyxovirinae	Respirovirus	Human parainfluenza virus1 (HPIV 1) Human parainfluenza virus3 (HPIV 3)	HN, **F**
	Rubulavirus	Human parainfluenza virus2 (HPIV 2) Human parainfluenza virus4 (HPIV 4) **Mumps virus**	HN, **F**
	Morbillivirus	**Measles**	H, **F**
	Henipavirus	Hendravirus Nipahvirus	G, F
Pneumovirinae	Pneumovirus	Respiratory syncytial virus	G, F
		Metapneumovirus	



- ss (-) RNA virus
- genome length 15-16 kb
- coding 8 proteins
- spherical symetry of capsid and diameter of 100-300 nm

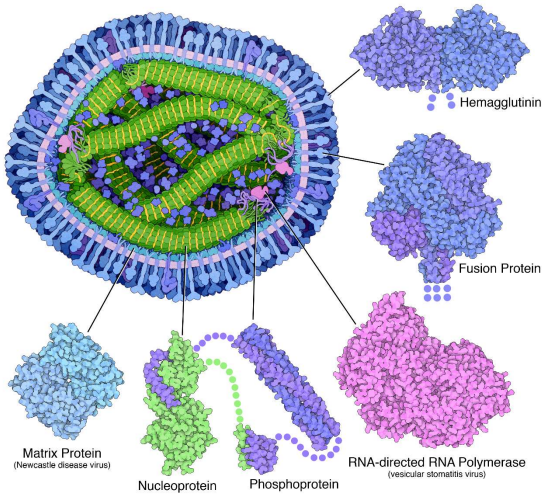
https://www.microbiologybook.org/mhunt/mump-meas.htm

Paramyxoviridae

Measles

Before the introduction of measles vaccine in 1963 and widespread vaccination, major epidemics occurred approximately every 2-3 years and caused an estimated 2.6 million deaths each year.

An estimated 128 000 people died from measles in 2021 – mostly children under the age of five years, despite the availability of a safe and cost-effective vaccine.



https://pdb101.rcsb.org/motm/231

Estimated cases – 20,000,000 / year.

Paramyxoviridae

Measles

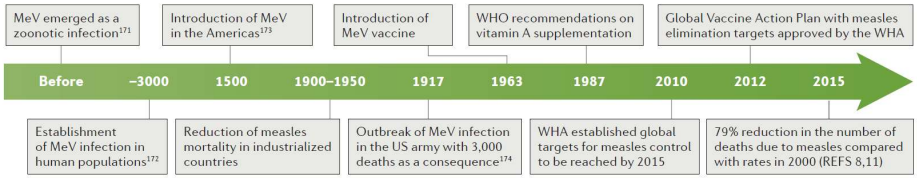


Figure 1 | **History of measles virus infection and elimination programmes.** Closely related to the recently eradicated cattle virus rinderpest[170], measles virus (MeV) probably evolved from an ancestral virus and emerged as a zoonotic infection in communities in which cattle and humans lived in close proximity[171]. MeV most likely became established in humans about 5,000 years ago when human populations achieved sufficient size in Middle Eastern agrarian civilizations to maintain virus transmission[172]. Measles did not always have a global distribution and probably first entered the Americas in the fifteenth century with the immigration of Europeans. MeV and smallpox infections probably facilitated the European conquest of Native American civilizations by causing large numbers of deaths among the fully susceptible Native Americans[173]. The outbreak of measles in the US Army from 1917 to 1918 that resulted in >95,000 cases of measles and 3,000 deaths provided a striking example of the devastating effect of measles and associated bacterial co-infections that occurred before the introduction of antibiotics or measles vaccines[174]. Increasing measles vaccine coverage prevented an estimated 17.1 million deaths between 2000 and 2014 (REF. 8). WHA, World Health Assembly.

Nat Rev Dis Primers. 2016 Jul 14:2:16049.
2 | 2016 | VOLUME 2 www.nature.com/nrdp

- Measles is a highly contagious, serious airborne disease caused by a virus that can lead to severe complications and death.
- Measles vaccination averted 57 million deaths being between 2000 and 2022.
- Even though a safe and cost-effective vaccine is available, in 2022, there were an estimated **136 000 measles** deaths globally, mostly among unvaccinated or under vaccinated children under the age of 5 years.
- The proportion of children receiving a first dose of measles vaccine was 83% in 2023, well below the 2019 level of 86%.

World Health Organization

Paramyxoviridae

Measles

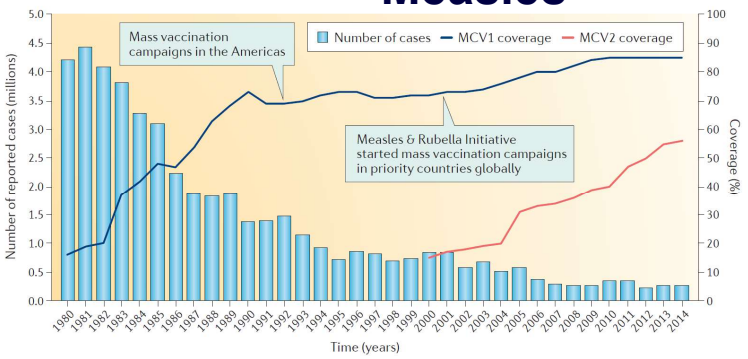


Figure 2 | **Global reported measles cases and estimated coverage with the first and second dose of measles-containing vaccine by year (1980–2014).** MCV, measles-containing vaccine. Figure adapted from data available from the WHO[175,176].

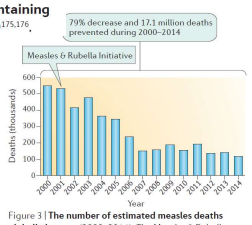


Figure 3 | **The number of estimated measles deaths globally by year (2000–2014).** The Measles & Rubella Initiative was established in 2001; global estimated measles mortality decreased by 79% during 2000–2014, preventing an estimated 17.1 million deaths[8]. Adapted with permission from REF. 7, CDC MMWR.

Nat Rev Dis Primers. 2016 Jul 14:2:16049.

Paramyxoviridae

Measles

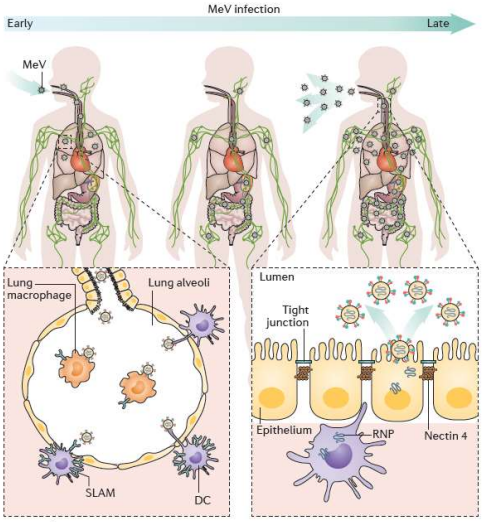


Figure 5 | **Measles virus infection and transmission.** Measles virus (MeV) is an airborne pathogen. MeV aspirated into the respiratory tract infects alveolar macrophages or dendritic cells (DCs) using signalling lymphocytic activation molecule (SLAM; also known as CD150) as a receptor. MeV infection is amplified in regional lymphoid tissues followed by a systemic infection throughout the body. MeV-infected lymphocytes and DCs migrate into the subepithelial cell layer and transmit MeV to epithelial cells of various organs or tissues using nectin 4 as a receptor. MeV infection is amplified in the epithelia, and a large amount of progeny viruses are released into the respiratory tract. RNP, ribonucleoprotein.

Cell receptor:

SLAM (Signalling lymphocyte activation molecule, known also as SLAMF1 and CD150)

tymocytes, macrofages, matured dendritic cell (DCs), Langerhans cells (LCs), lymfocytes and thrombocytes

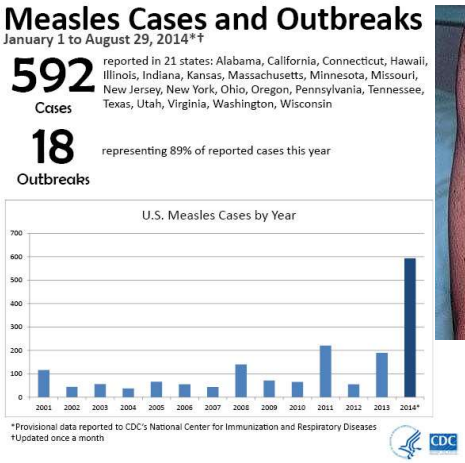
Nectin 4 (PVRL4) – epitelial cell

DC-specific intercellular adhesion molecule 3-grabbing non-integrin 1 (**DC-SIGN**; CD209) a C-type lectin domain family 4 member K (**Langerin**) helping in DCs and LCs infection

Nat Rev Dis Primers. 2016 Jul 14:2:16049.

