ORTHOMYXOVIRUS

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- ***Orthomyxoviridae*** (orthós, Greek for "straight"; mýxa, Greek for "mucus") is a family of RNA viruses. It includes seven genera:

1. **Alphainfluenzavirus**: (influenza A virus) infects humans, other mammals, and birds, and causes all flu pandemics
2. **Betainfluenzavirus**: (influenza B virus) infects humans and seals
3. **Deltainfluenzavirus**: (influenza D virus) infects pigs and cattle
4. **Gammainfluenzavirus** (influenza C virus) infects humans, pigs, and dogs.
5. Isavirus, infect salmon
6. **Thogotovirus**: are arboviruses, infecting vertebrates and invertebrates, such as ticks and mosquitoes
7. **Quaranjavirus**: are also arboviruses, infecting arthropods as well as birds

- The first four genera (influenza **A,B,C,D**) contain viruses that cause influenza in vertebrates, including birds (avian influenza), humans, and mammals.
- The four genera of Influenza virus (**A,B,C,D**) which are identified by antigenic differences in their **nucleoprotein and matrix protein**.

Classification:

The taxonomy of *orthomyxovirus* is

1- According to **Baltimore** Classification System

Type V single strand RNA virus (negative-sense ssRNA virus)

2- According to **International Committee on Taxonomy of Viruses** (ICTV)

Order "Mononegavirales"

Family "Orthomyxoviridae"

Genera

- Alphainfluenzavirus: (influenza A virus)
- Betainfluenzavirus: (influenza B virus)
- Deltainfluenzavirus: (influenza D virus)
- Gammainfluenzavirus (influenza C virus)
- Isavirus
- Thogotovirus
- Quaranjavirus

Serotypes of Alphainfluenzavirus

A serotype or serovar is a variation within a species of virus. These viruses, are classified based on their surface antigens

Serotypes of (influenza **A** virus) are:

- H1N1 caused "Spanish flu" in 1918 and "Swine flu" in 2009.
- H2N2 caused "Asian Flu".
- H3N2 caused "Hong Kong Flu".
- H5N1, "avian" or "bird flu".
- H7N7 has unusual zoonotic potential.
- H1N2 is endemic in humans and pigs
- H9N2, H7N2, H7N3, H10N7.

Types

1- Influenza A

Influenza A viruses are virulent human pathogens further classified, based on the viral surface proteins hemagglutinin (HA or H) and neuraminidase (NA or N).

Sixteen H subtypes (or serotypes) and nine N subtypes of influenza A virus have been identified.

The standard nomenclature specifying depending on

a) Virus type

b) Geographical location where first isolated

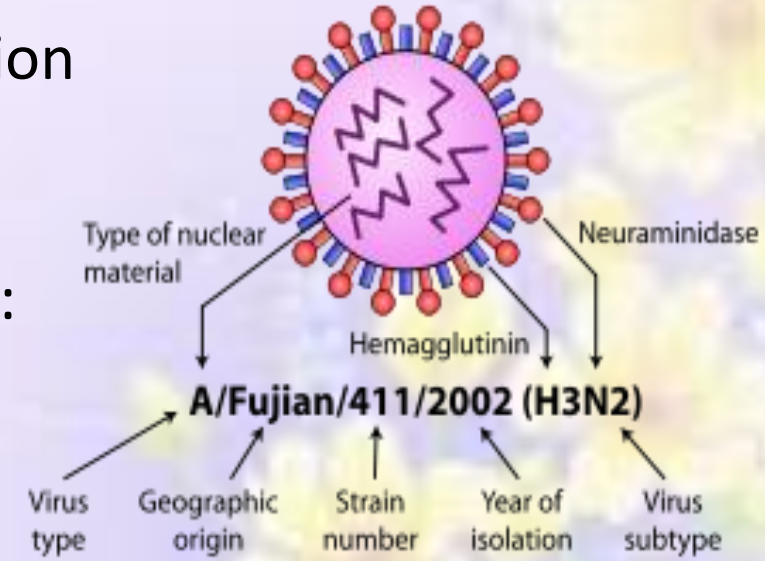
c) Sequential number of isolation

d) Year of isolation

e) HA and NA subtype

Examples of the nomenclature are:

1. A/Brisbane/59/2007 (H1N1)
2. A/Moscow/10/99 (H3N2).



2- Influenza B

Influenza B virus is a human pathogen, and is less common than influenza A. The only other animal known to be susceptible to influenza B infection is the seal. This type of influenza mutates at a rate 2–3 times lower than type A.

