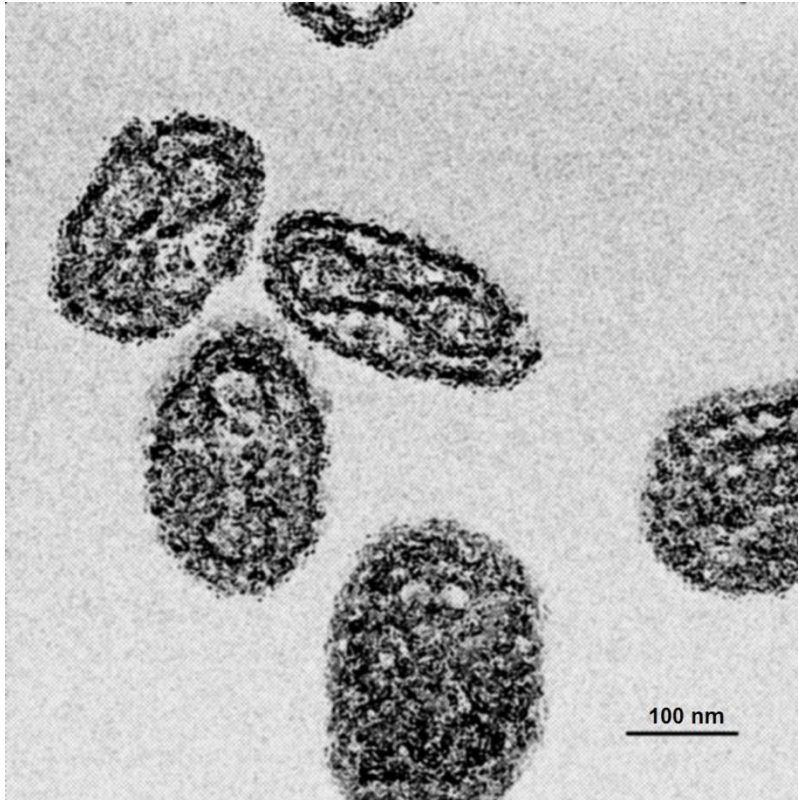


POX VIRIDAE: Variola (Small Pox))



https://commons.wikimedia.org/wiki/File:EM_smallpox,_grown_via_tissue,_isolate_by_centrifuge.jpg

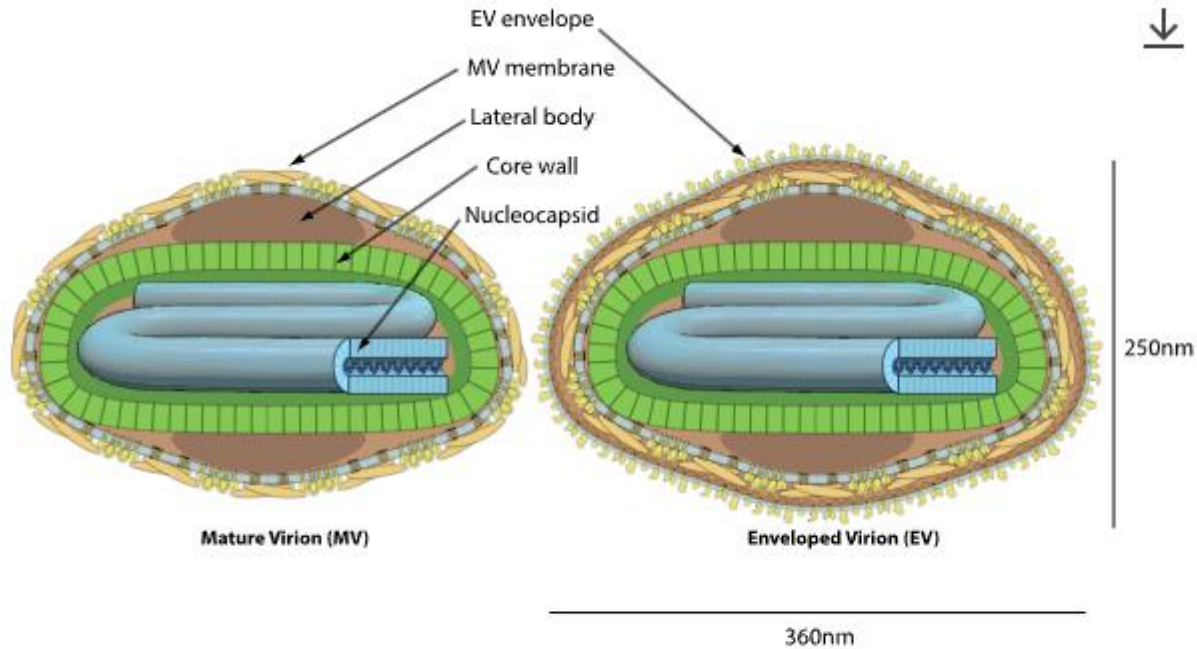
- Group I: ds DNA
- Family poxviridae
- Subfamily Chordopoxvirinae
- Genus Orthopoxvirus
- Virus : Variola