Paramyxoviridae

Measles



Estimated cases – 20,000,000 / year.
Estimated kills - 128,000 people in world/year.

Paramyxoviridae

Measles

https://o.quizlet.com/Zw7Q.J7v4Lrq4L7cWY7u1w.png

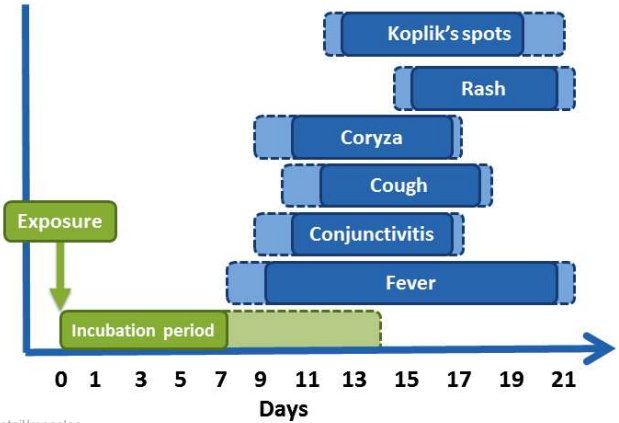
Paramyxoviridae

Measles

- Droplet spread infection. It is so contagious that any child who is exposed to it and is not immune will probably get the disease.
- Measles virus normally grows in the cells that line the back of the throat and lungs
- incubation period 8-12 days

Symptoms

- Measles starts with fever, runny nose, conjunctivitis, white spots in the cheeks.
- Rash starts 7-18 days after exposure at head and neck and spreads from this areas to whole body (3 days); 5-6 days of fading.

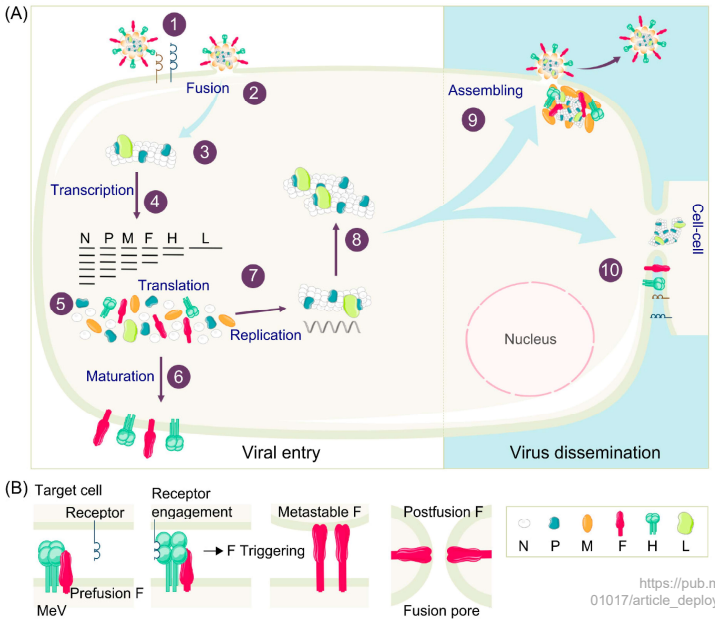


https://www.who.int/news-room/fact-sheets/detail/measles

https://www.wikidoc.org/index.php/File:Measles_Symptoms.png

Paramyxoviridae

Measles



https://pub.mdpi-res.com/viruses/viruses-11-01017/article_deploy/html/images/viruses-11-01017-g001.png?1574991076

Paramyxoviridae

Measles

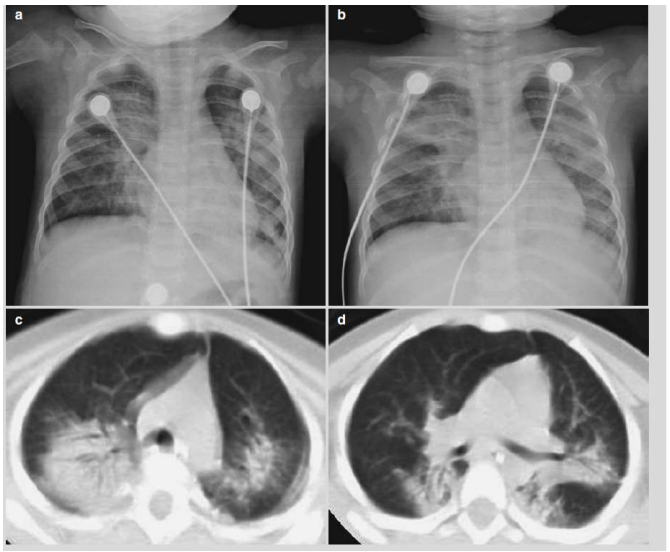
Headache, cough, myalgia…

Complications

- About 1 / 10 children gets an ear infection
- 1 out of 20 gets pneumonia.
- 1 out of 1,000 gets encephalitis,

- **1-2 out of 1,000 die.**

There is vaccination against measles.



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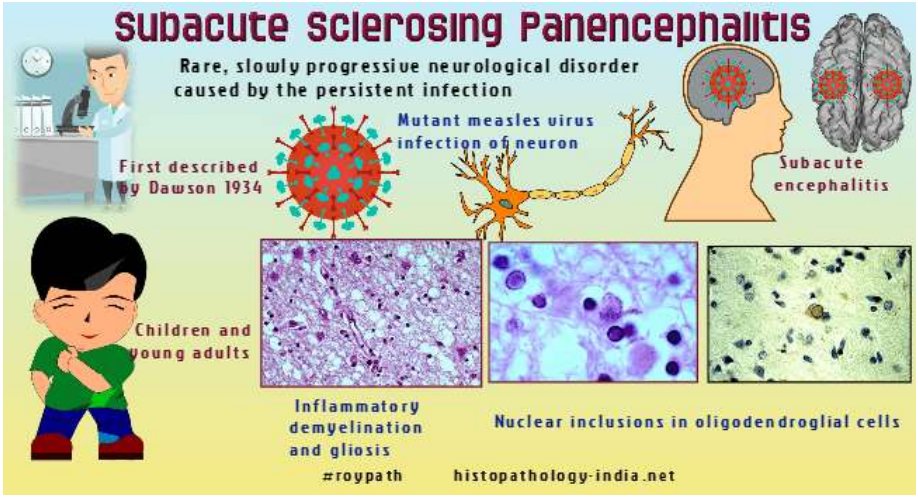
Paramyxoviridae