3- Influenza C

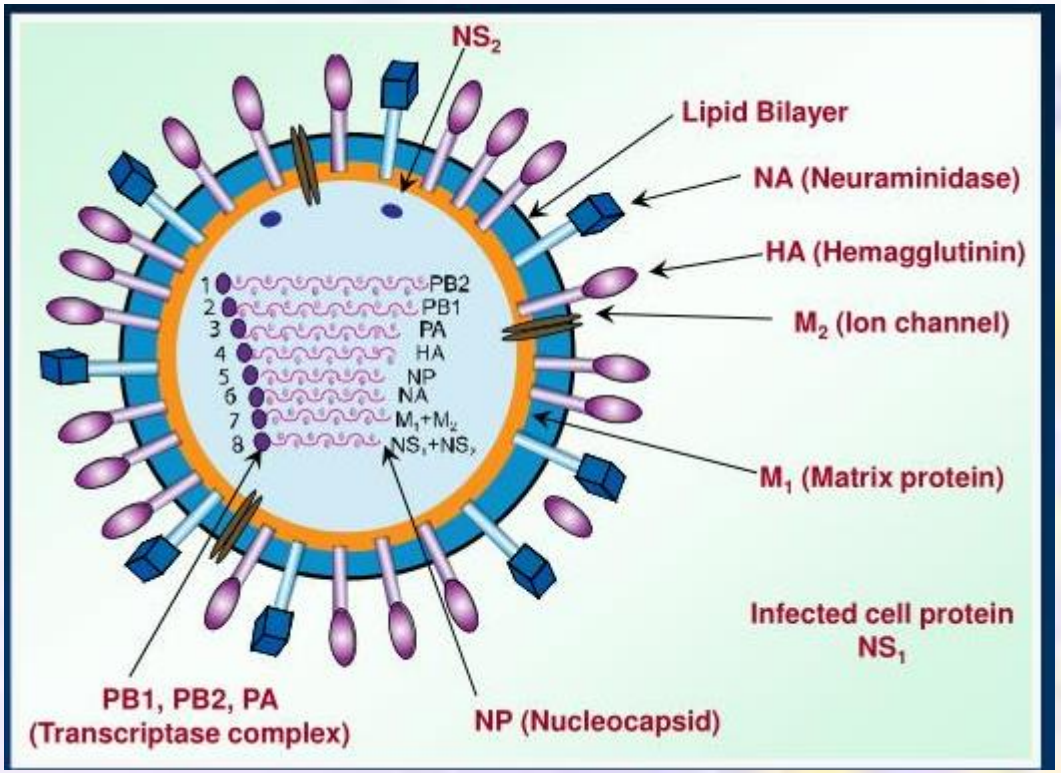
The influenza C virus infects humans and pigs, and can cause severe illness and local epidemics. Influenza C is less common than the other types and usually causes mild disease in children.

4- Influenza D

This is a genus that was classified in 2016, the members of which were first isolated in 2011. This genus appears to be most closely related to Influenza C. this genus has two strains. The main hosts appear to be cattle, but the virus has been known to infect pigs.

Viral structure:

- The virion is pleomorphic;
- the envelope (lipid bilayer membrane) can occur in spherical and filamentous forms.
- Lipid bilayer membrane has protruding glycoproteins (HA and NA) and enclose the nucleocapsids.
- The ribonuclear proteins (RNA + NP) are filamentous and They have a helical symmetry.
- The major glycoprotein (HA) is interposed irregularly by clusters of neuraminidase (NA), with a ratio of HA to NA of about 4–5 to 1.
- There are some 500 distinct spike-like surface projections of the envelope each projecting 10 to 14 nm from the surface with varying surface densities.



Viral Genome

The viruses contain (8 segments) of linear negative-sense single stranded RNA. They are filamentous and they have a helical symmetry.