Variola Virus

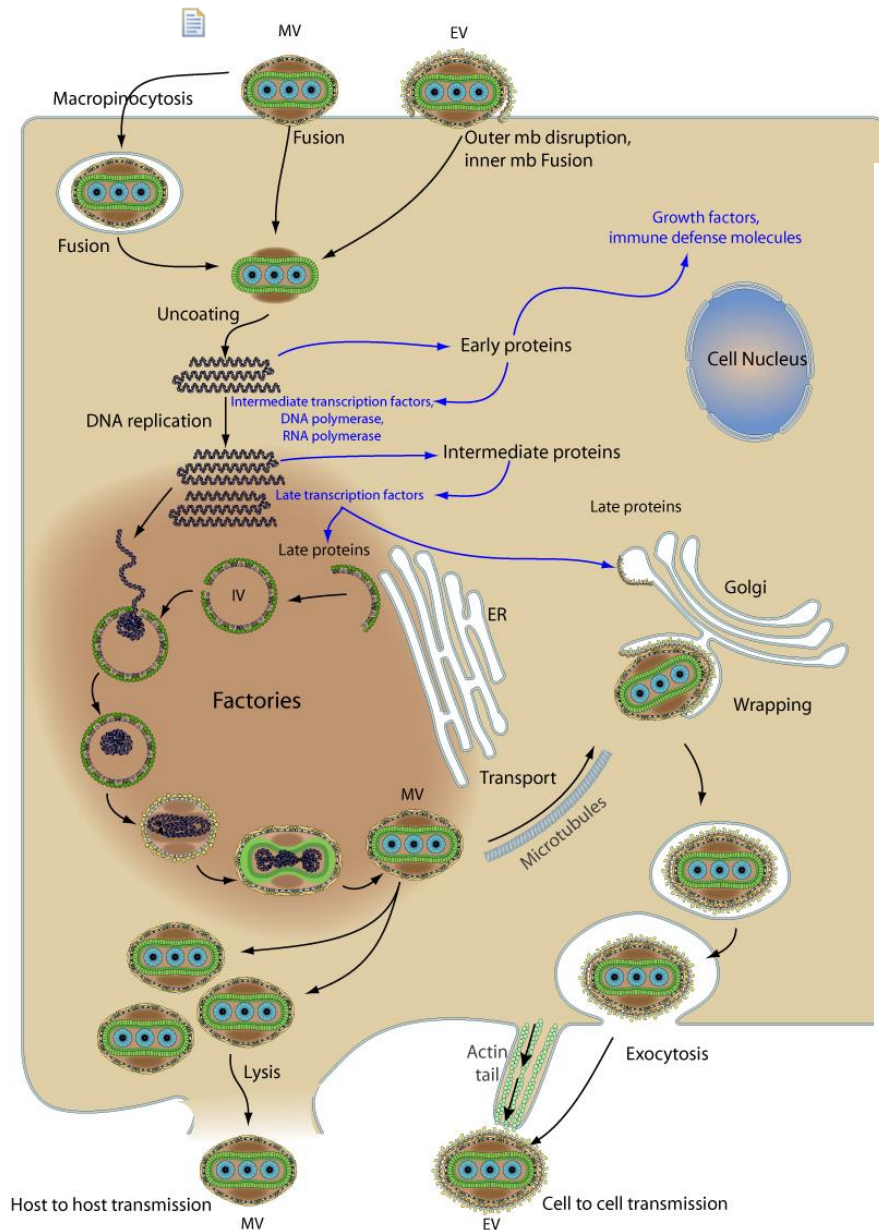
- Enveloped ds DNA Virus (300x200x100 nm)
- Brick Shaped
- Complex virus symmetry
- Biconcave ds DNA surrounded by Double layered membrane

