

Exanthematic viruses



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Viral exanthematic diseases

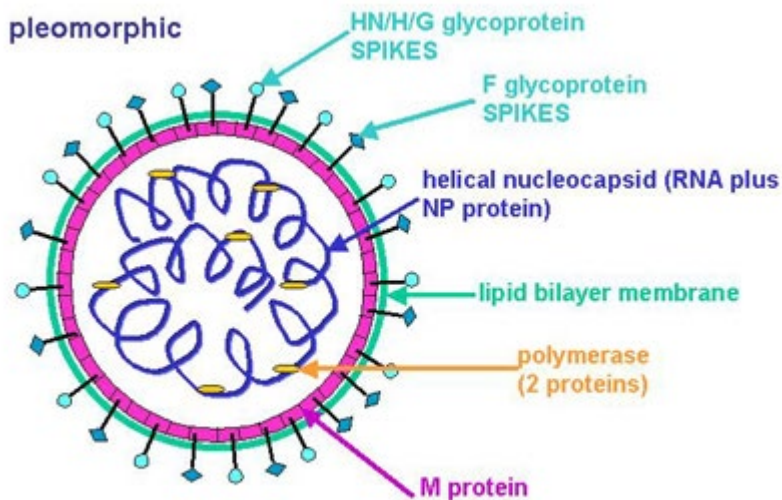
Childhood exanthema diseases

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

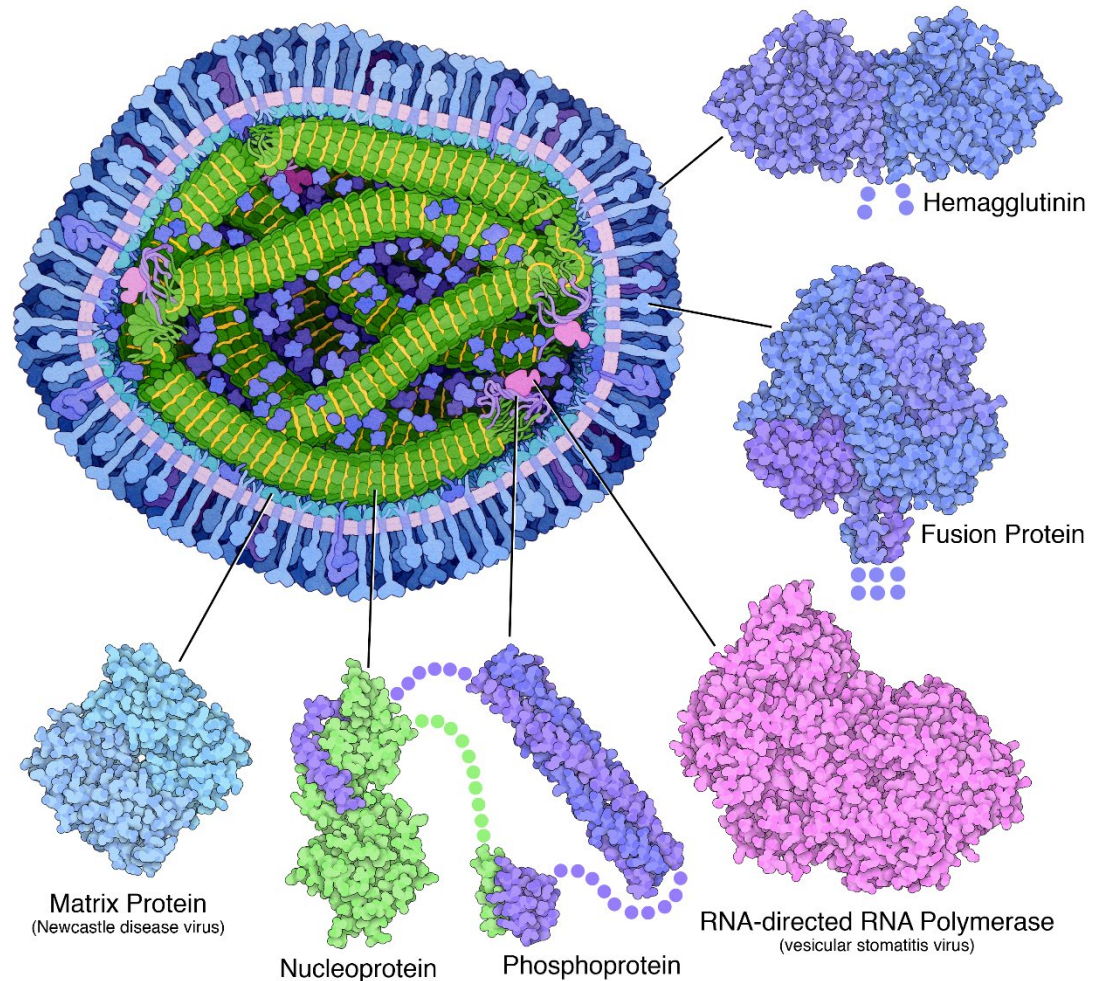


- ss (-) RNA virus
- genome length 15-16 kb
- coding 8 proteins
- spherical symmetry of capsid and diameter of 100-300 nm

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.



Estimated cases – 20,000,000 / year.

Measles

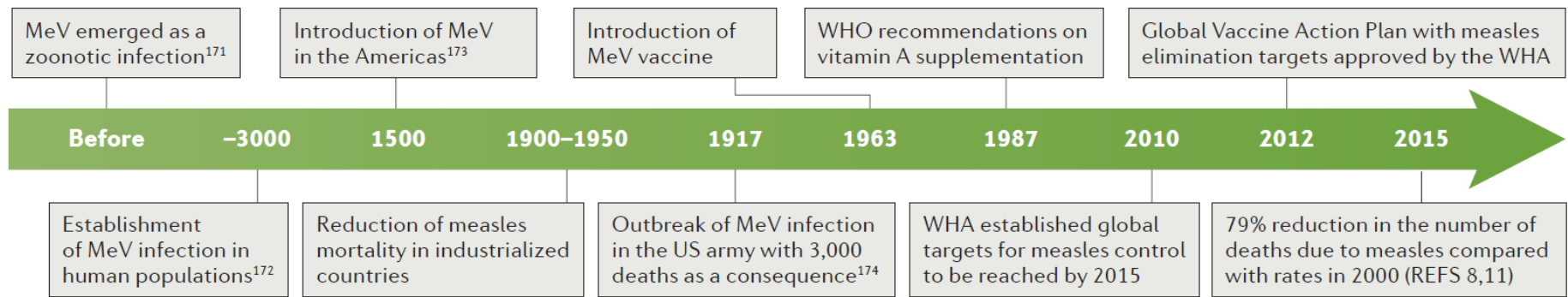


Figure 1 | **History of measles virus infection and elimination programmes.**

Closely related to the recently eradicated cattle virus rinderpest¹⁷⁰, 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 proximity¹⁷¹. 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 transmission¹⁷². 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 Americans¹⁷³. 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 vaccines¹⁷⁴. 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%.

Measles

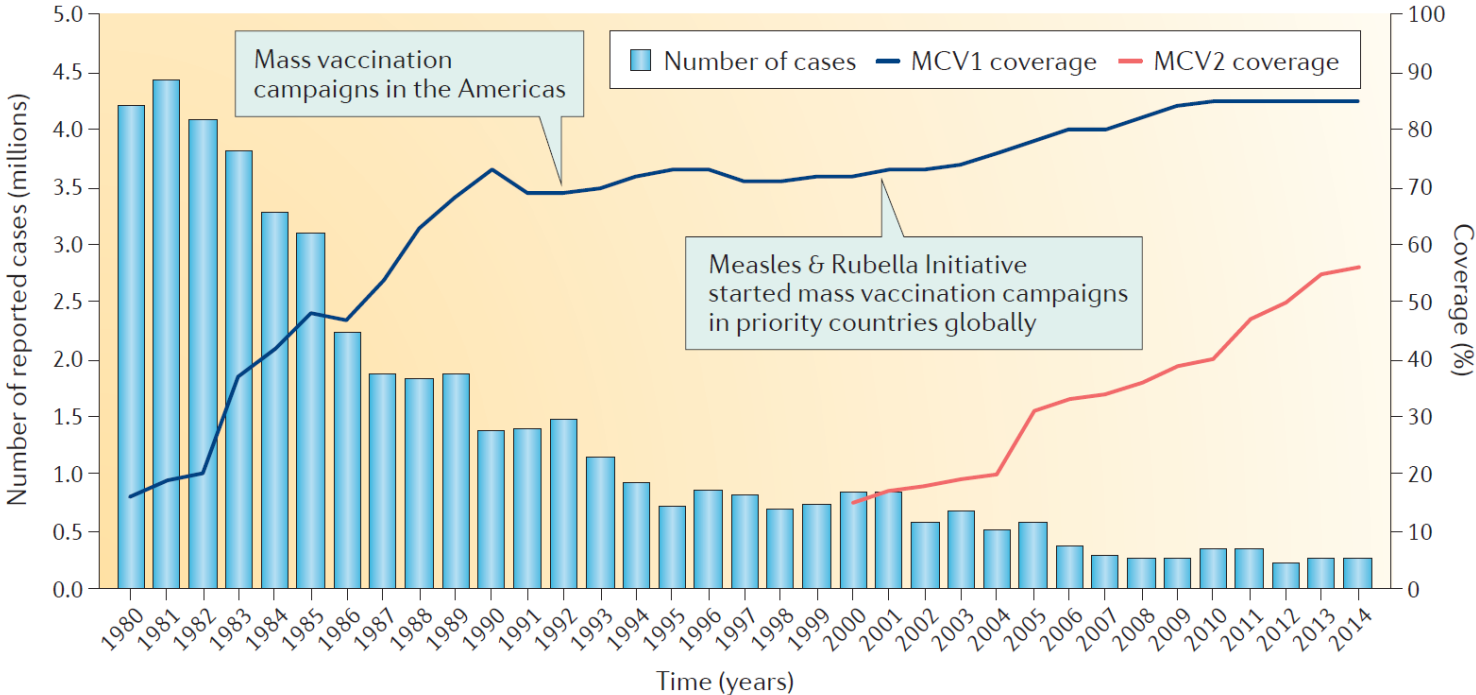


Figure 2 | **Global reported measles cases and estimated coverage with the first and second dose of measles-containing vaccine by year (1980–2014).** MCV, measles-containing vaccine. Figure adapted from data available from the WHO^{175,176}.

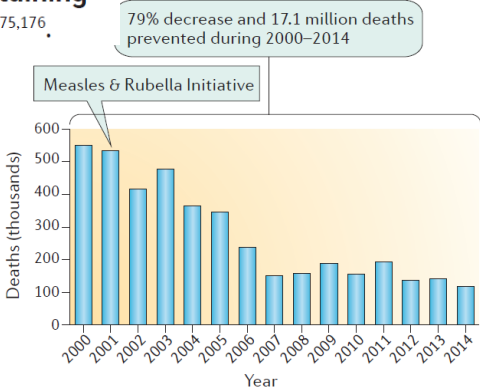


Figure 3 | **The number of estimated measles deaths globally by year (2000–2014).** The Measles & Rubella Initiative was established in 2001; global estimated measles mortality decreased by 79% during 2000–2014, preventing an estimated 17.1 million deaths⁸. Adapted with permission from REF. 7, CDC MMWR.