These segments in viral genome of influenza A virus

1. Segment 1, Segment 2 and segment 3 are encodes RNA polymerase subunit (PB2, PB1, PA(.PB1-F2 protein, which induces cell death.

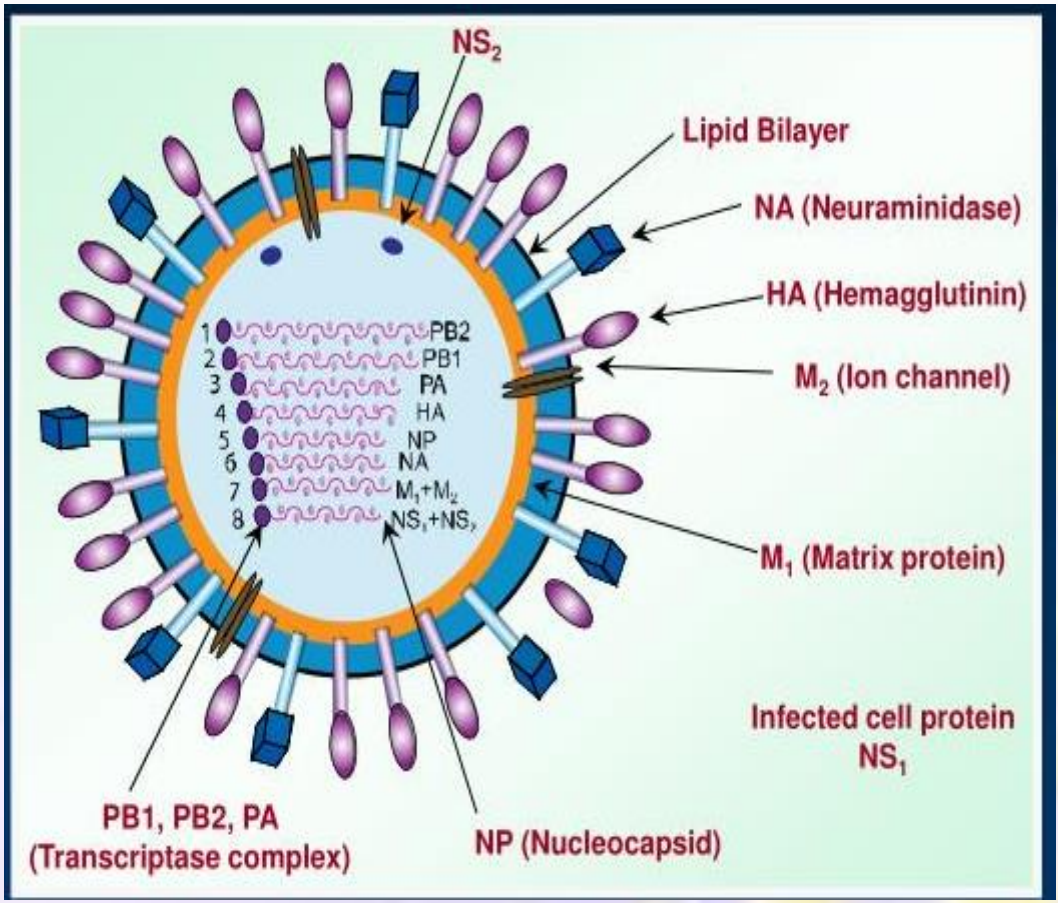
2. Segment 4 encodes for HA (hemagglutinin). About 500 molecules of hemagglutinin are needed to make one virion. HA determines the severity of a viral infection in a host organism.

3. Segment 5 encodes NP, which is a nucleoprotein.

4. Segment 6 encodes NA (neuraminidase). About 100 molecules of neuraminidase are needed to make one virion.

5. Segment 7 encodes two matrix proteins (M1matrix protein) and (M2 ion channel). About 3,000 matrix protein molecules are needed to make one virion.

6. Segment 8 encodes two non-structural proteins (NS1).



Replication cycle

1- **Attachment**: The viruses bind to the surfaces of epithelial cell through interactions between its hemagglutinin glycoprotein and sialic acid sugars on cells of lung and throat

2- **Penetration** (Entry): The cell imports the virus by endocytosis.