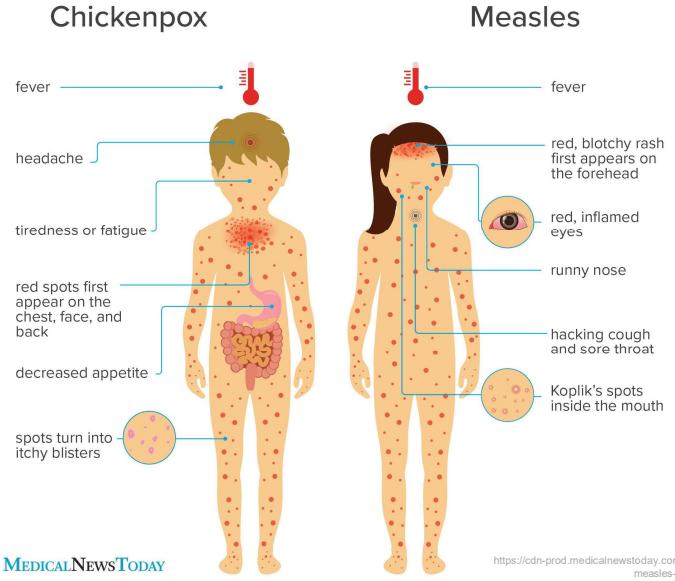
Measles



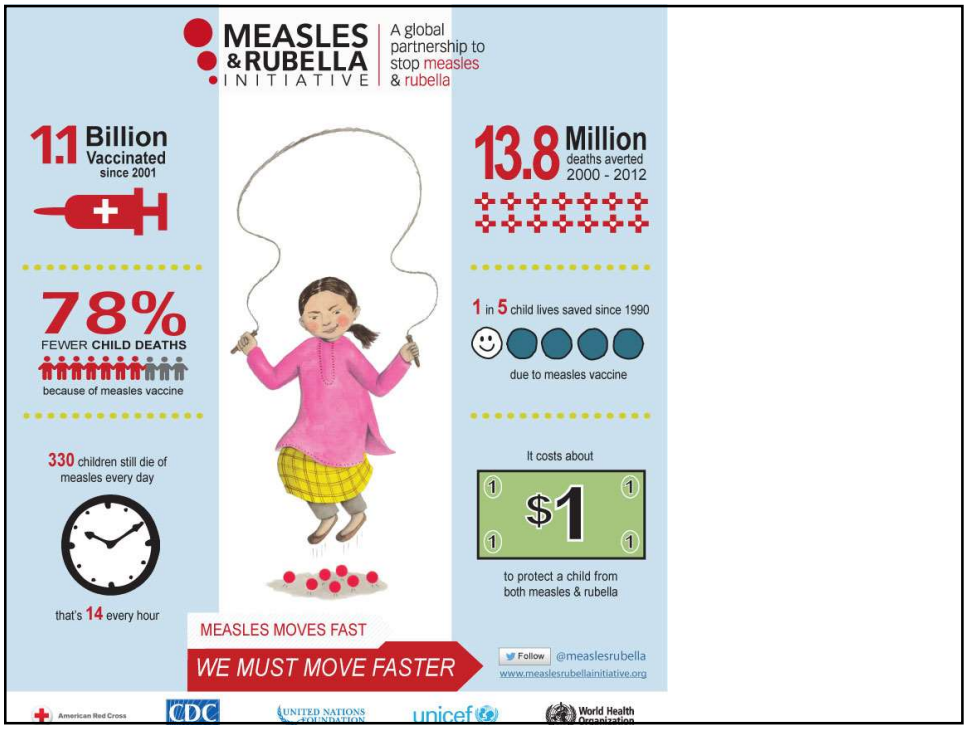
http://www.histopathology-india.net/SSPE.htm

Paramyxoviridae

Chickenpox vs. Measles

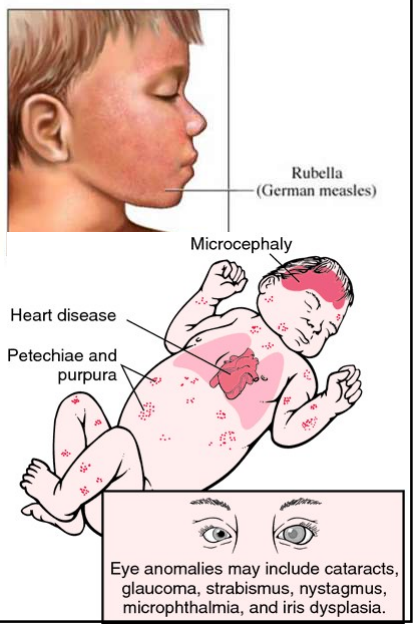


https://cdn-prod.medicalnewstoday.com/content/images/articles/322/322637/chickenpox-vs-measles-infographic-br-image-credit-stephen-kelly-2018-br.jpg



Togaviridae

Rubella - German measles



- Rubivirus (RNA)
- incubation period avr. 18 days (12-23)
- viraemia 5th-7th day after exposition with subsequent speading to the organs

Togaviridae

Rubella - German measles

The infection is usually mild with fever and rash. In pregnancy the virus can cause serious birth defects.

Symptoms:

In 25-50% of rubella cases the disease is usually so mild there may be few or no signs or symptoms.

In typical cases the incubation period is between 12-23 days, most people show symptoms within 16-18 days after exposure.

Common symptoms include: Slight fever, sore throat, runny nose and malaise (may occur prior to appearance of rash, more so in adults than in children).

Tender or swollen glands almost always accompany rubella, most commonly behind the ears (retroauricular) and at the back of the neck (occipital and posterior cervical lymph nodes). Lymphadenopathy may occur in patients with rubella that do not have a rash.

Mucosal involvement results in the Forchheimer sign, in which pinpoint or larger petechiae are noted on the soft palate and uvula during the prodromal period of rubella.

Rash begins on the face that spreads to the neck, trunk and extremities.

Appear as pink or light red spots about 2–3 mm in size. Lasts up to 5 days (average is 3 days). May or may not be itchy.

As rash passes, affected skin may shed in flakes. Usually not as widespread as in MeV.

Other symptoms include pain and swelling in joints (arthralgia and arthritis). This is more common in adults, particularly women, and may persist longer than 2 weeks. The arthritis may become chronic and persist for months or years.

Togaviridae

Rubella - German measles

https://dermnetnz.org/topics/rubella

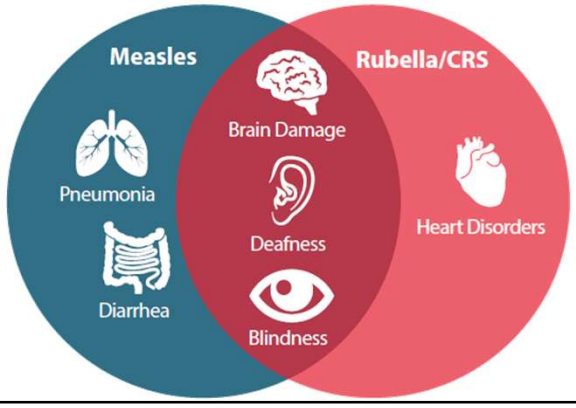
Togaviridae

Rubella - German measles

About ½ of the people do not have symptoms.

In rare cases, serious problems can occur. These include brain infections and bleeding problems.

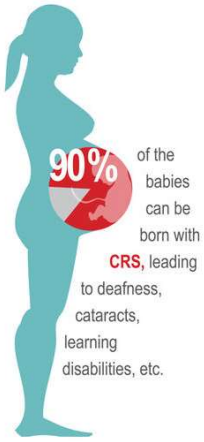
Spreading: through coughs or sneezes; most contagious when the person has a rash. But it can spread up to 7 days before the rash appears. People without symptoms can still spread rubella.



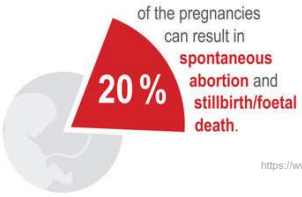
https://www.cdc.gov/globalhealth/measles/about/index.html

Rubella

Rubella and pregnancy

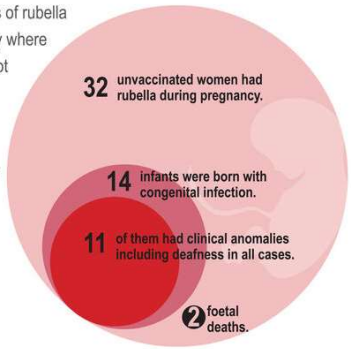


90% of the babies can be born with **CRS**, leading to deafness, cataracts, learning disabilities, etc.



20 % of the pregnancies can result in **spontaneous abortion** and **stillbirth/foetal death**.

Consequences of rubella in a community where people were not vaccinated (example from the Netherlands in 2004/2005).



32 unvaccinated women had rubella during pregnancy.

14 infants were born with congenital infection.

11 of them had clinical anomalies including deafness in all cases.

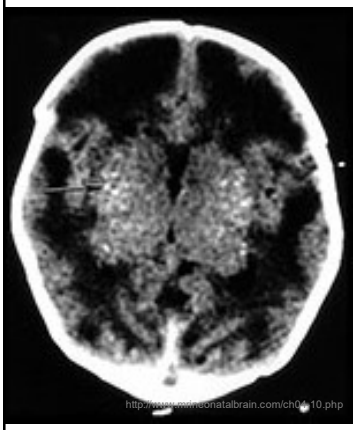
2 foetal deaths.

https://www.ecdc.europa.eu/en/publications-data/infographic-protect-unborn-babies-rubella

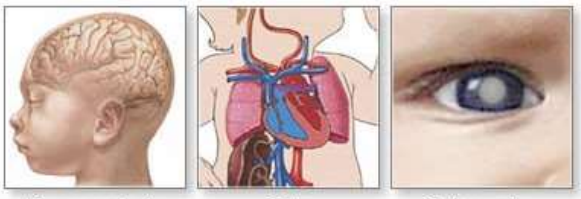
In pregnancy: miscarriage or birth defects like deafness, intellectual disability, and heart defects. 85% of babies born to mothers who had rubella in the first 3 months of her pregnancy will have a birth defect.