Variola Virus- Morphology

VIRION



Enveloped, brick-shaped or ovoid virion, 220-450 nm long and 140-260 nm wide. The surface membrane displays surface tubules or surface filaments. Two distinct infectious virus particles exist: the intracellular mature virus (IMV) and the extracellular enveloped virus (EEV).



Poxvirus replication cycle

- Virus entry:
 - Extracellular virions can enter by [macropinocytosis](#) or by direct entry at the cell surface. Host receptors are unknown. Macropinocytosis can involve [apoptotic mimicry](#)
- Transcription in cytoplasmic factories
 - early: Viral replication machinery, host-modulating factors, core-associated enzymes and extracellular virion membrane proteins (about 118 genes in vaccinia virus_)
 - Postreplicative events:
 - Intermediate:DNA binding/packaging and core-associated nonenzymatic proteins (53 Genes in vaccinia virus_)
 - late: redox disulfide bond enzymes, virion morphogenesis, crescent formation proteins, mature virion membrane proteins and components of the entry-fusion complex (38 genes in vaccinia virus_)
- Virion assembly
- virus exit
 - by budding of Enveloped virion (EV), supported by [Actin-dependent outward viral transport](#)
 - by cell lysis, releasing mature virions (MV).

Entry

Intracellular mature virion (IMV) particles bind to unknown receptor(s) and fuse with the cell membrane. Extracellular enveloped virion (EEV) particles bind to unknown receptor(s) and are endocytosed into the cell.

Initial Uncoating

The viral core particle (CORE) containing the viral genome, the viral DNA-dependent RNA polymerase, and other enzymes is released into the cytoplasm.

Early Transcription

Early genes (including those coding for immunomodulatory proteins, enzymes, and replication and transcription factors) are transcribed and translated immediately upon core particle entry into the cytoplasm of the cell.

Translocation

The viral core particle translocates to the outside of the cell nucleus.

Secondary Uncoating

The viral nucleoprotein (NP) complex, which contains the viral genome, is released. At this point the viral genome is replicated as a concatemer and transcription and translation of intermediate genes (mainly coding for transcription factors) occurs.