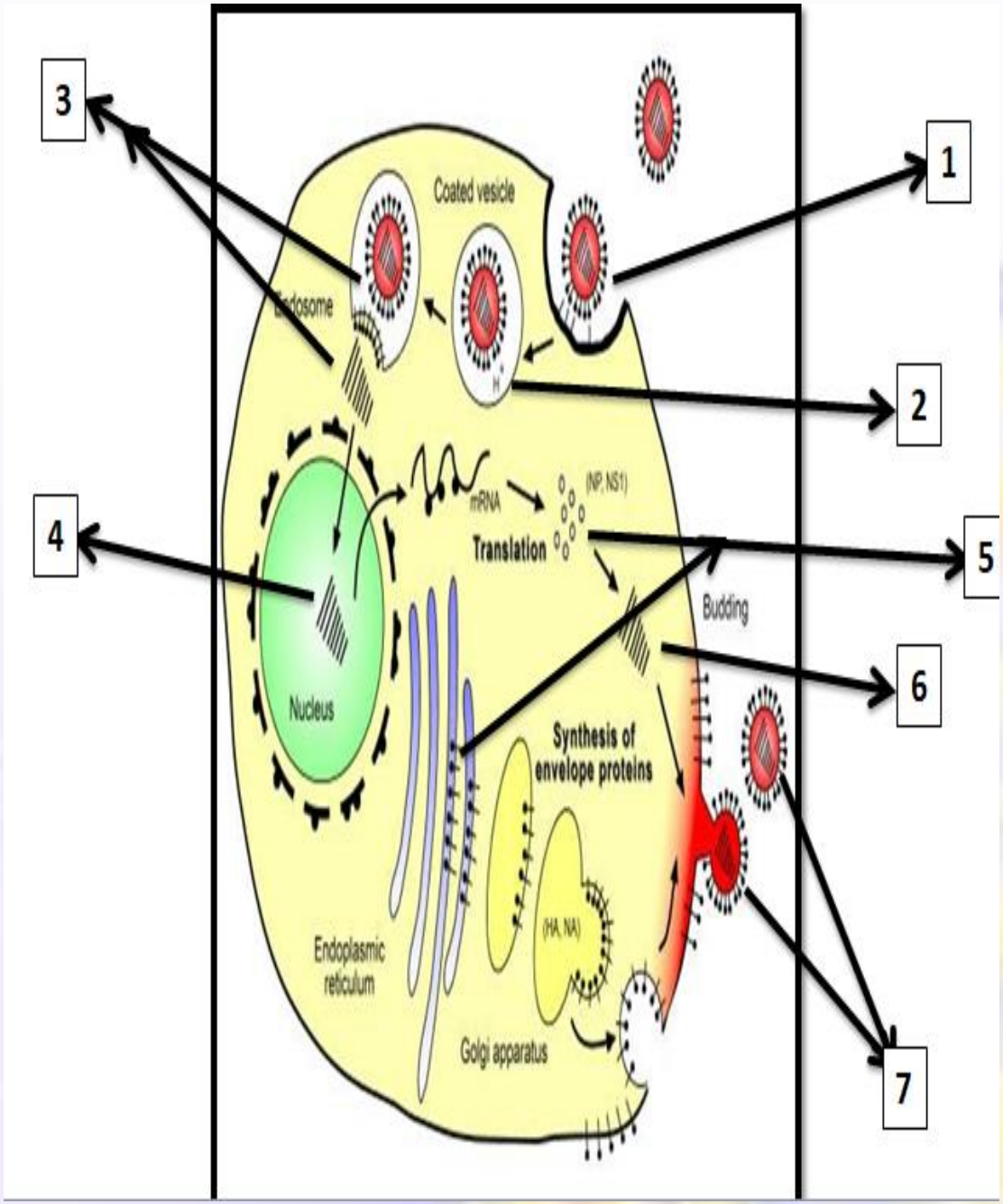
3- **Uncoating**: In the acidic endosome, part of the haemagglutinin protein fuses the viral envelope with the vacuole's membrane, releasing the viral RNA (vRNA) molecules, accessory proteins and RNA-dependent RNA polymerase into the cytoplasm.