Togaviridae

Rubella - German measles



Rubella syndrome



Microcephaly PDA Cataracts

Infection between 8th-10th week of gestation leads to development of congenital rubella syndrome in 90%.

Congenital infections with Venezuelan Equine Encephalitis Virus are symptomatically similar.

Box 1: Clinical features of congenital rubella syndrome

Classic triad

- *Congenital heart disease* (e.g., patent ductus arteriosis, pulmonary artery stenosis, pulmonary valvular stenosis)
- *Ocular defects* (e.g., congenital cataracts, microphthalmos, pigmentary retinopathy, congenital glaucoma)
- *Hearing loss*

Congenital rubella syndrome is usually associated with a failure to thrive and developmental delay as well as microcephaly. Other common presentations at birth include:

- purpuric rash
- hepatosplenomegaly
- meningoencephalitis
- radiolucent bone
- hepatitis
- thrombocytopenia

http://www.cmaj.ca/content/172/13/1678/F1.expansion.html

Togaviridae

Rubella - German measles

Congenital Rubella

Crosses placenta when mother has acute infection.

The earlier the fetus is infected -> more serious disease.

May result in serious congenital abnormalities

- Intrauterine growth retardation
- Hepatosplenomegaly
- Cataracts
- Mental retardation
- Sensorineural hearing loss
- Heart- Patent ductus arteriosis
- Pulmonary stenosis
- Thrombocytopenic purpura

Blueberry Muffin Rash

PDA

Cataracts

Classic triad:

- PDA
- Cataracts, and deafness
- +/- "blueberry muffin" rash

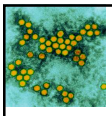
https://pbs.twimg.com/media/ERid_0yWAAAMZ9r.jpg

Rubella and measles

The MMR vaccine protects against rubella.

Details e.g. also in:

http://ecdc.europa.eu/en/publications/Publications/systematic-review-incubation-period-shedding-children.pdf



Picornaviridae

Filatov-Duke‘s disease

Called also *unreal scarlet fever, pseudoscarlatina*, *Filatov-Duke‘s disease*, or *Fourth child‘s disease*.

Caused by coxsackie and echoviruses.

Parvovirus B19

Described in Australia in 1975 by Yvonne Cossart, in microtitration plate „B19“.

Proliferation in erythroid cells of bone marrow (dysregulation of cell cycle through NS1 protein.

Transmission by droplets, mainly. Incubation: 2 weeks (4-28 day) lasting for a week.

Erythema infectiosum („slapped cheek“) – „Fifths disease“.

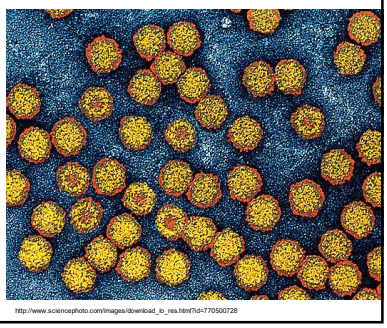
Teenage - "Papular Purpuric Gloves and Socks Syndrome".

Adults – urticas; Pregnant hydrops foetalis

Immunosupressed patients - „pure red cell aplasia“.

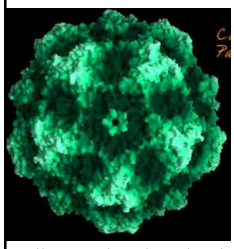
http://snotty-noses.com/illnesses/parvovirus.html

Described possible related complication of B19 infection is myocarditis.



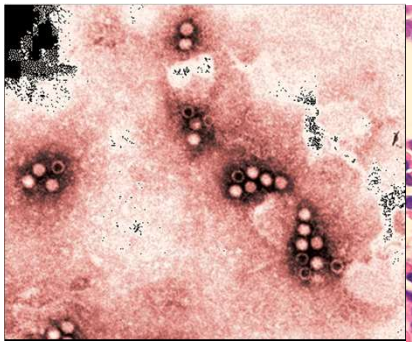
http://www.sciencephoto.com/images/download_lo_res.html?id=770500728

Parvovirus B19

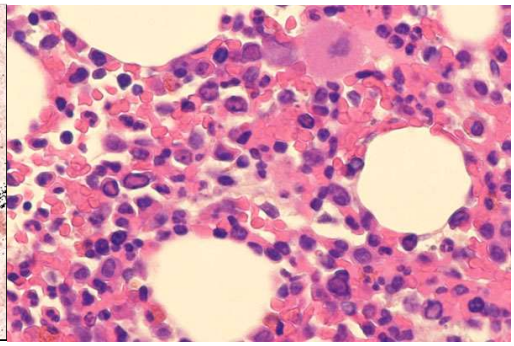


http://fai.unne.edu.ar/biologia/virologia/images/virolo6.jpg

- small ss DNA +/-
- Capsid 20-26 nm, genome: 5 kbp
- E.g. Aplastic anaemia…



http://www.wadsworth.org/databank/hirez/gradyp2.gif

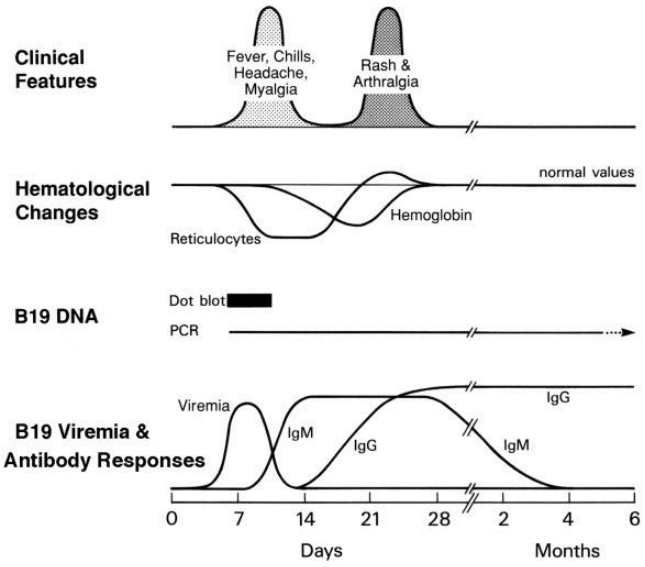


http://www.yamagiku.co.jp/pathology/image/210/1.jpg

Parvovirus B19

https://www.mayoclinic.org/content/dam/media/global/images/2023/04/05/parvovirus-infection-face-rash.jpg

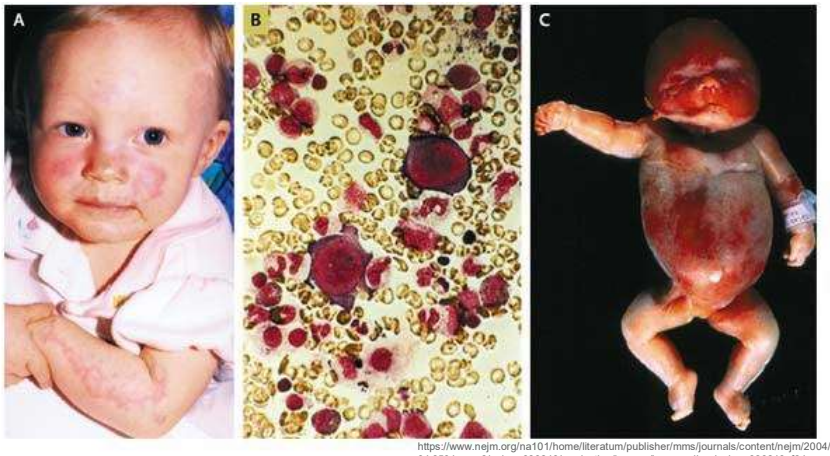
Parvovirus B19



https://web.stanford.edu/group/virus/parvo/2005/B19.html

Almeida/publication/232222814/figure/fig1/AS:601664516026370@1520459407172/Papular-purpuric-exanthem-involving-the-distal-extremities-in-a-gloves-and-socks-pattern.png