Measles

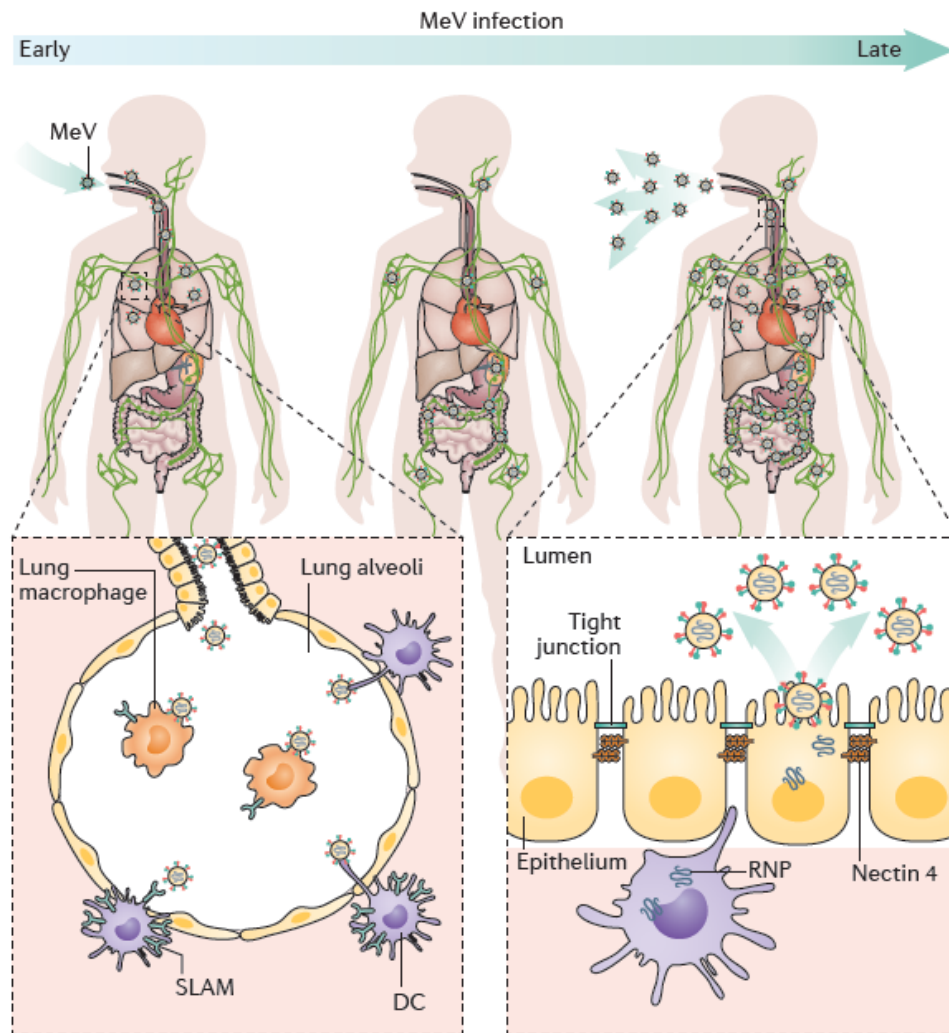


Figure 5 | Measles virus infection and transmission. Measles virus (MeV) is an airborne pathogen. MeV aspirated into the respiratory tract infects alveolar macrophages or dendritic cells (DCs) using signalling lymphocytic activation molecule (SLAM; also known as CD150) as a receptor. MeV infection is 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, macrophages, matured dendritic cell (DCs), Langerhans cells (LCs), lymphocytes and thrombocytes

Nectin 4 (PVRL4) – epithelial 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

Measles

Measles Cases and Outbreaks

January 1 to August 29, 2014*†

592

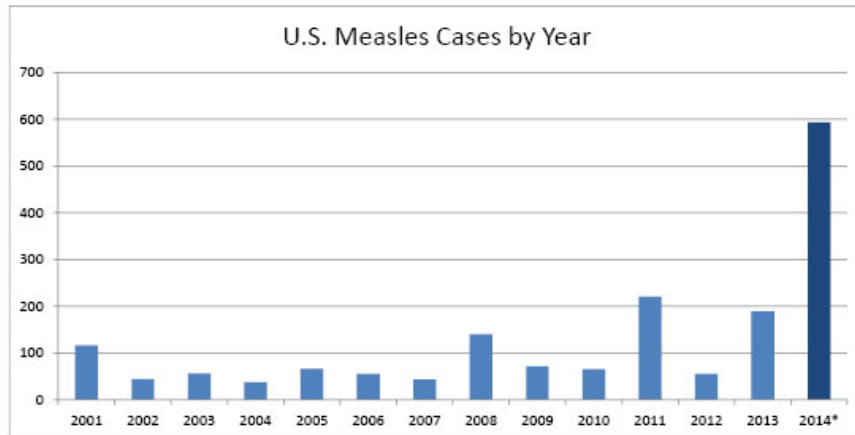
Cases

reported in 21 states: Alabama, California, Connecticut, Hawaii, Illinois, Indiana, Kansas, Massachusetts, Minnesota, Missouri, New Jersey, New York, Ohio, Oregon, Pennsylvania, Tennessee, Texas, Utah, Virginia, Washington, Wisconsin

18

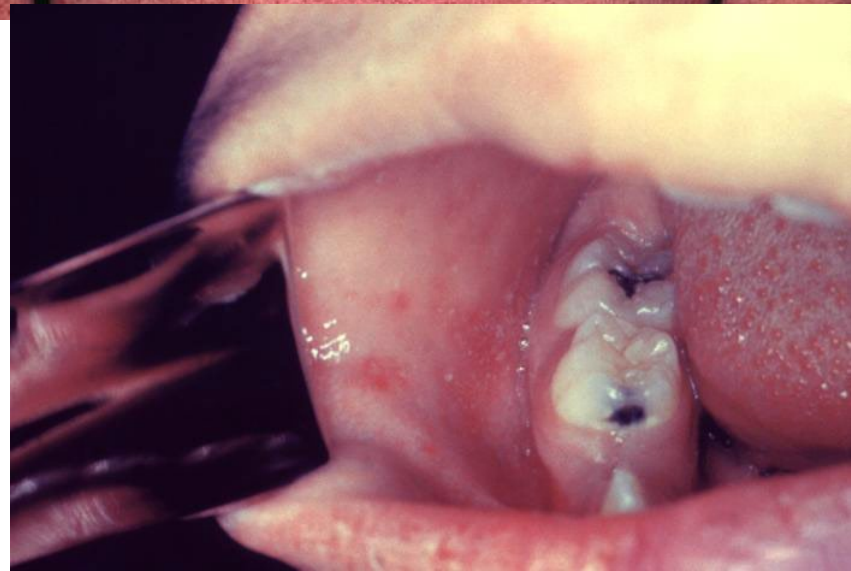
Outbreaks

representing 89% of reported cases this year



*Provisional data reported to CDC's National Center for Immunization and Respiratory Diseases