4- **Transcription of viral RNA**: These accessory proteins and vRNA (negative sense) form a complex that is transported into the cell nucleus, where the RNA-dependent RNA polymerase begins transcribing complementary positive-sense cRNA

5- **Translation of viral protein**: The complementary positive-sense cRNA is exported into the cytoplasm and translated to viral protein. HA and NA synthesized in endoplasmic reticulum, then inserted into plasma membrane

6- **Assembly**: the nucleocapsid assemble in the nucleus, then move out to the cell surface

7- **Releasing**: the mature viruses detach from the host cell via neuraminidase which cleaved sialic acid residues. This process called budding.

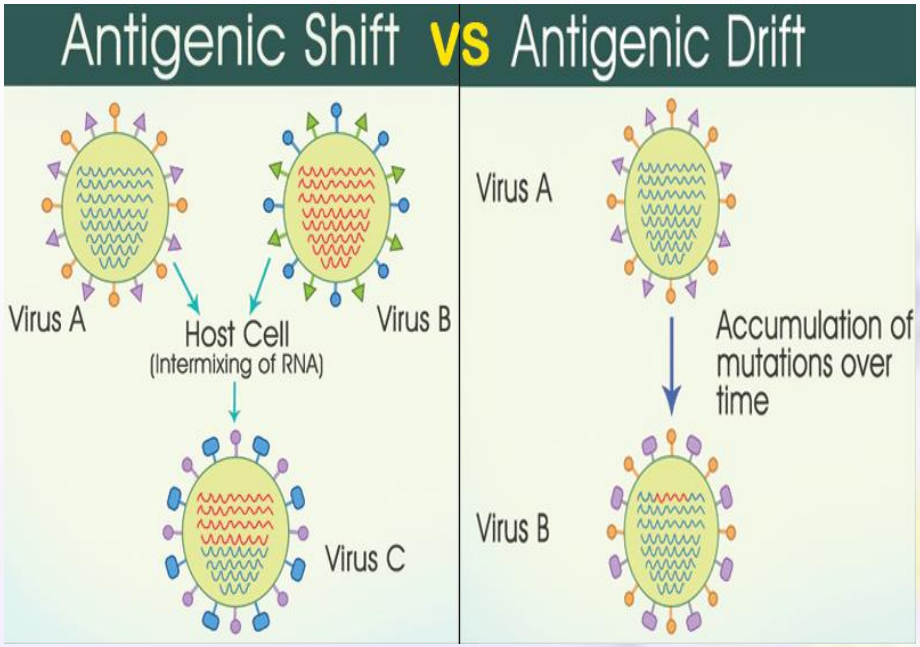


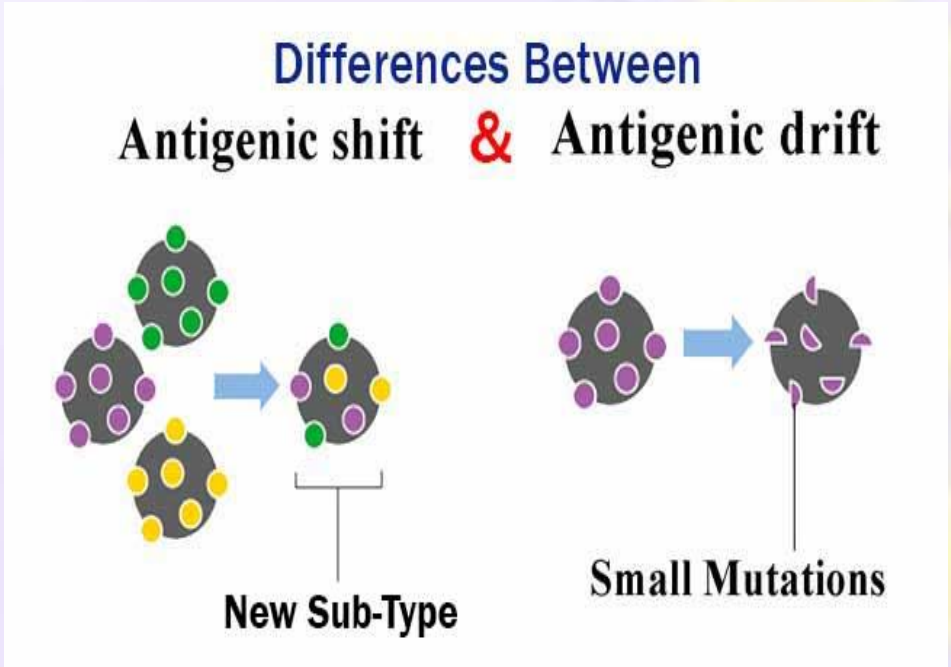
How the flu virus changes over time: (why the influenza virus is unique):