https://ars.els-cdn.com/content/image/1-s2.0-S0190962299700277-gr2.jpg



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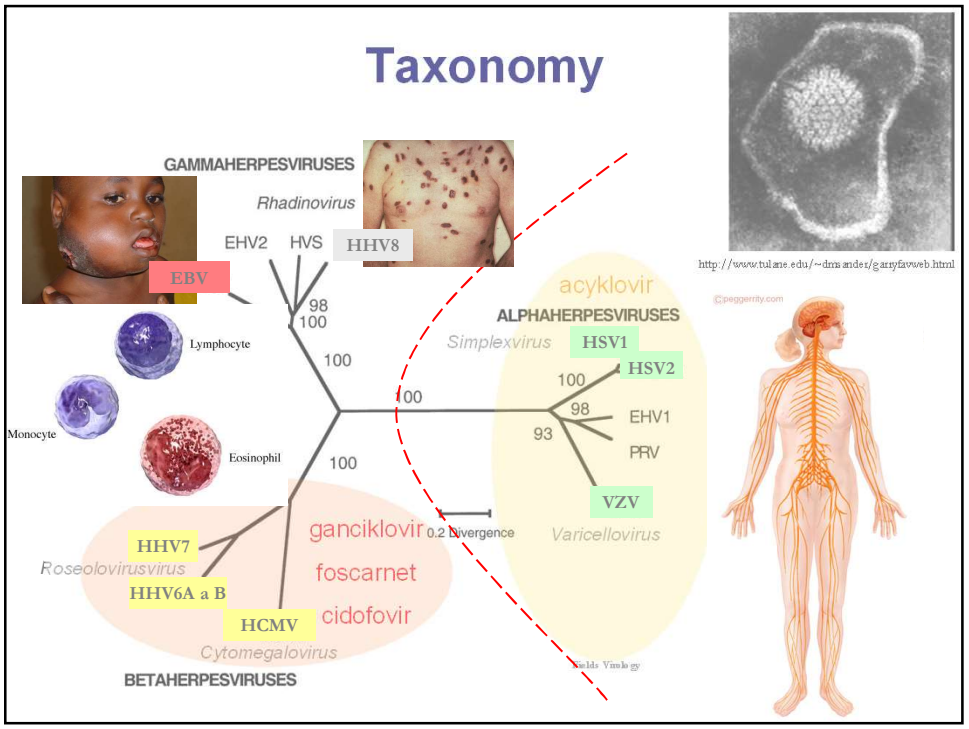
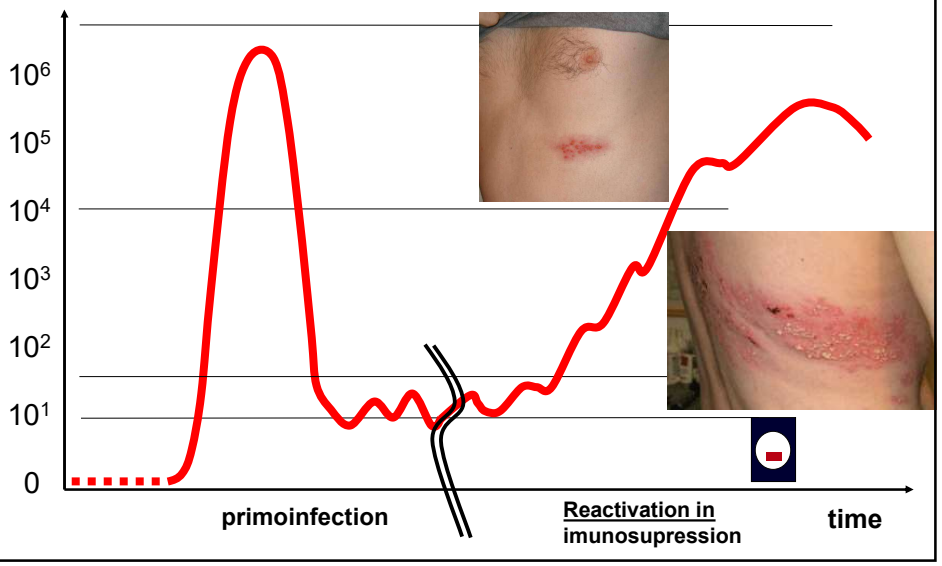
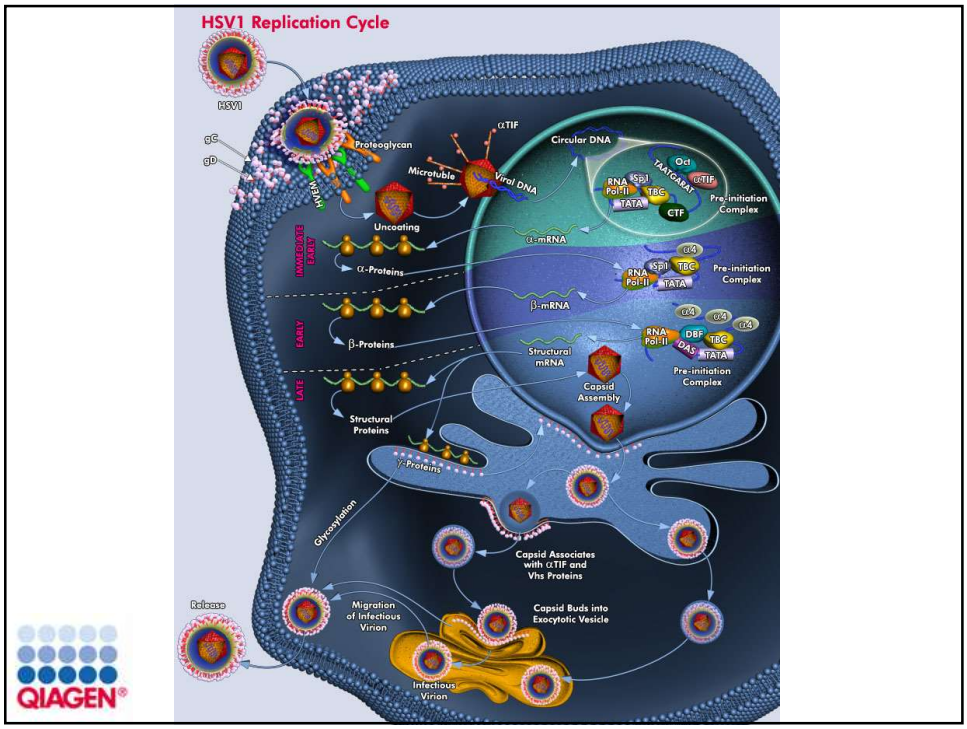
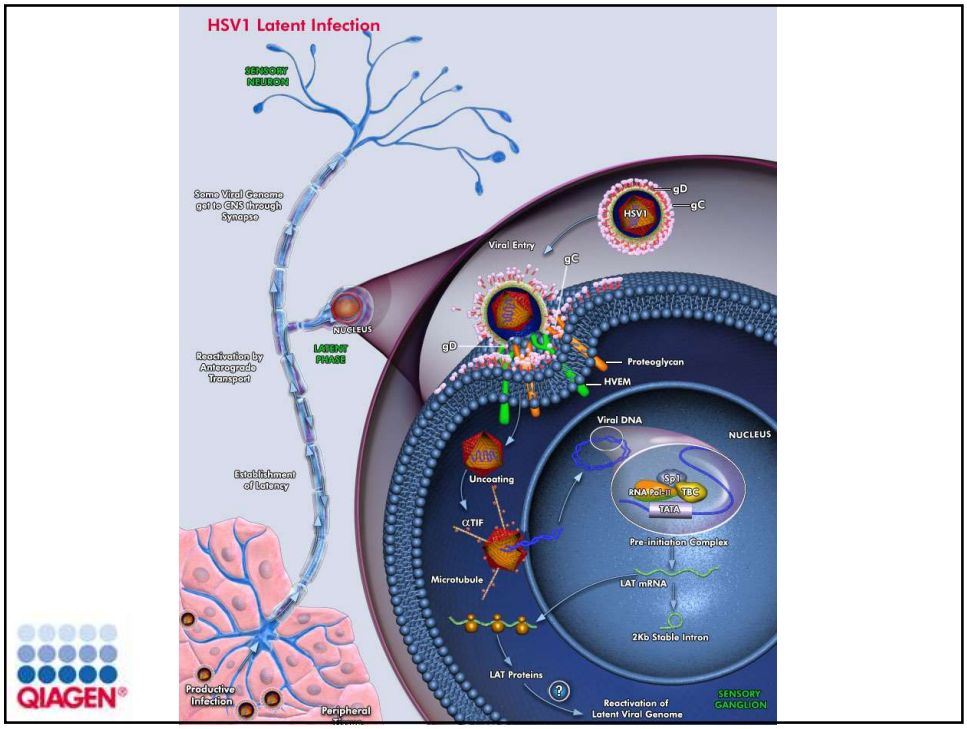