†Updated once a month



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

Measles

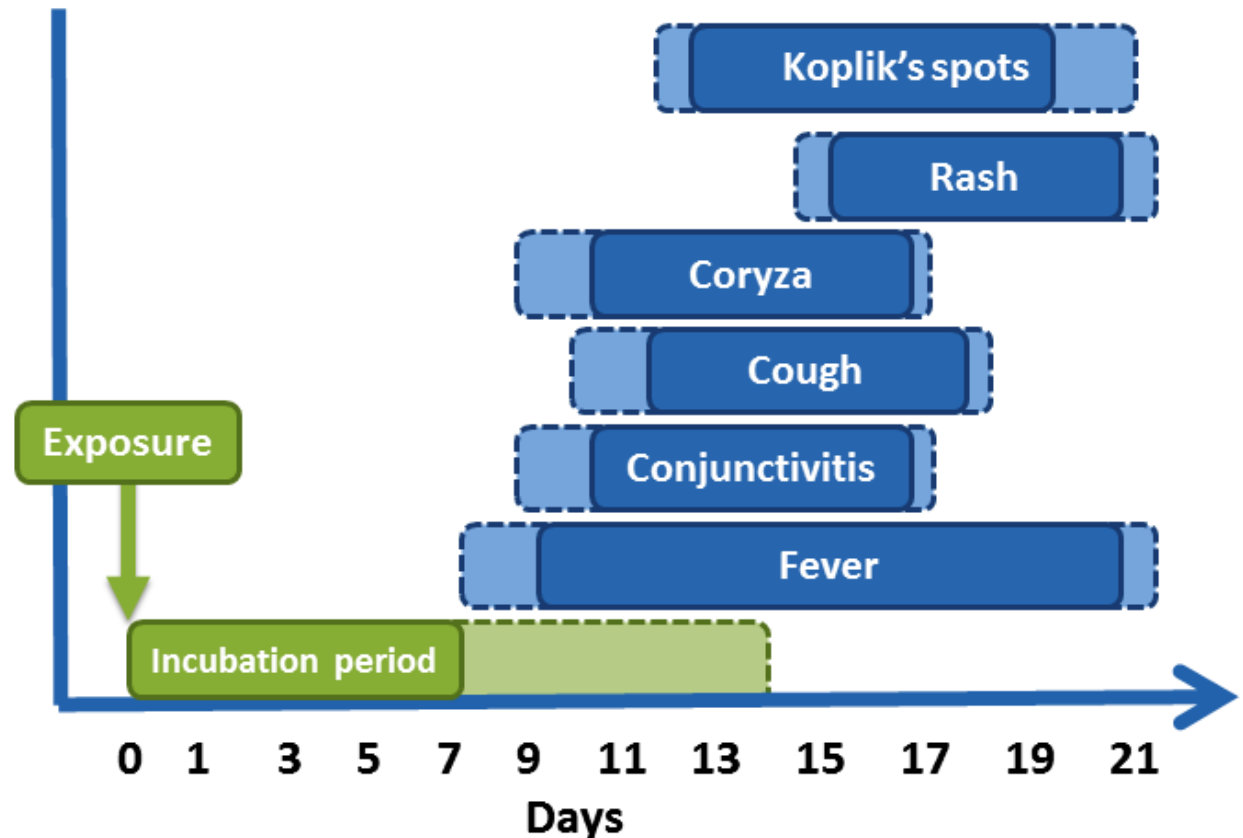


Measles

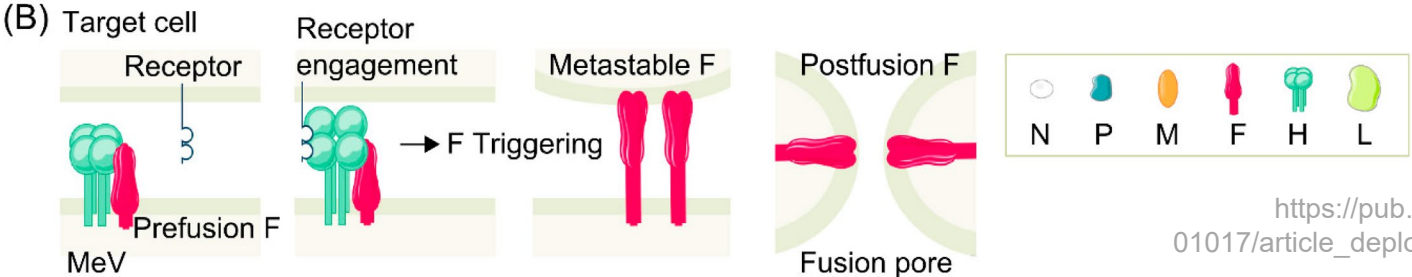
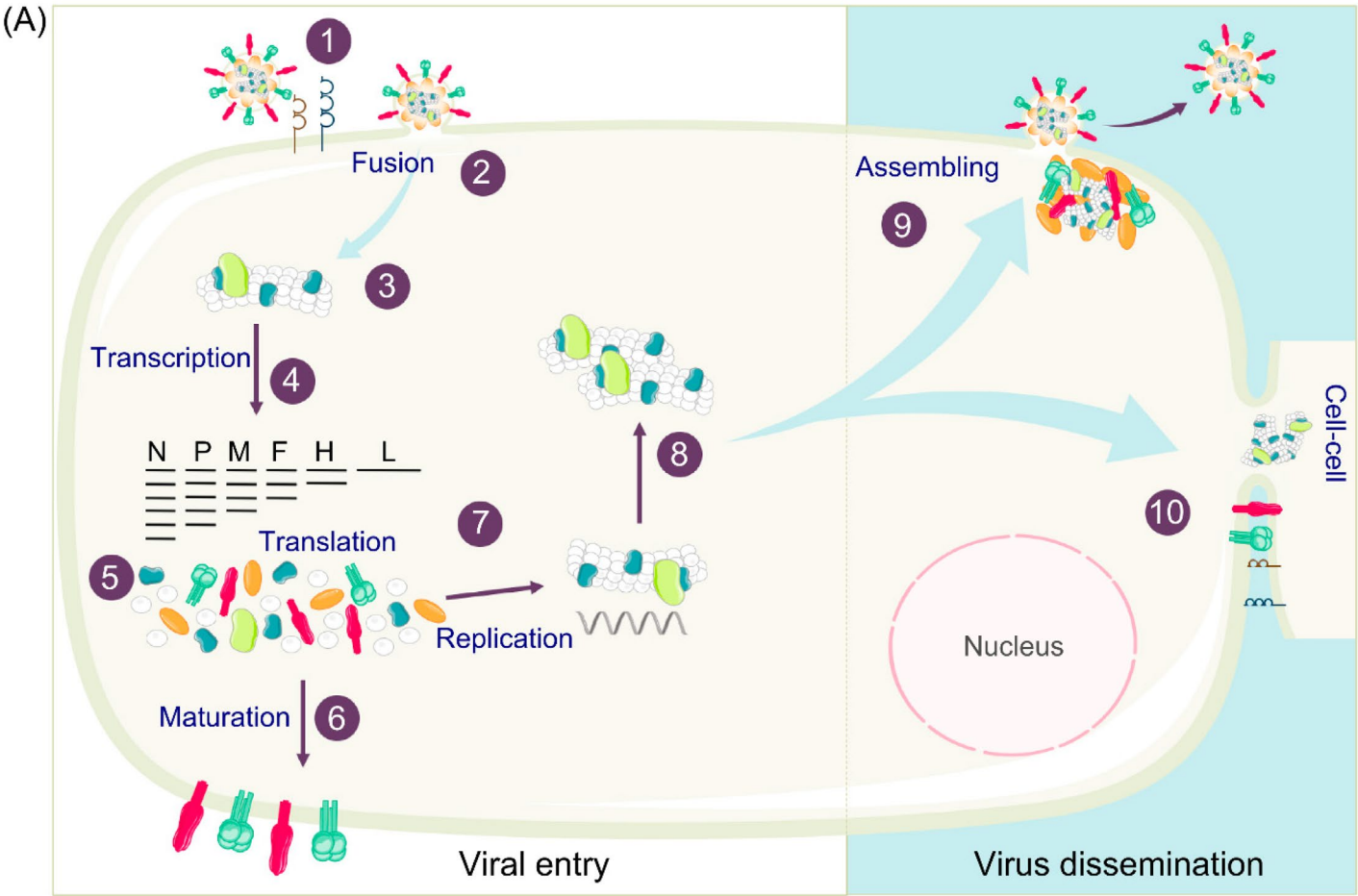
- Droplet spread infection. It is so contagious that any child who is exposed to it and is not immune will probably get the disease.
- Measles virus normally grows in the cells that line the back of the throat and lungs
- incubation period 8-12 days

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.



Measles



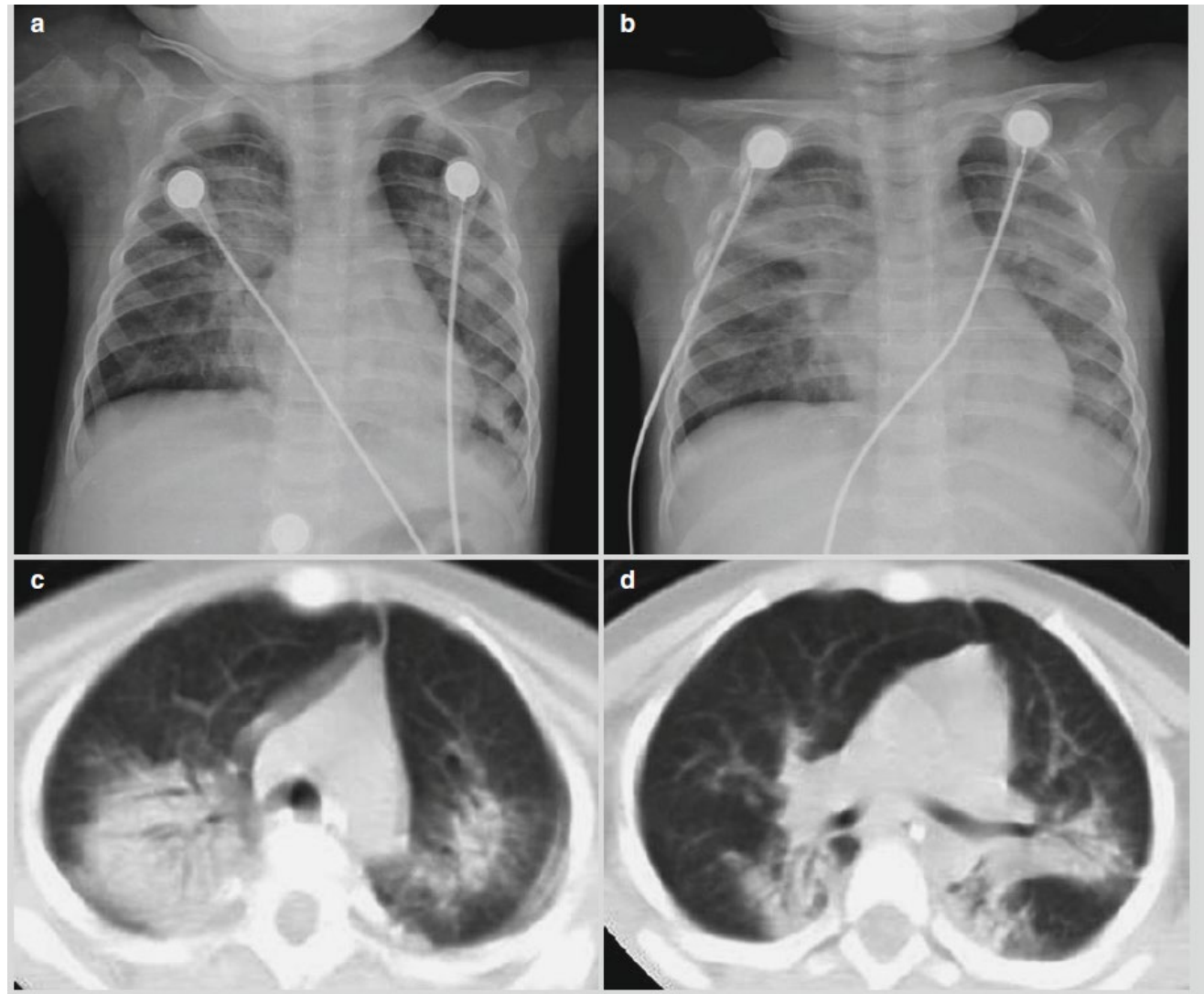
Measles

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.



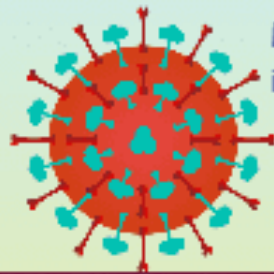
Measles

Subacute Sclerosing Panencephalitis

Rare, slowly progressive neurological disorder caused by the persistent infection



First described by Dawson 1934



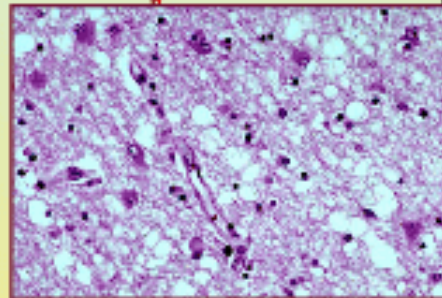
Mutant measles virus infection of neuron



Subacute encephalitis

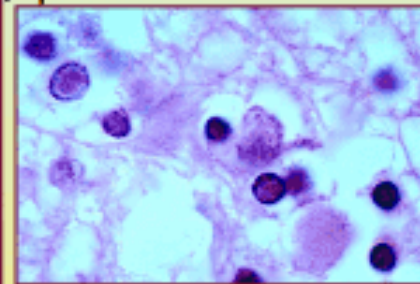


Children and young adults

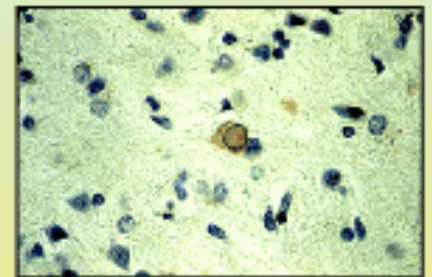


Inflammatory demyelination and gliosis

#roypath



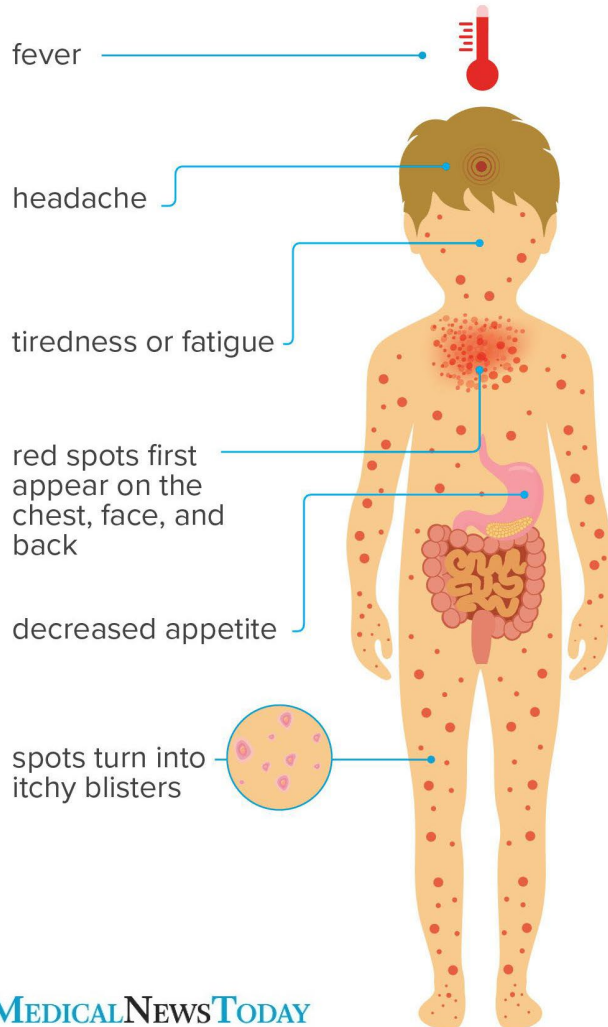
Nuclear inclusions in oligodendroglial cells