Influenza strains are constantly mutating because the virus has segmented genome. This mutation occurs in the viral genome and referred to **antigenic drift** and **antigenic shift (reassortment)**

Antigenic drift: is minor antigenic changes due to mutation in H gene (lead to changes in its surface proteins hemagglutinin (HA) and neuraminidase (NA)) and not recognized by the immune system. **Therefore** the main reason why people getting flu more than one time (seasonal flu)

Antigenic shift (reassortment): is a more major change in the influenza virus. Results due to genetic recombination between 2 or more viruses results in new or novel virus subtype. Occurs in pigs, human and cause pandemic



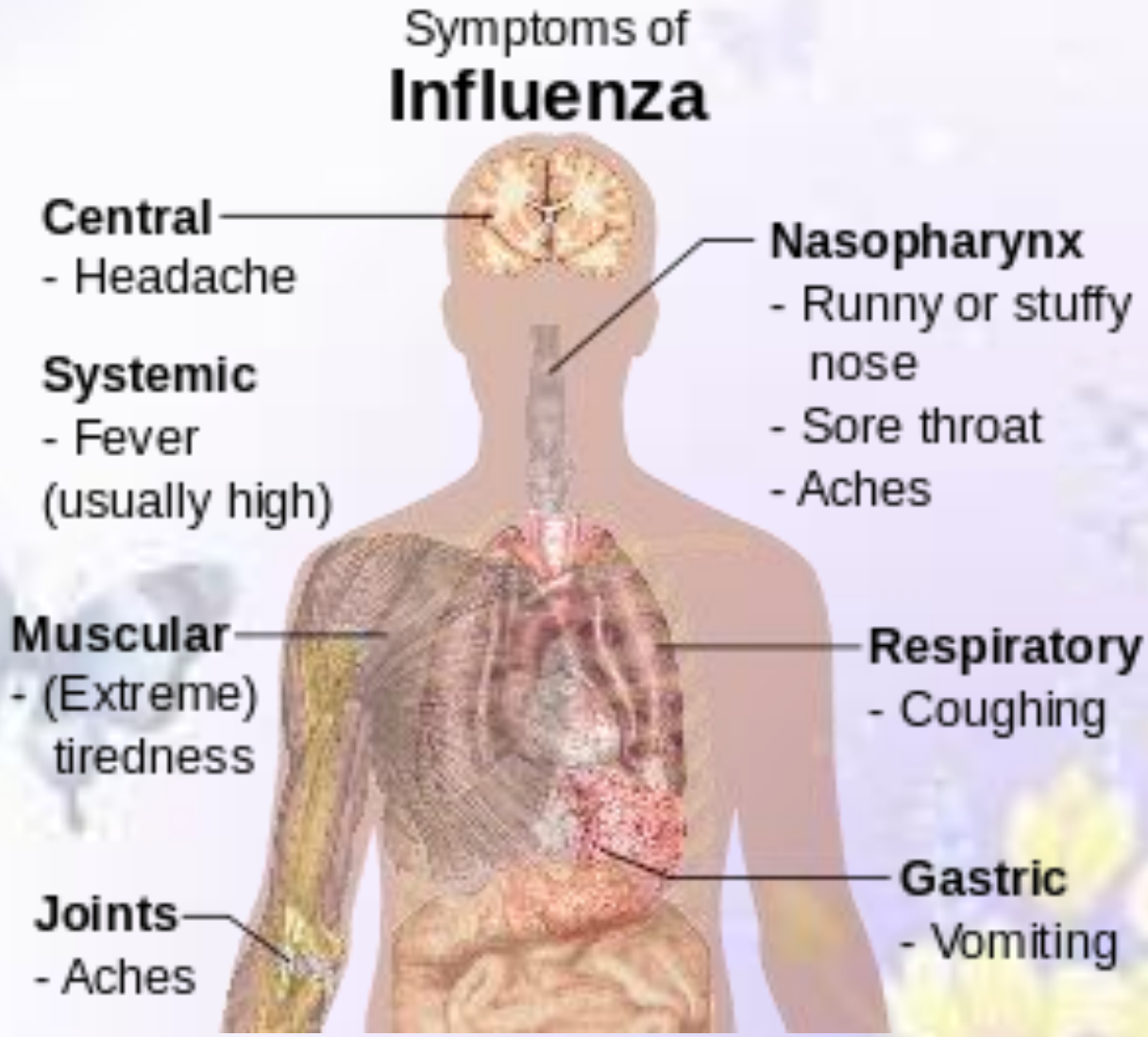


Influenza

commonly called "**the flu**", is an infectious disease caused by influenza viruses. Symptoms range from mild to severe and often include fever, runny nose, sore throat, muscle pain, headache, coughing, and fatigue. These symptoms typically **begin** 1–4 days after exposure to the virus and **last** for about **2–8 days**.

- Influenza viruses are primarily transmitted through **respiratory droplets** produced from coughing and sneezing. Transmission through aerosols, intermediate objects and surfaces contaminated by the virus.