Latency with posibility of reactivation

Transmission – by body fluids (saliva, urine, breast milk, blood, …)




HSV1 Replication Cycle
HSV1
gC
gD
Proteoglycan
HVEM
Microtubule
αTIF
Viral DNA
Circular DNA
Oct
TAATGARAT
αTIF
RNA Pol II
Sp1
TBC
TATA
CTF
Pre-initiation Complex
Uncoating
IMMEDIATE EARLY
α-mRNA
α-Proteins
α4
Sp1
TBC
RNA Pol-II
TATA
Pre-initiation Complex
β-mRNA
EARLY
β-Proteins
α4
α4
α4
RNA Pol-II
DBF
TBC
DAS
TATA
Pre-initiation Complex
Structural mRNA
Capsid Assembly
LATE
Structural Proteins
γ-Proteins
Glycosylation
Capsid Associates with αTIF and Vhs Proteins
Release
Migration of Infectious Virion
Capsid Buds into Exocytotic Vesicle
Infectious Virion
QIAGEN


HSV1 Latent Infection
SENSORY NEURON
Some Viral Genome get to CNS through Synapse
NUCLEUS
LATENT PHASE
Reactivation by Anterograde Transport
Establishment of Latency
Productive Infection
Peripheral
HSV1
gD
gC
Viral Entry
gC
gD
Proteoglycan
HVEM
Viral DNA
NUCLEUS
Uncoating
αTIF
Microtubule
Sp1
RNA Pol II
TBC
TATA
Pre-initiation Complex
LAT mRNA
2Kb Stable Intron
LAT Proteins
?
Reactivation of Latent Viral Genome
SENSORY GANGLION
QIAGEN

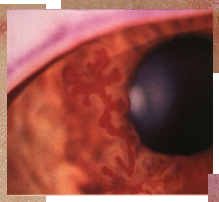
Pathological impact of HSV and VZV

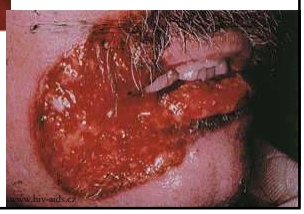
HSV – herpes simplex, benign crbl. ataxia, gingivostomatitis, faryngotonsititis, **encefalitis, pneumonie, hepatitis**

VZV – varicella, herpes zoster, encefalitis, pneumonie, hepatitis

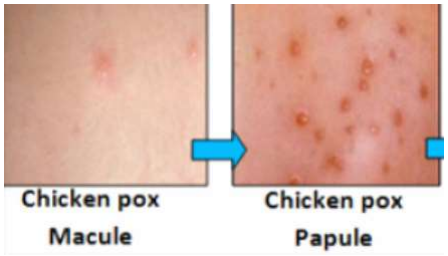
– *In allogeneic HSCT setting less frequently in case of acyclovir prophylaxis; reactiovation of HSV without ACV prophylaxis in 80% of patients*

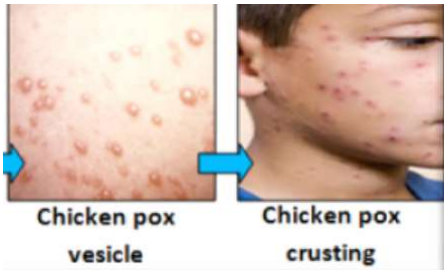
Varicella – chicken pox



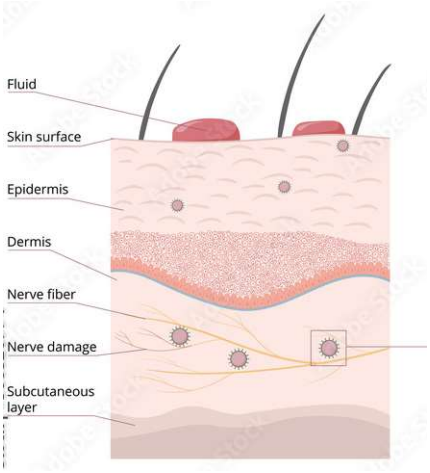


VZV and HSV





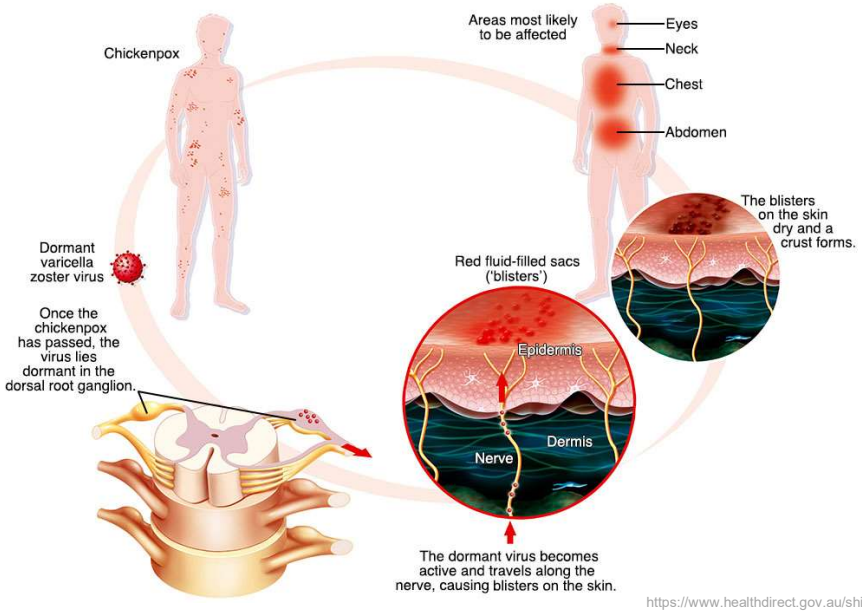
https://lallenkeyanocollege.weebly.com/clinical-manifestations-and-treatment.html



https://as2.ftcdn.net/v2/jpg/05/08/32/09/1000_F_508320994_kOwlpyiLC1tOFQFYLDQhOZD1SPNF1dlj.jpg

https://www.youtube.com/watch?v=JI8OeAh_Q8Y

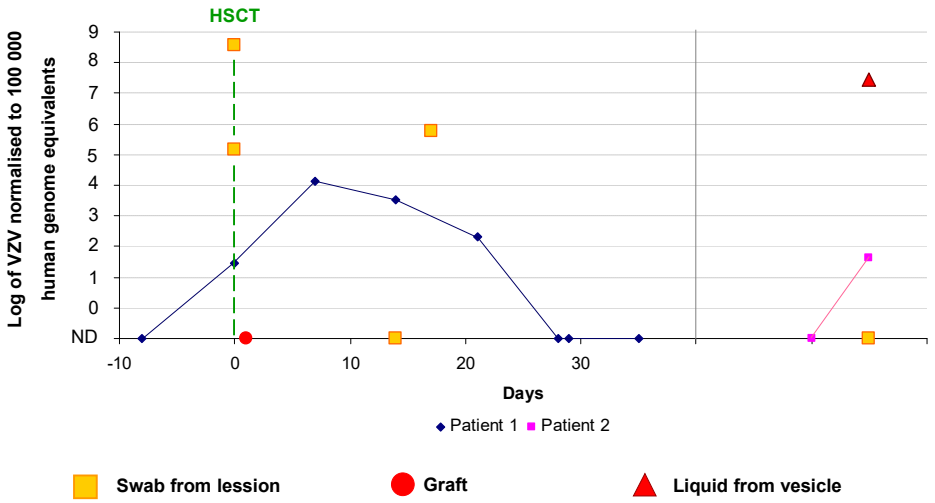
Varicella-Zoster Virus



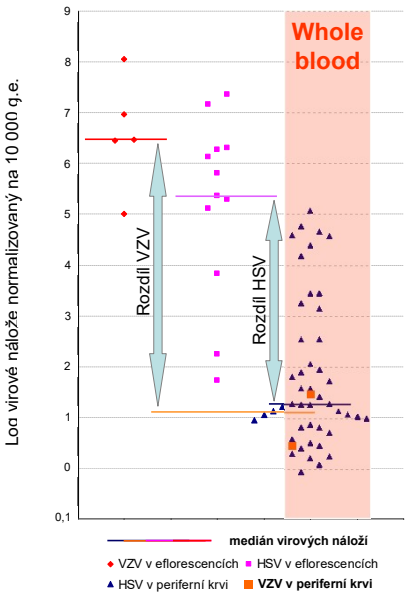
https://www.healthdirect.gov.au/shingles