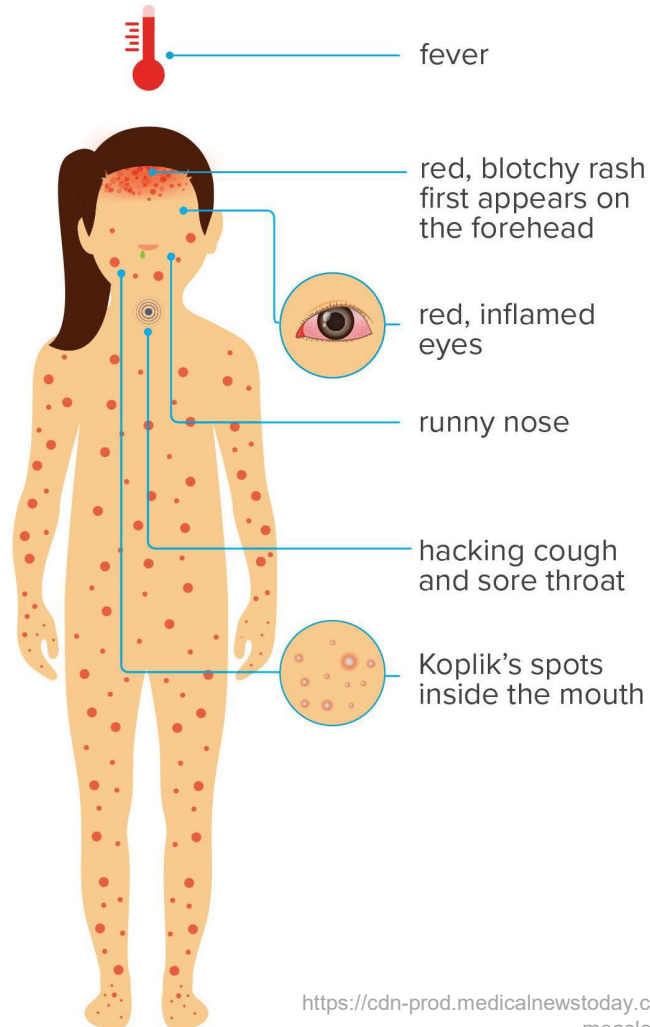
histopathology-india.net

Chickenpox vs. Measles

Chickenpox



Measles



MEASLES & RUBELLA INITIATIVE

A global partnership to stop **measles** & **rubella**

1.1 Billion
Vaccinated
since 2001



78%

FEWER CHILD DEATHS



because of measles vaccine

330 children still die of
measles every day



that's **14** every hour



13.8 Million
deaths averted
2000 - 2012



1 in **5** child lives saved since 1990



due to measles vaccine

It costs about



to protect a child from
both measles & rubella

MEASLES MOVES FAST

WE MUST MOVE FASTER

Follow

@measlesrubella

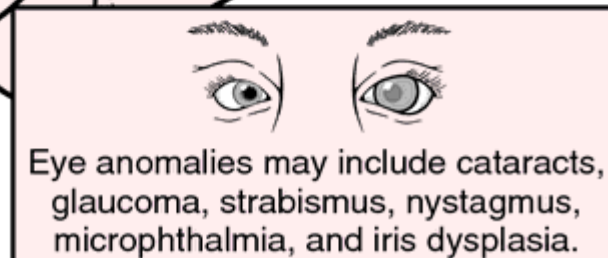
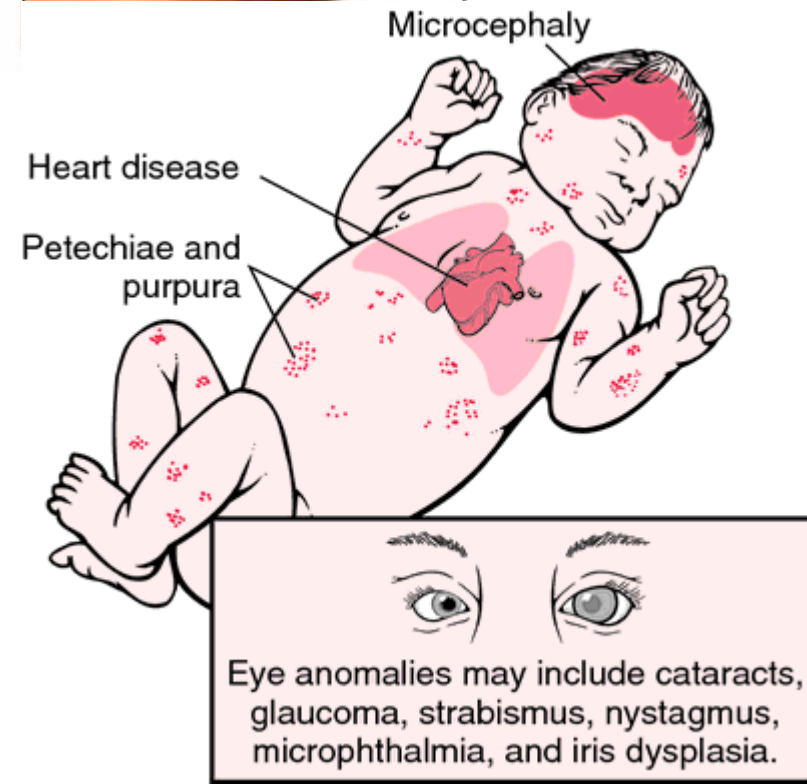
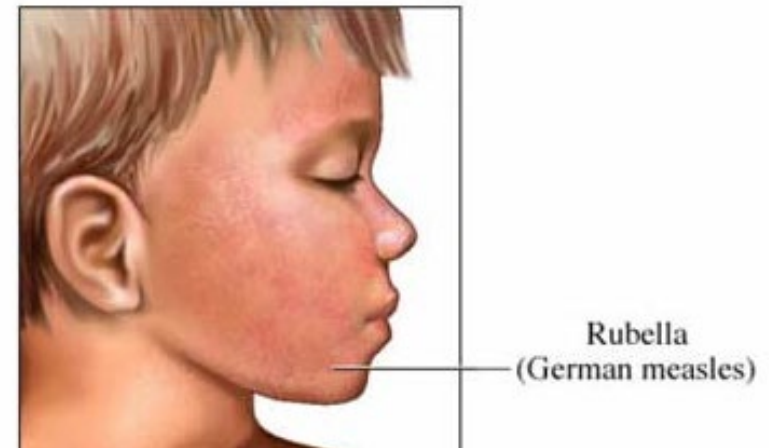
www.measlesrubellainitiative.org

Rubella - German measles

WHAT IS RUBELLA?

- An infection that affects your skin and lymph nodes.
- Can be known as "German measles"
- "The Scarlet Scourge"
- A rash that normally spreads from your face and anything below

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



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.

Rubella - German measles

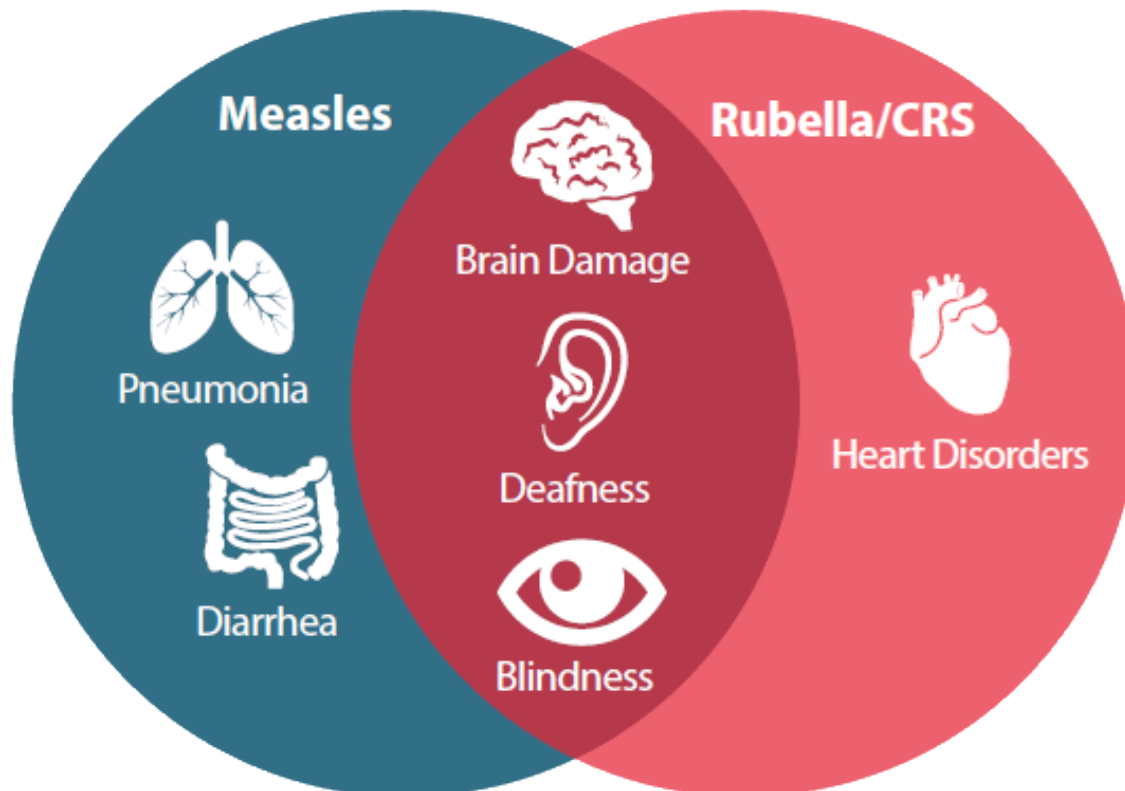


Rubella - German measles

About ½ of the people do not have symptoms.

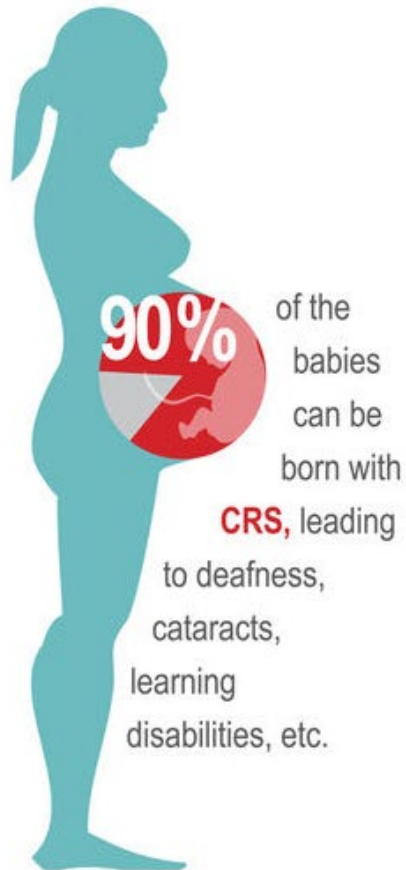
In rare cases, serious problems can occur. These include brain infections and bleeding problems.

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.