Signs and symptoms



Diagnosis

1- Clinical signs

2- Laboratory examination

a. **Direct examination:** include

i. **Viral isolation** : Viruses can be grown in a cell culture or embryonated eggs to monitor cytopathic effect and pathological changes.

ii. **Rabid diagnosis** by RT-PCR to detection the viral genome

b. **Indirect examination:** Serologically by enzyme-linked immunosorbent assay (ELISA).

Prevention

Vaccination:

Vaccines are available for the prophylaxis of influenza virus infections. Vaccines are composed of either inactivated or live attenuated virions of the H1N1 and H3N2 human influenza A viruses, as well as those of influenza B viruses.

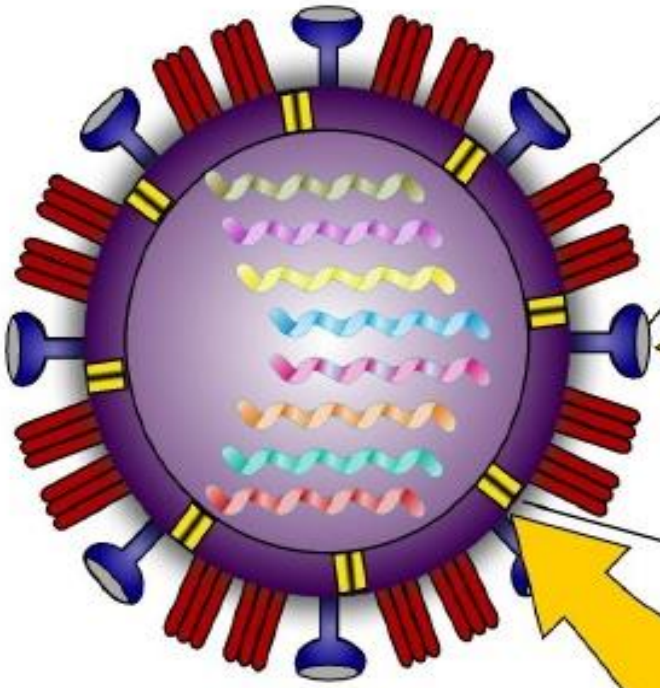
Prevention

Treatment:

Drugs are available for the treatment of influenza virus infections include

- **Amantadine and Rimantadine:** is antiviral that block the M2 ion channel due to incomplete the viral uncoating step
- **Oseltamivir (Tamiflu), Zanamivir (Relenza), Laninamivir (Inavir), and Peramivir:** is antiviral which block the neuraminidase enzyme of the influenza virus, by preventing its reproduction by budding from the host cell.