Difference in materials

VZV – chicken pox at D+0



Source for viral detection



January 2004 to August 2011

- HSV in 735 samples from 266 patients
  VZV in 587 samples from 148 patients
- 569 whole blood samples
- 43 swab samples from skin, mucousal tissue and aspirates from vesicles (from 15 p.)
- 227 samples from other biological materials (stool, urine, CSF, tissues)

HSV detected

- in 12 samples from eflorescence from 9 pts; median of quantity 439,465 NVC
  (range 53-23,380,000 NVC)
- 6 pts in whole blood samples; median of viral load 18.7 NVC
  (range 0.88 – 1,216,650 NVC)
- 4 in stool with median 53,662 NVC
  (range 1,248-900,000 NVC)

VZV detected

- in 8 samples from skin eruption from 5 pts; median of quantity 2,856,124 NVC
  (range 13,939-114,464,380 NVC)
- in 2 pts. In whole blood (quantity 30 and 2.9 NVC)

Human herpesvirus 6

Previously two variants of HHV-6.
Recently 2 distinct viral species

HHV-6 A

Unknown

„Orphan virus“

HHV-6 B

Immunocompetent host

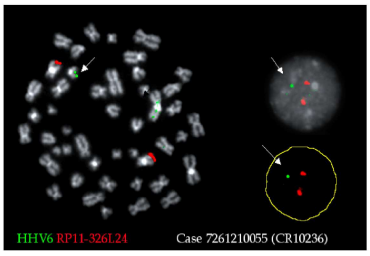
- **Sixth disease**
- **Febrile seizures**
- **Encephalitis**

Immunocompromised host

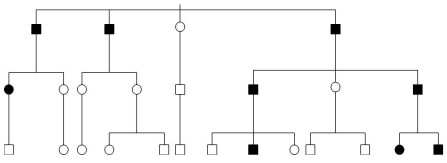
- **Encephalitis**
- **Myelosupression**
- Hepatitis
- Pneumonitis
- Pericarditis
- **Delayed engraftment after HSCT**

Chromosomally integrated HHV-6 (CI-HHV-6)

- **Viral DNA integrated into human chromosomes**
  - **Inherited from parents to child**
  - **Viral DNA is present in every body cell** (e.g.hair roots, nails)
  - **Ratio of viral DNA : human DNA = 1:1**
- **Described frequency in population between 0.2-2.9%** (Tanaka-Taya 2004, Ward 2007)
- **Both variants (A or B) integrates**
- **No clear observed reactivation CI-HHV-6 to active infection in vivo**
- **In vitro reactivations are doubtful**

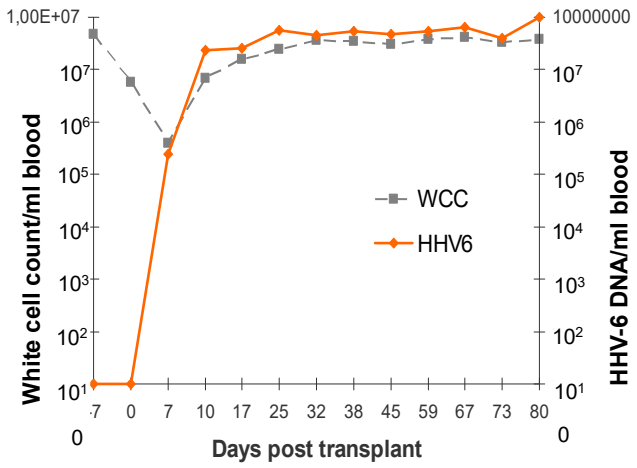


HHV-6 integration at 22q13.3 control probe on 9q34.4



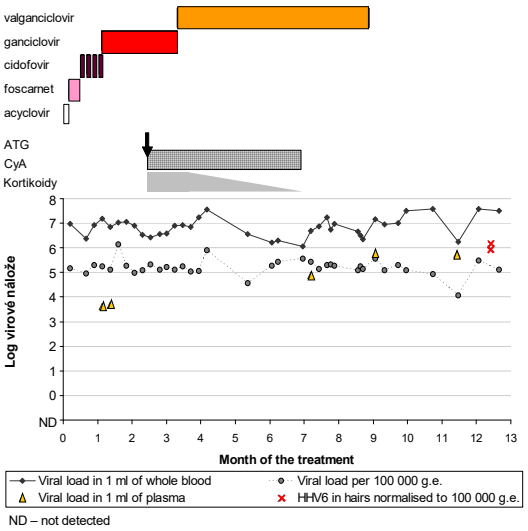
HHV6 DNA in blood after HSCT

donor with Ci-HHV-6



Clark et al., JID 2006

Chromosomally integrated HHV-6 (Ci-HHV-6)



ND – not detected

Patient with SAA

50 years

After start of the IS therapy– partial response only

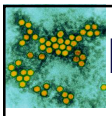
Dependent of thrombocyte infusion

G-CSF therapy

Died due to peracute sepsis of *St. aureus*.

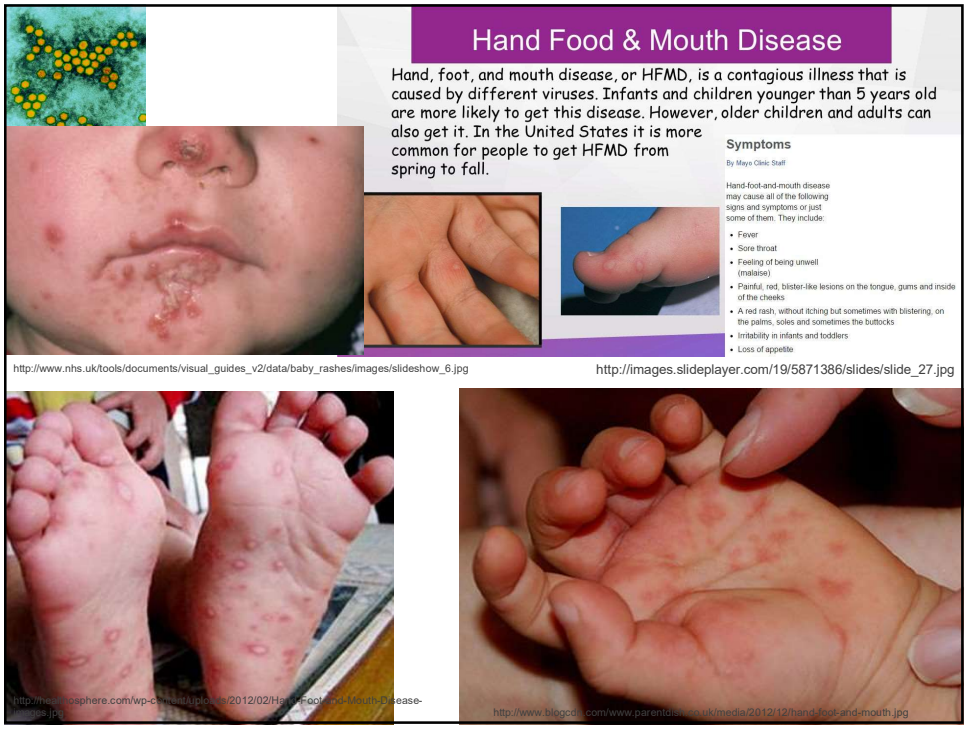
Detection of high HHV-6 DNA quantity is NOT NECESSARY an active infection.

Detection in hair, or nails detects Ci-HHV-6 safely.