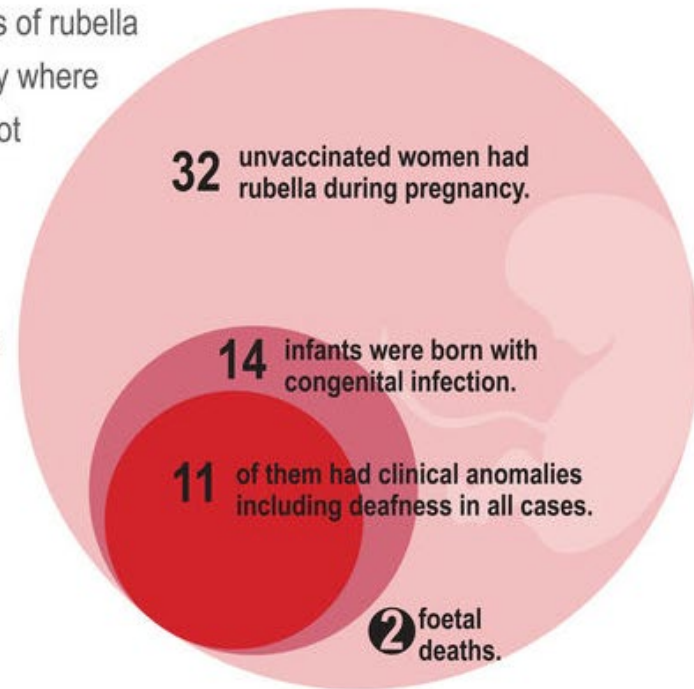


Rubella

Rubella and pregnancy



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



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

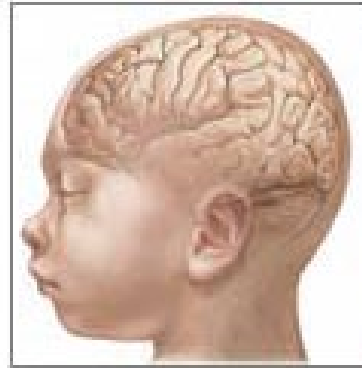
In pregnancy: miscarriage or birth defects like deafness, intellectual disability, and heart defects. 85% of babies born to mothers who had rubella in the first 3 months of her pregnancy will have a birth defect.

Rubella - German measles

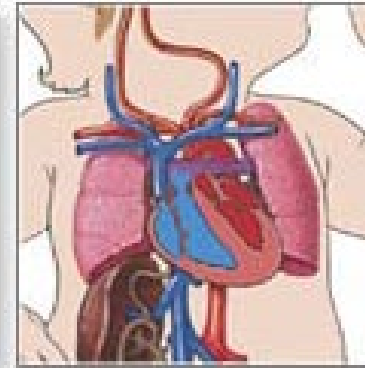
Rubella syndrome



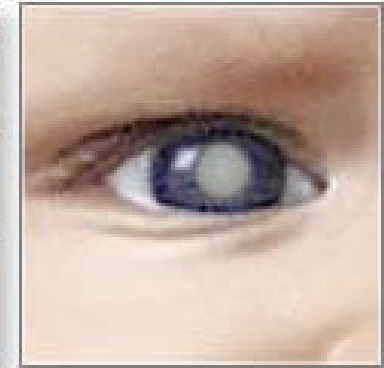
http://www.mriofonatalbrain.com/ch04_10.php



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 arteriosus, 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

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 arteriosus**
- **Pulmonary stenosis**
- **Thrombocytopenic purpura**



Blueberry Muffin Rash



PDA



Cataracts

Classic triad:

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

Rubella and measles



The MMR vaccine protects against rubella.

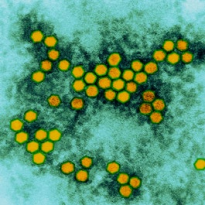
Details e.g. also in:



SCIENTIFIC ADVICE

**Systematic review on the
incubation and infectiousness/
shedding period of communicable
diseases in children**

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

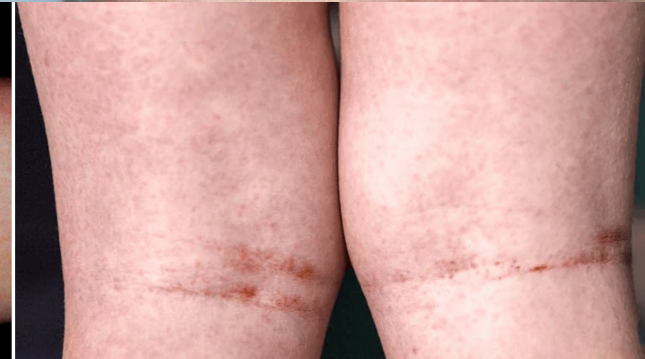


Picornaviridae

Filatov-Duke's disease

Called also
*unreal scarlet
fever*,
*pseudoscarlatin
a*, *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".

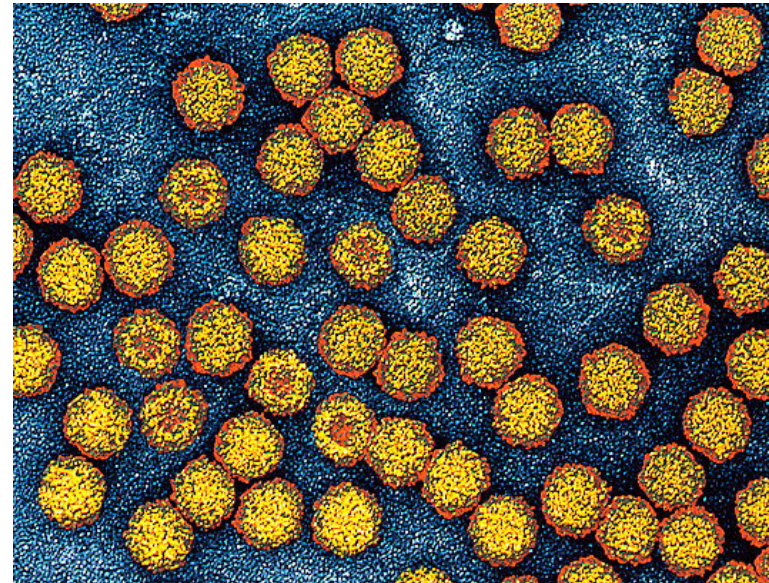
Adults – urticas; Pregnant hydrops foetalis

Immunosupressed patients - „pure red cell aplasia“.



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

Described possible related complication of B19 infection is myocarditis.



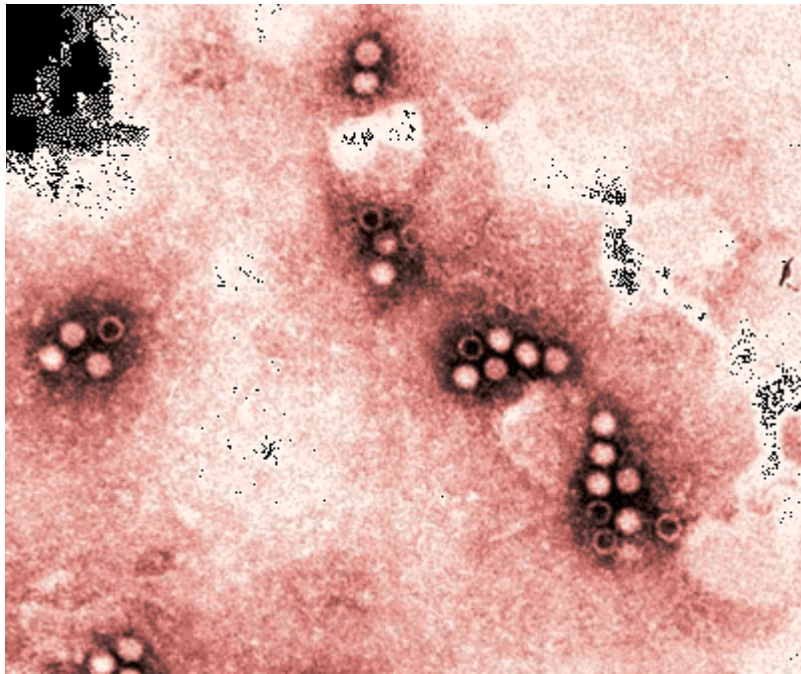
http://www.sciencephoto.com/images/download_lo_res.html?id=770500728

Parvovirus B19

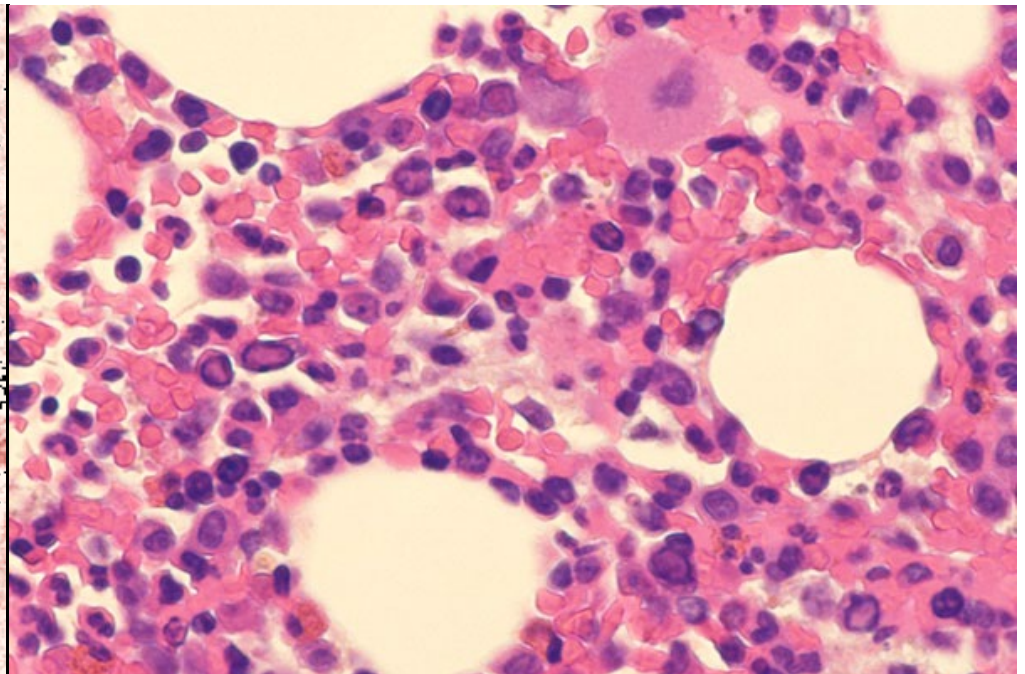
- small ss DNA +/-
- Capsid 20-26 nm, genome: 5 kbp
- E.g. Aplastic anaemia...