Late Transcription

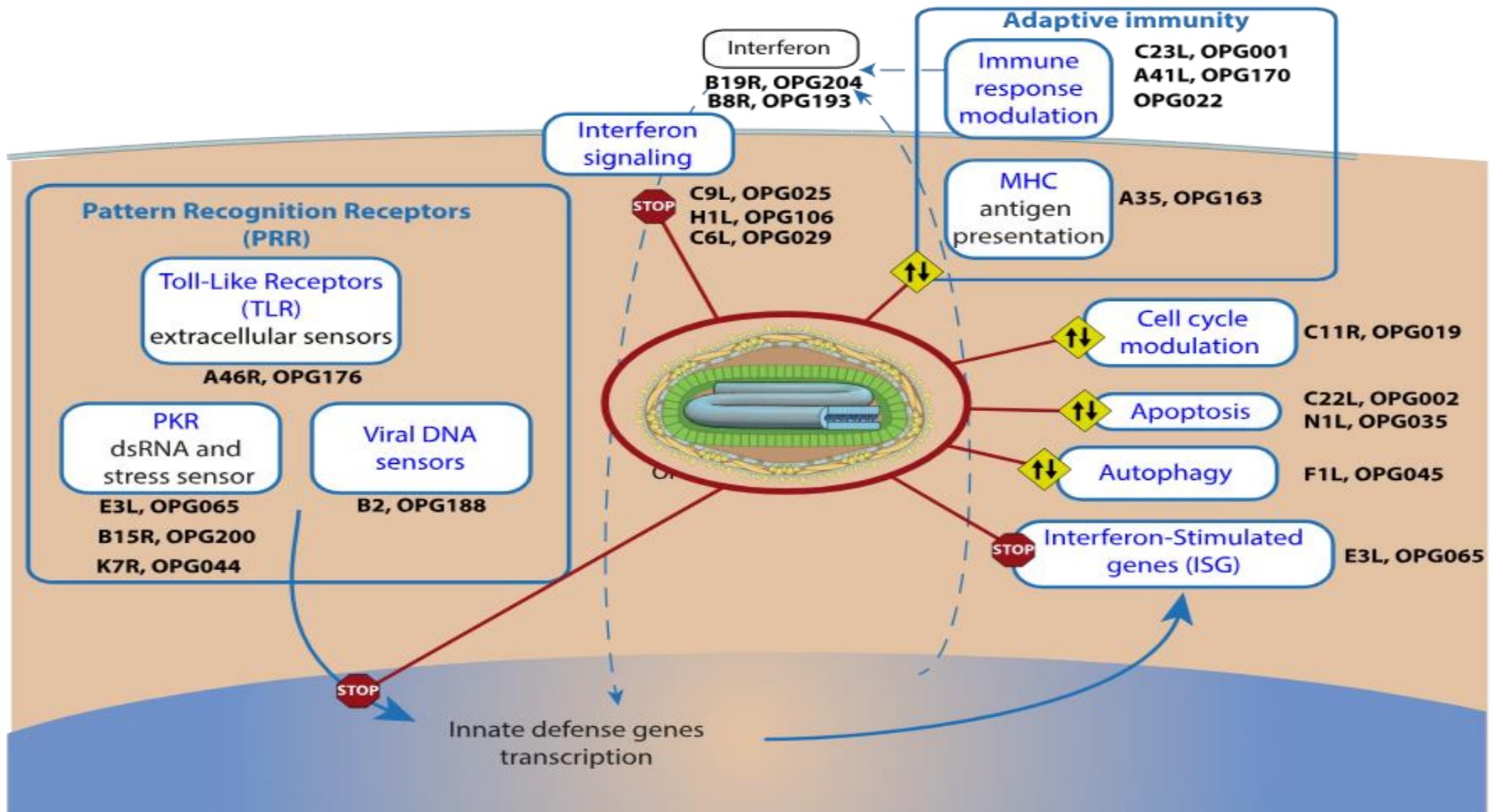
The viral late genes (coding for structural proteins, enzymes, and transcription factors) are transcribed and translated.

Assembly

Concatemeric intermediates are resolved into linear double-stranded DNA and packaged with late viral proteins into immature virions (IV).

Release

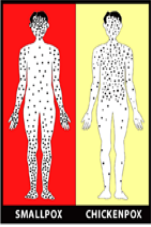
IVs mature into IMVs via an undescribed mechanism which may include processing of the IV through the Golgi apparatus. The IMVs are transported to the periphery of the cell where they are released in one of three ways. IMVs released via cell lysis remain IMVs. Alternatively, IMVs can bud through to the cell surface, picking up a viral envelope from the cell plasma membrane. On the surface cell-associated enveloped virions (CEVs) are pushed via an actin tail into contact with a second cell. Lastly the IMV can bud through the plasma membrane picking up an envelope and becoming an EEV.



Small Pox Pathogenesis

- Inhalation of air droplet
- Mucosal replication
- Viremia
- Incubation Phase (7-17 days)
- 2nd Viremia
- Toxemia phase
- Rash (3-4 days), high fever, myalgia-
- The smallpox rash progresses from macules to papules to vesicles over 4–5 days, then to pustules on days 7 and 9, and finally to scabs on day 13. The pustules are round, firm, and deep-seated within the dermis. The scabs crust over, and the scabs fall off after about three weeks, leaving pitted scars. The rash is most dense on the face, arms and hands, legs and feet, and has fewer pocks on the trunk
- Head to Arms and Hands to Legs and Trunks
- The most common complication of smallpox is severe scarring. Other complications include: Blindness, Encephalitis, Disfigurement from losing nasal or facial tissue, and Eye infections and other eye complications