Picornaviridae - Coxackieviruses

- Previously, there were Human coxsakievirus A1 to A24 and B1 to B6 – recently there are part of Enterovirus A, Enterovirus B and Enterovirus C group.
- Coxsackie virus is named after the town Coxsackie (NY, USA), where it was discovered by Gilbert Dalldorf (1948-1949).
- ss (+) RNA virus, délka genomu 7,2-8,5 kb
- Coxackie A – muscle necrosis and paralysis, conjunctivitis
- Coxackie B – less severe damage of the organs (susp. T1DM)
  - Both are able to cause menigitis, myocarditis and pericarditis
- Coxsackie A serotype 16 is cause of Hand, Foot and Mouth disease
- Encephalitida/myeloencephalitida



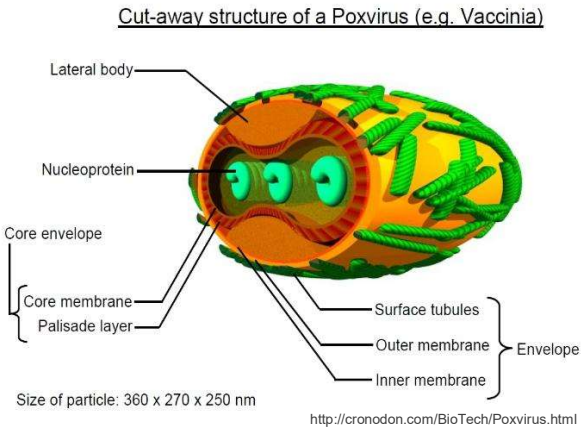
Hand Food & Mouth Disease

http://healthosphere.com/wp-content/uploads/2012/02/Hand-Foot-and-Mouth-Disease1.jpg

And now what?

Poxviry

- Complex structure
  (symetria)
- Enveloped but resistant to inactivation
- linear ds DNA
- Genome 130–375 kb coding approx. 250 genes
  (>100 polypeptides-often immunogenic)
- Replication in cytoplasma
- Highly species specific
- Used for genome vector constructions
- Human pathology is associated with 4 genera:
  - Orthopoxvirus
  - Parapoxvirus
  - Yatapoxvirus
  - Molluscipoxvirus



http://cronodon.com/BioTech/Poxvirus.html

Orthopoxvirus

- Variola virus
  - Variola major (mortality 20%), variola minor (mortality 1-2%)
  - Eradicated (last diagnosed in 1977)
  - All eruptions in same status of development
  - Primary replication in air-ways
- Vaccinia virus (used for vaccination and eradication of variola)
- Cow pox virus
  (first vaccination against variola – Edward Jenner – 1796)

http://www.smithsonianmag.com/ist/?next=/smart-news/queen-elizabeth-1-loved-live-

http://www.wikihealth.com/wp-content/uploads/2014/07/rsz_smallpox.jpg

Parapoxvirus

- Zoonosis
- Human infections causes
  - Bovine papular stomatitis virus
  - Orf virus
  - Pseudocowpox virus
- Aftous eruptions on mucous and/or skin
  Clinically called
  -“farmyard pox“

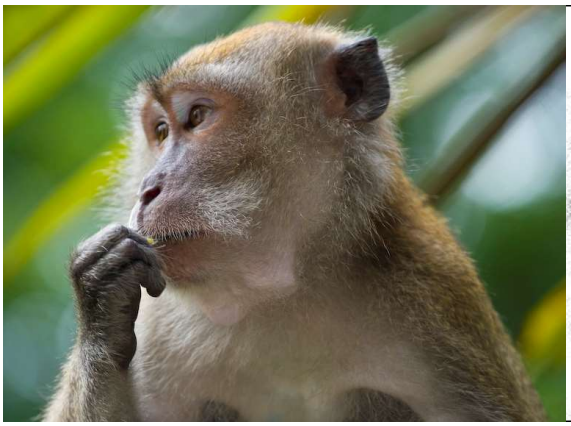
Orf (Ecthyma contagiosum)

- **C/P:**
  - Typically presents as a papule/nodule on the dorsal index finger.
  - ***Progression through several stages:***
    - maculopapular
    - targetoid
    - weeping nodule
    - regenerative dry stage with black dots
    - papillomatosis
    - regression with a dry crust
  - ***Other Findings;*** Ascending *lymphangitis*, *lymphadenopathy*, *malaise*, and *fever* may occur.
  - Bacterial superinfection may occur.
  - Erythema multiforme occasionally occurs 10 to 14 ds. later

http://www.slideshare.net/HimaFarag/viral-diseases-of-the-skin-other

Yatapoxvirus

- Yaba monkey pox virus
  - Oncogenic virus – histiocytomas (tumour from macrophages) in humans and monkeys (e.g. *Macaca fascicularis*)
  - Presence by the river Niger

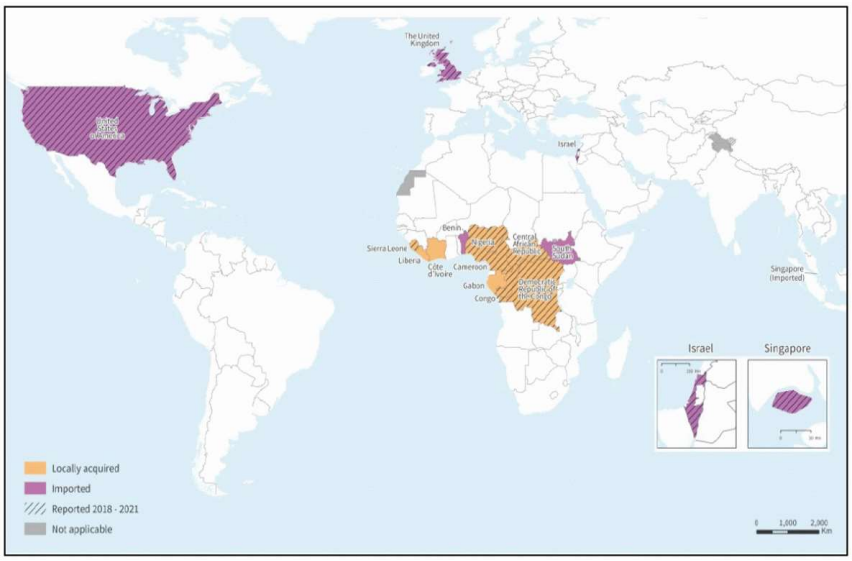


https://upload.wikimedia.org/wikipedia/commons/9/9f/Macaca_fascicularis.jpg

https://en.wikipedia.org/wiki/Monkeypox_virus#/media/File:Monkeypox.gif

Yatapoxvirus

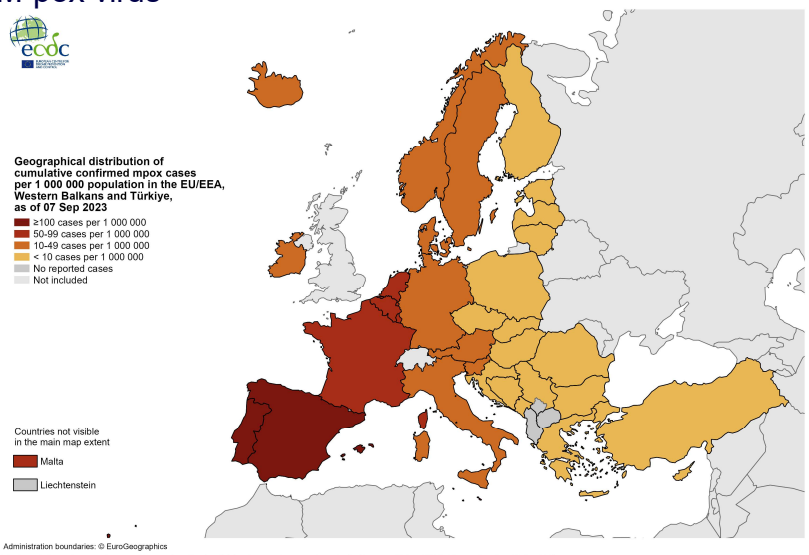
- M-pox virus



https://www.cdc.gov/mmwr/volumes/72/wr/mm7203a4.htm?s_cid=mm7203a4_w#F1_down

Yatapoxvirus

- M-pox virus



https://monkeypoxreport.ecdc.europa.eu/

Molluscipoxvirus

- Molluscum contagiosum
  - Viral infection of skin, rarely mucous membranes
  - Charakteristic skin lessions
  - Infection of human, primate and kangaroos
- 4 types
- Often STD (MCV 1,2)
- Incubation period – up to months

http://www.dermapics.com/molluscum%20contagiosum.html

http://www.molluscumrx.com/molluscum-contagiosum-pictures/