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



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

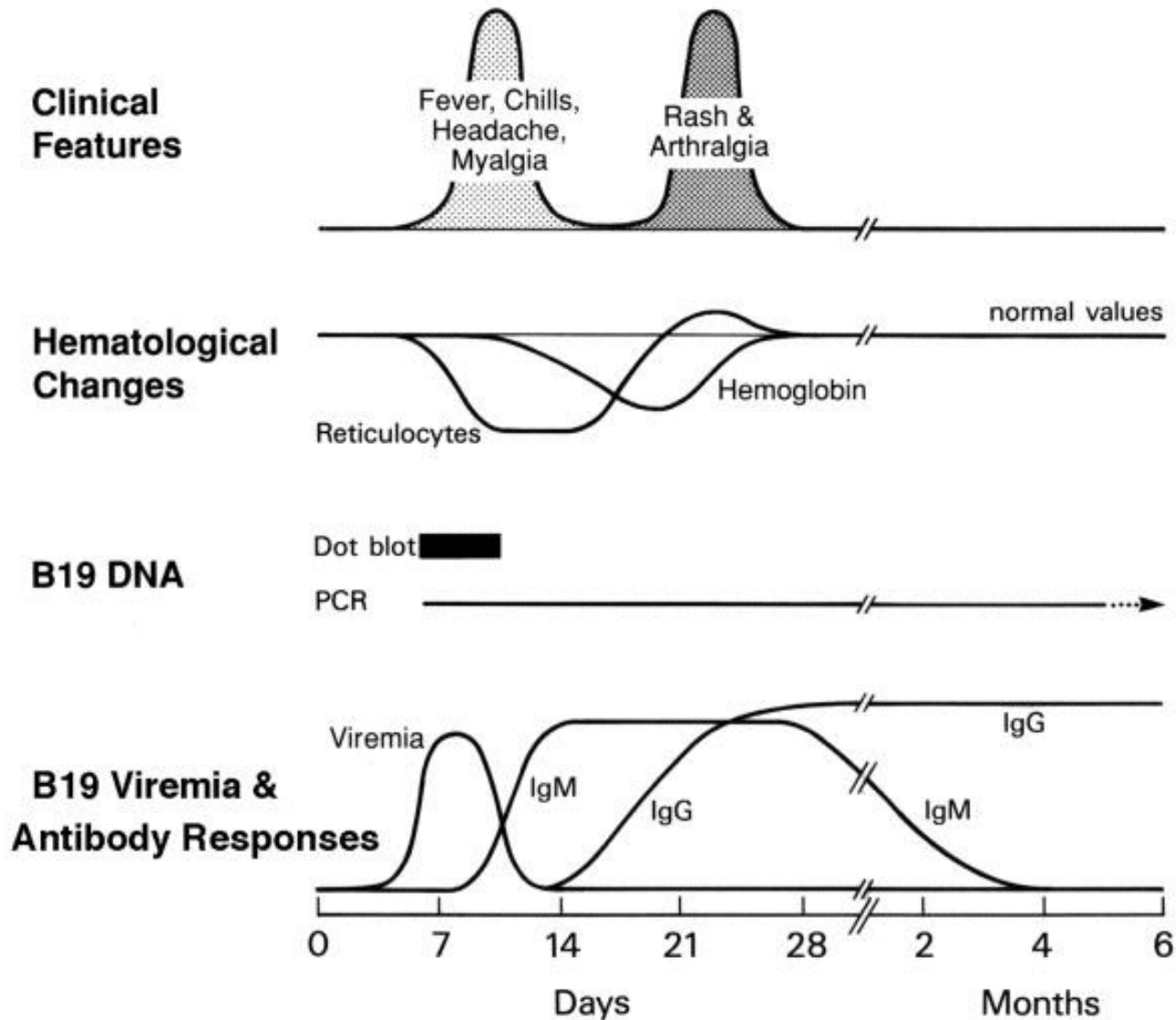


<http://www.yamagiku.co.jp/pathology/image/210/1.jpg>

Parvovirus B19



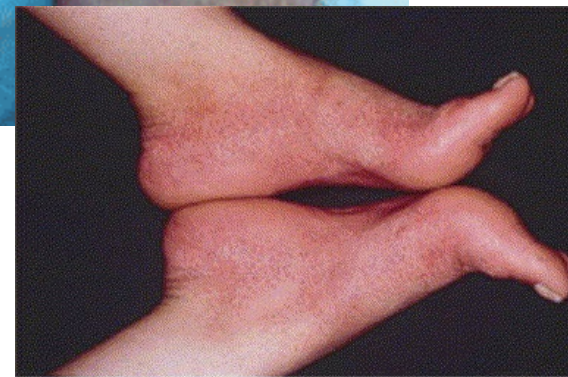
Parvovirus B19

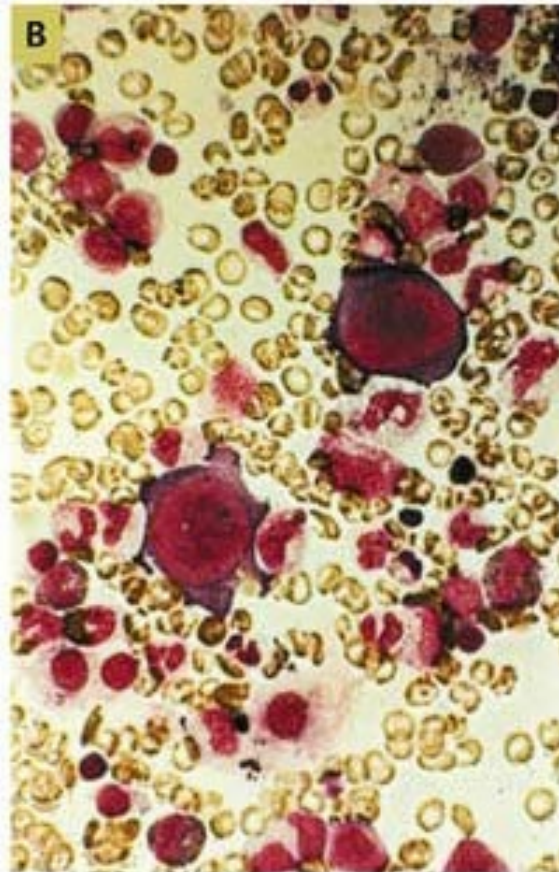




Almeida/publication/232222814/figure/fig1/AS:601664516026370@1520459407172/Papular-purpuric-exanthem-involving-the-distal-extremities-in-a-gloves-and-socks-pattern.png

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





https://www.nejm.org/na101/home/literatum/publisher/mms/journals/content/nejm/2004/nejm_2004.350.issue-6/nejmra030840/production/images/img_medium/nejmra030840_f3.jpeg

Taxonomy

GAMMAHERPESVIRUSES



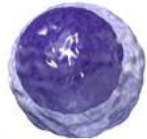
EBV

Rhadinovirus

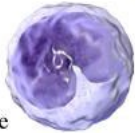
EHV2

HVS

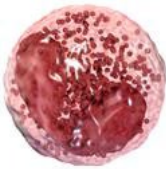
HHV8



Lymphocyte



Monocyte



Eosinophil

HHV7

Roseolovirusvirus

HHV6A a B

HCMV

Cytomegalovirus

BETAHERPESVIRUSES

ganciklovir

foscarnet

cidofovir

acyklovir

ALPHAHERPESVIRUSES

Simplexvirus

HSV1

HSV2

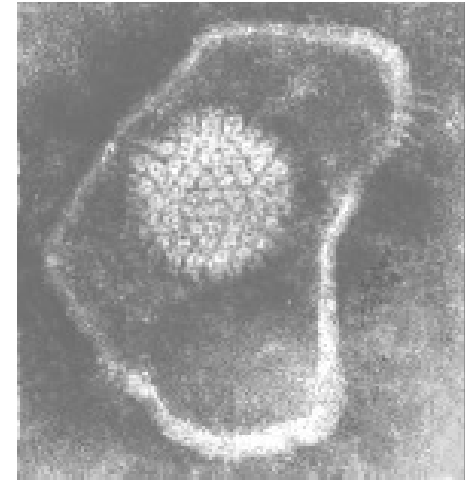
EHV1

PRV

VZV

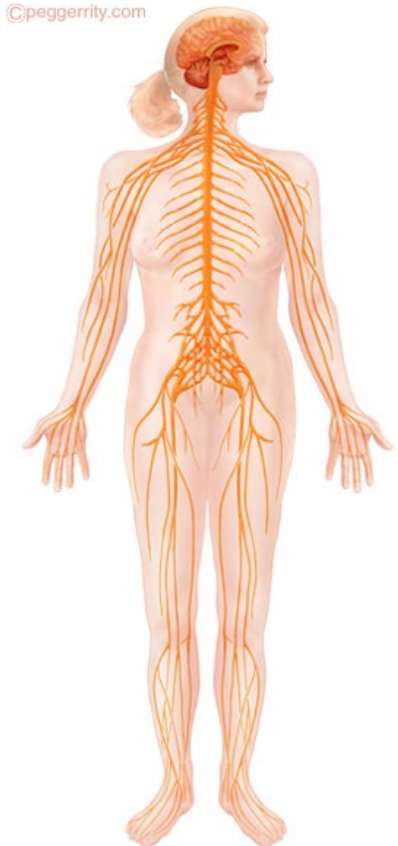
Varicellovirus

0.2 Divergence



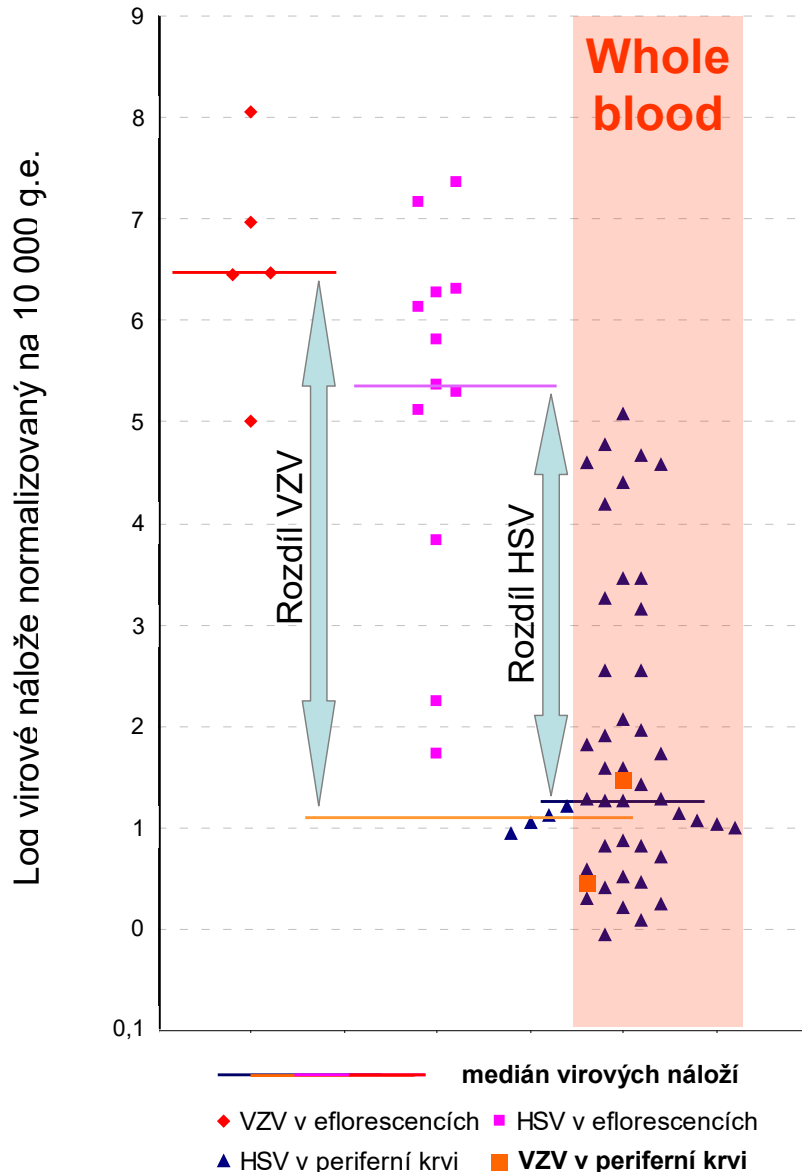
<http://www.tulane.edu/~dmsander/garryfavweb.html>