Smallpox Disease

<p>Incubation Period (Duration: 7 to 17 days) <i>Not contagious</i></p>	<p>Exposure to the virus is followed by an incubation period during which people do not have any symptoms and may feel fine. This incubation period averages about 12 to 14 days but can range from 7 to 17 days. During this time, people are not contagious.</p>
<p>Initial Symptoms(Prodrome) (Duration: 2 to 4 days) <i>Sometimes contagious*</i></p>	<p>The first symptoms of smallpox include fever, malaise, head and body aches, and sometimes vomiting. The fever is usually high, in the range of 101 to 104 degrees Fahrenheit. At this time, people are usually too sick to carry on their normal activities. This is called the <i>prodrome</i> phase and may last for 2 to 4 days.</p>
<p>Early Rash (Duration: about 4 days) <i>Most contagious</i> Rash distribution: View enlarged</p> 	<p>A rash emerges first as small red spots on the tongue and in the mouth. These spots develop into sores that break open and spread large amounts of the virus into the mouth and throat. At this time, the person becomes most contagious. Around the time the sores in the mouth break down, a rash appears on the skin, starting on the face and spreading to the arms and legs and then to the hands and feet. Usually the rash spreads to all parts of the body within 24 hours. As the rash appears, the fever usually falls and the person may start to feel better. By the third day of the rash, the rash becomes raised bumps. By the fourth day, the bumps fill with a thick, opaque fluid and often have a depression in the center that looks like a bellybutton. (This is a major distinguishing characteristic of smallpox.) Fever often will rise again at this time and remain high until scabs form over the bumps.</p>
<p>Pustular Rash (Duration: about 5 days) <i>Contagious</i></p>	<p>The bumps become pustules—sharply raised, usually round and firm to the touch as if there’s a small round object under the skin. People often say the bumps feel like BB pellets embedded in the skin.</p>
<p>Pustules and Scabs (Duration: about 5 days) <i>Contagious</i></p>	<p>The pustules begin to form a crust and then scab. By the end of the second week after the rash appears, most of the sores have scabbed over.</p>
<p>Resolving Scabs (Duration: about 6 days) <i>Contagious</i></p>	<p>The scabs begin to fall off, leaving marks on the skin that eventually become pitted scars. Most scabs will have fallen off three weeks after the rash appears. The person is contagious to others until all of the scabs have fallen off.</p>
<p>Scabs resolved <i>Not contagious</i></p>	<p>Scabs have fallen off. Person is no longer contagious.</p>

* Smallpox may be contagious during the *prodrome* phase, but is most infectious during the first 7 to 10 days following rash onset.

Epidemiology

- There are four types of variola major smallpox:
- ordinary (the most frequent type, accounting for 90% or more of cases);
- modified (mild and occurring in previously vaccinated persons);
- flat; and
- hemorrhagic (both rare and very severe).
- Historically, variola major has an overall fatality rate of about 30%; however, flat and hemorrhagic smallpox usually are fatal.
- Variola minor is a less common presentation of smallpox, and a much less severe disease, with death rates historically of 1% or less.
- Small Pox eradicated 1979 (WHO) using small pox vaccine
- 1796. Edward Jenner used cow pox extract
- Live attenuated strain of cow pox maintained at CDC, Georgia and Institute of Virus Preparation, Moscow.

Small Pox Vaccine

- The World Health Organization maintained a stockpile of 200 million doses in 1980, to guard against reemergence of the disease, but 99% of the stockpile was destroyed in the late 1980s when smallpox failed to return
- 3rd generation Small Pox Vaccines
- The United States had received 269 million doses of ACAM2000 (vaccine developed by Acambis) and 28 million doses of MVA-BN (Modified Ankara Virus) by 2019, but only 100 million doses of ACAM2000 and 65,000 doses of MVA-BN were still available from the stockpile at the start of the 2022 monkeypox outbreak (Wikipedia)



The smallpox vaccine (live virus) diluent in a syringe alongside a vial of Dryvax dried smallpox vaccine and bifurcated needle