©peggerrity.com



Fields Virology

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 efluorescence 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“



Rash during sixth disease
Fitzpatrick's Dermatology

HHV-6 B

Immunocompetent host

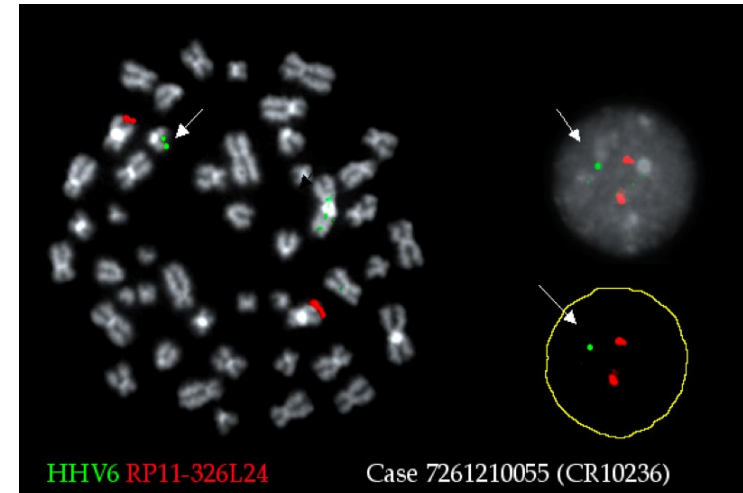
- Sixth disease
- Febrile seizures
- Encephalitis

Immunocompromised host

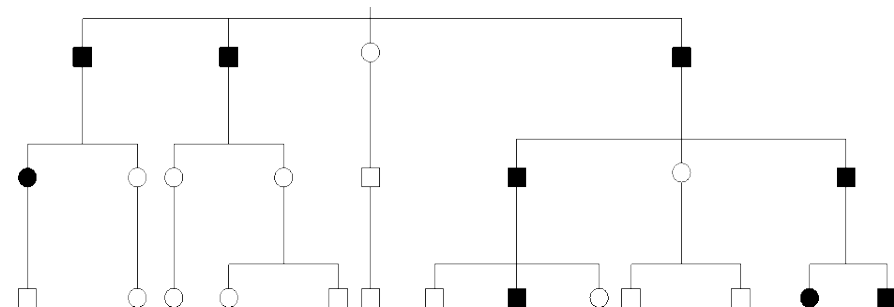
- Encephalitis
- Myelosuppression
- Hepatitis
- Pneumonitis
- Pericarditis
- **Delayed engraftment after HSCT**

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

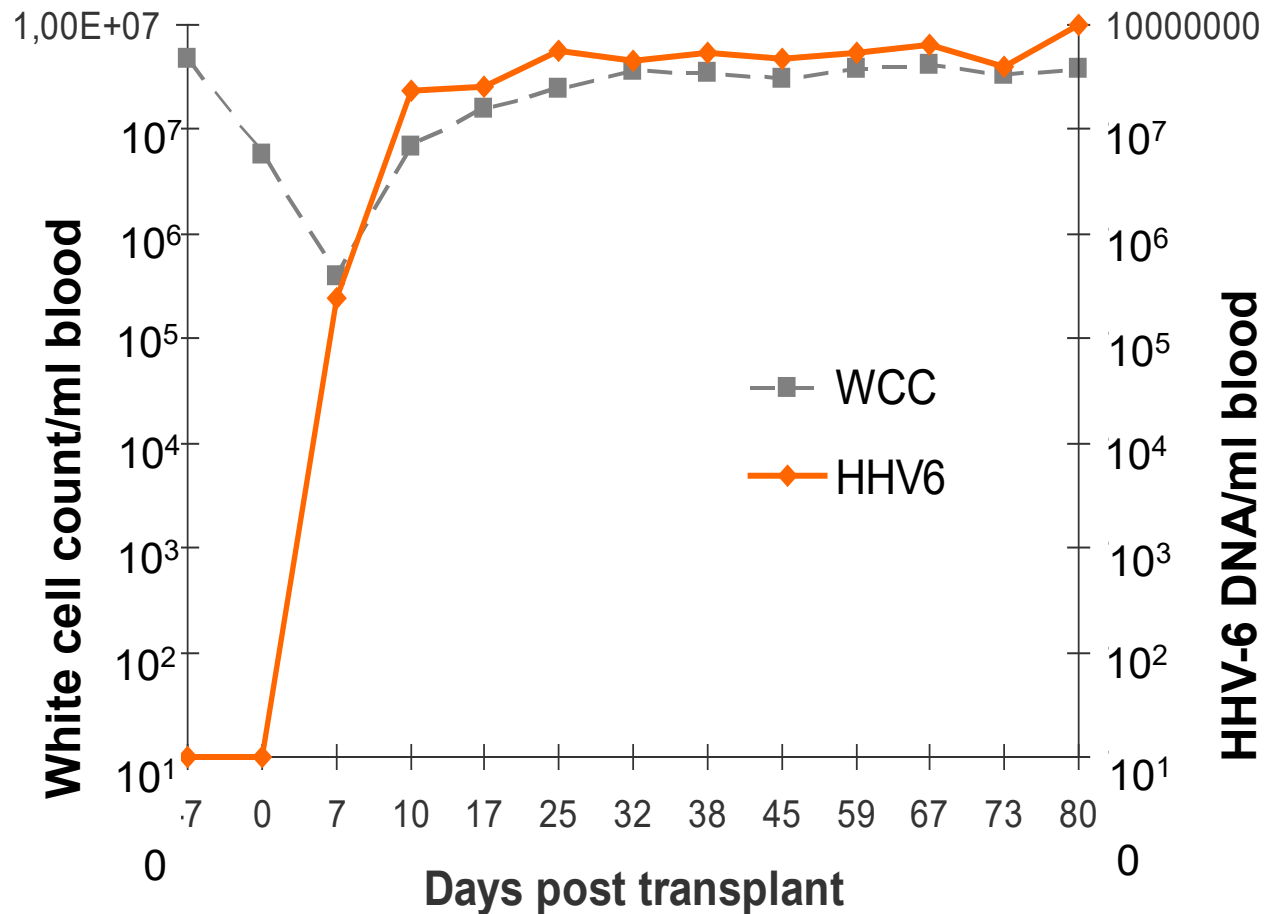


HHV-6 integration at 22q13.3 control probe on 9q34.4



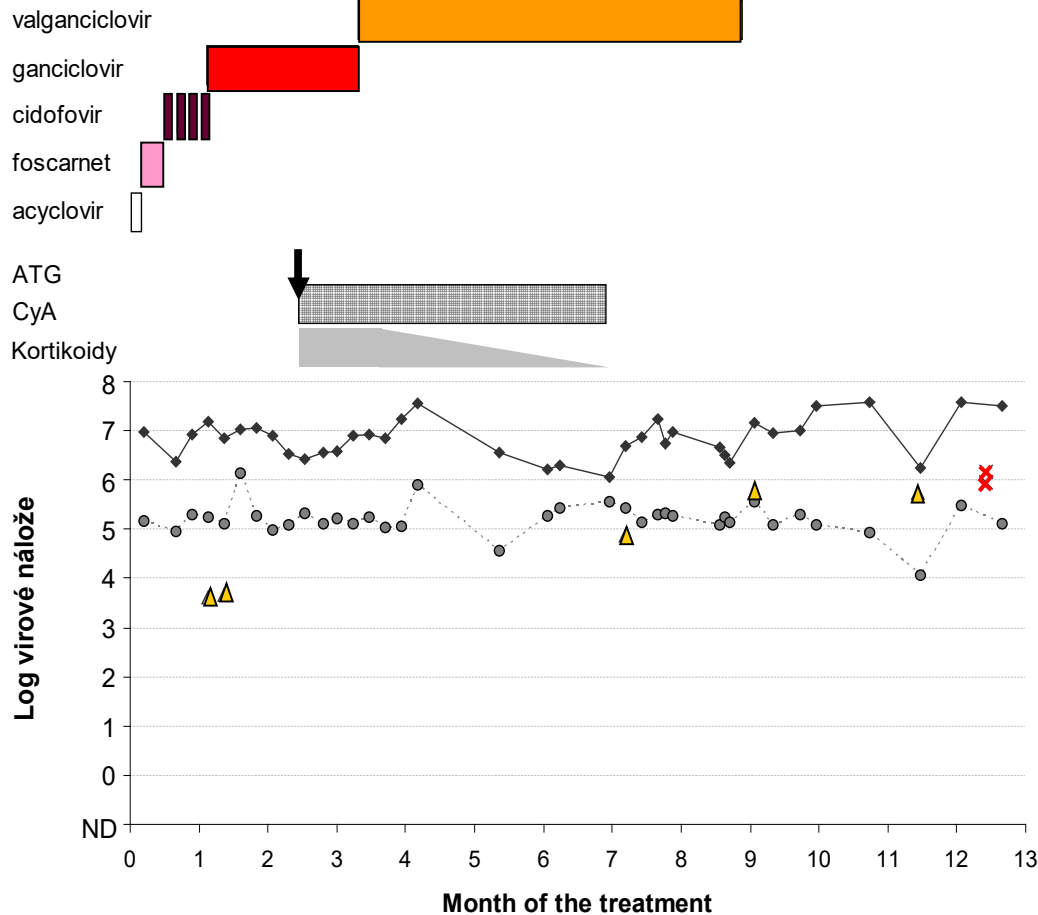
HHV6 DNA in blood after HSCT

donor with Ci-HHV-6



Clark et al., JID 2006

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



Patient with SAA

50 years

After start of the IS
therapy– partial response
only

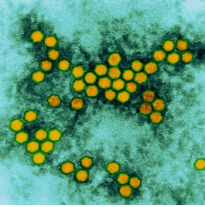
Dependent of thrombocyte
infusion

G-CSF therapy

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

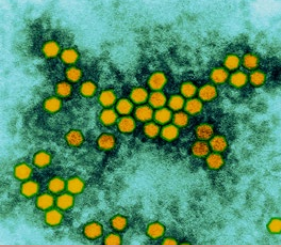
**Detection of high
HHV-6 DNA quantity is
NOT NECESSARY an
active infection.**

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



Picornaviridae - Coxsackieviruses

- Previously, there were Human coxsackievirus 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
- Coxsackie A – muscle necrosis and paralysis, conjunctivitis
- Coxsackie B – less severe damage of the organs (susp. T1DM)
 - Both are able to cause meningitis, myocarditis and pericarditis
- Coxsackie A serotype 16 is cause of Hand, Foot and Mouth disease
- Encephalitida/myeloencephalitida



Hand Food & Mouth Disease

Hand, foot, and mouth disease, or HFMD, is a contagious illness that is caused by different viruses. Infants and children younger than 5 years old are more likely to get this disease. However, older children and adults can also get it. In the United States it is more common for people to get HFMD from spring to fall.

Symptoms

By Mayo Clinic Staff

Hand-foot-and-mouth disease may cause all of the following signs and symptoms or just some of them. They include:

- Fever
- Sore throat
- Feeling of being unwell (malaise)
- Painful, red, blister-like lesions on the tongue, gums and inside of the cheeks
- A red rash, without itching but sometimes with blistering, on the palms, soles and sometimes the buttocks
- Irritability in infants and toddlers
- Loss of appetite



http://www.nhs.uk/tools/documents/visual_guides_v2/data/baby_rashes/images/slideshow_6.jpg

http://images.slideplayer.com/19/5871386/slides/slide_27.jpg



<http://healthosphere.com/wp-content/uploads/2012/02/Hand-Foot-and-Mouth-Disease-images.jpg>

<http://www.blogcdn.com/www.parentdish.co.uk/media/2012/12/hand-foot-and-mouth.jpg>

Hand Food & Mouth Disease



Blisters In & Around The Mouth



Blisters On Palms of Hands



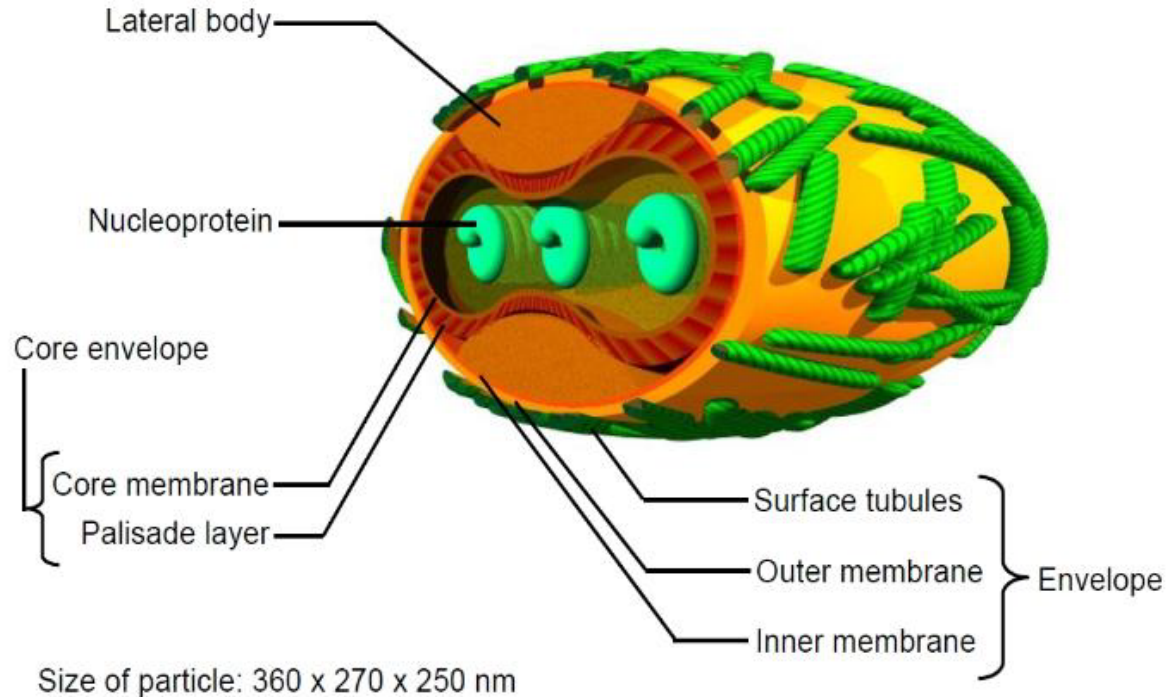


And now what?

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

Cut-away structure of a Poxvirus (e.g. Vaccinia)



<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)



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



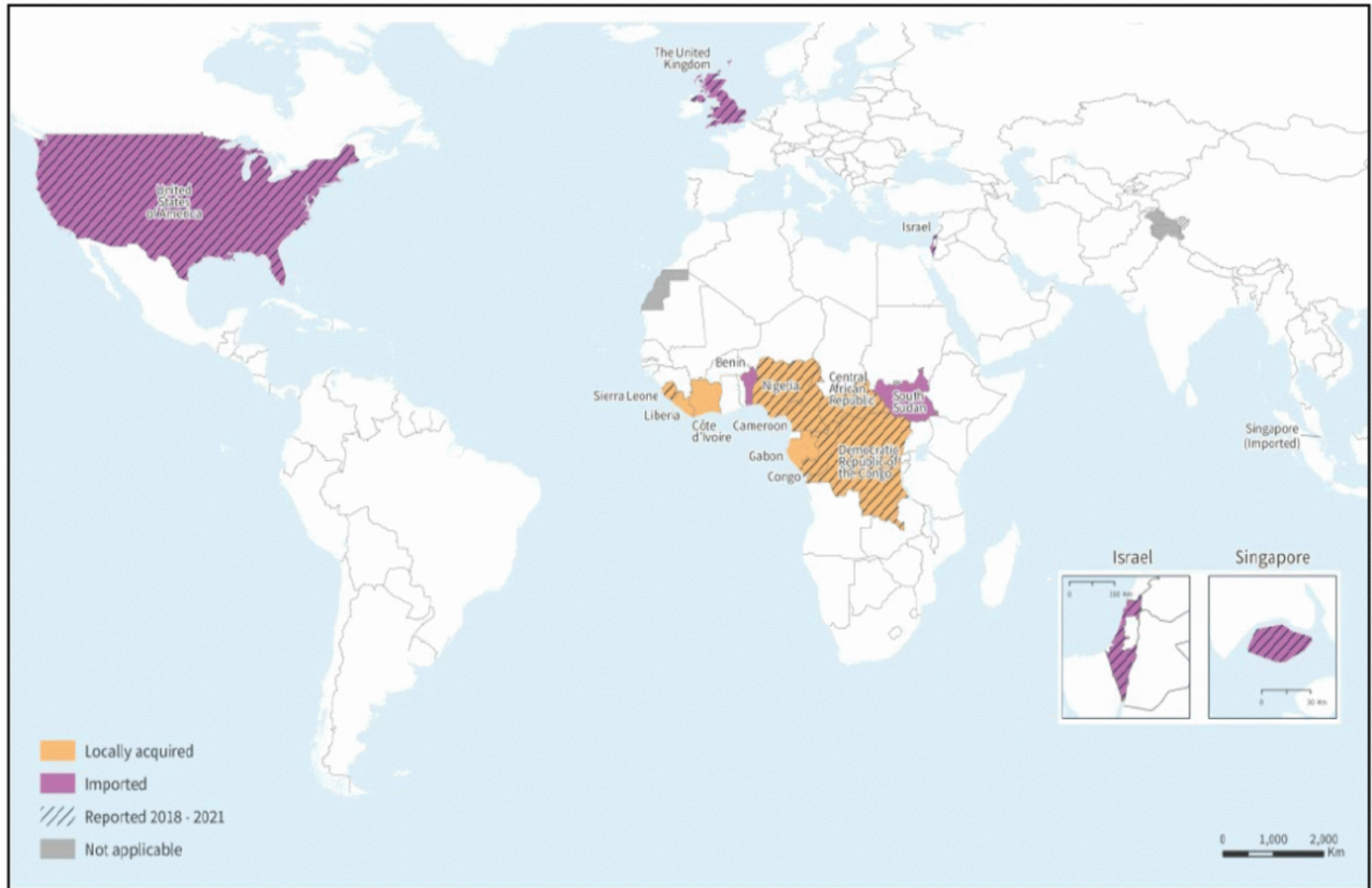
Yatapoxvirus

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



Yatapoxvirus

- M-pox virus

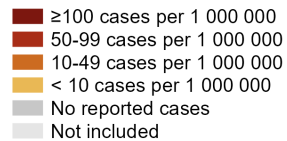


Yatapoxvirus

- M-pox virus



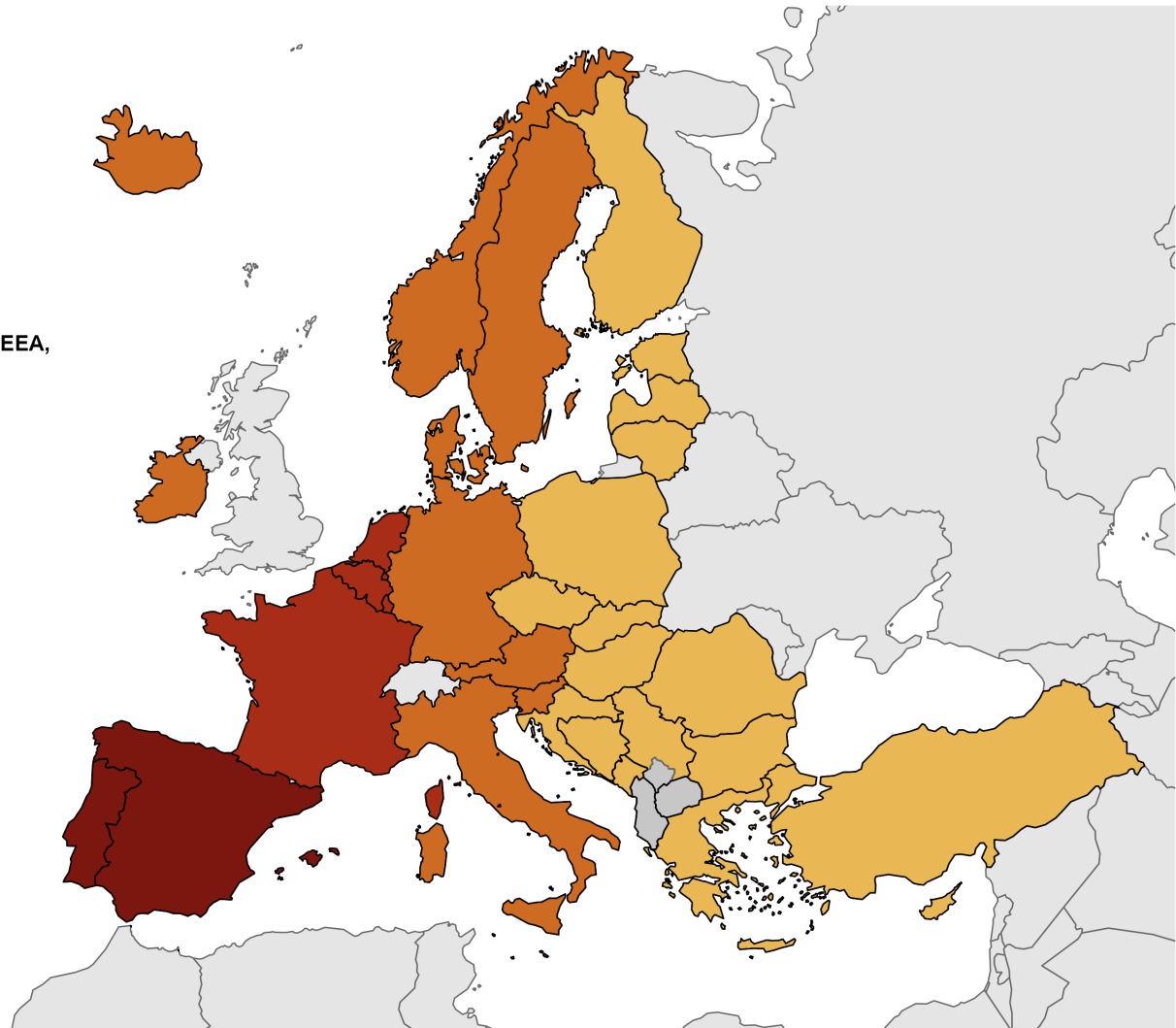
Geographical distribution of cumulative confirmed mpox cases per 1 000 000 population in the EU/EEA, Western Balkans and Türkiye, as of 07 Sep 2023



Countries not visible in the main map extent

Malta

Liechtenstein



Administration boundaries: © EuroGeographics

The boundaries and names shown on this map do not imply official endorsement or acceptance by the European Union. ECDC. Map produced on 07 Sep 2023

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



Thank you for your attention



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