Antiviral Therapies for Influenza



Hemagglutinin (H)

Neuraminidase (N)

M2 Protein

(Injectable **Peramivir** has completed phase-1 trials)

Tamiflu! (oral)

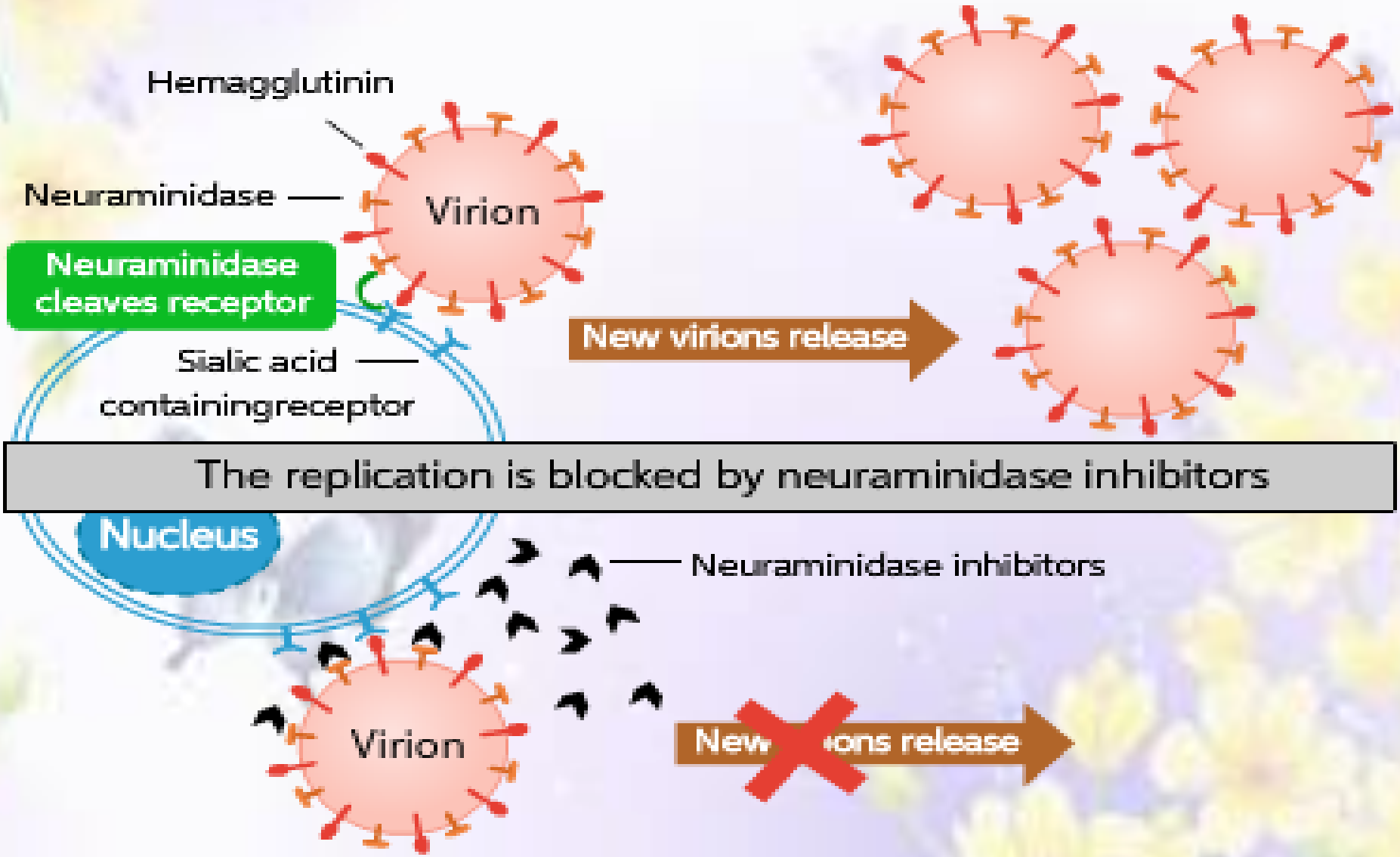
Oseltamivir
Zanamivir

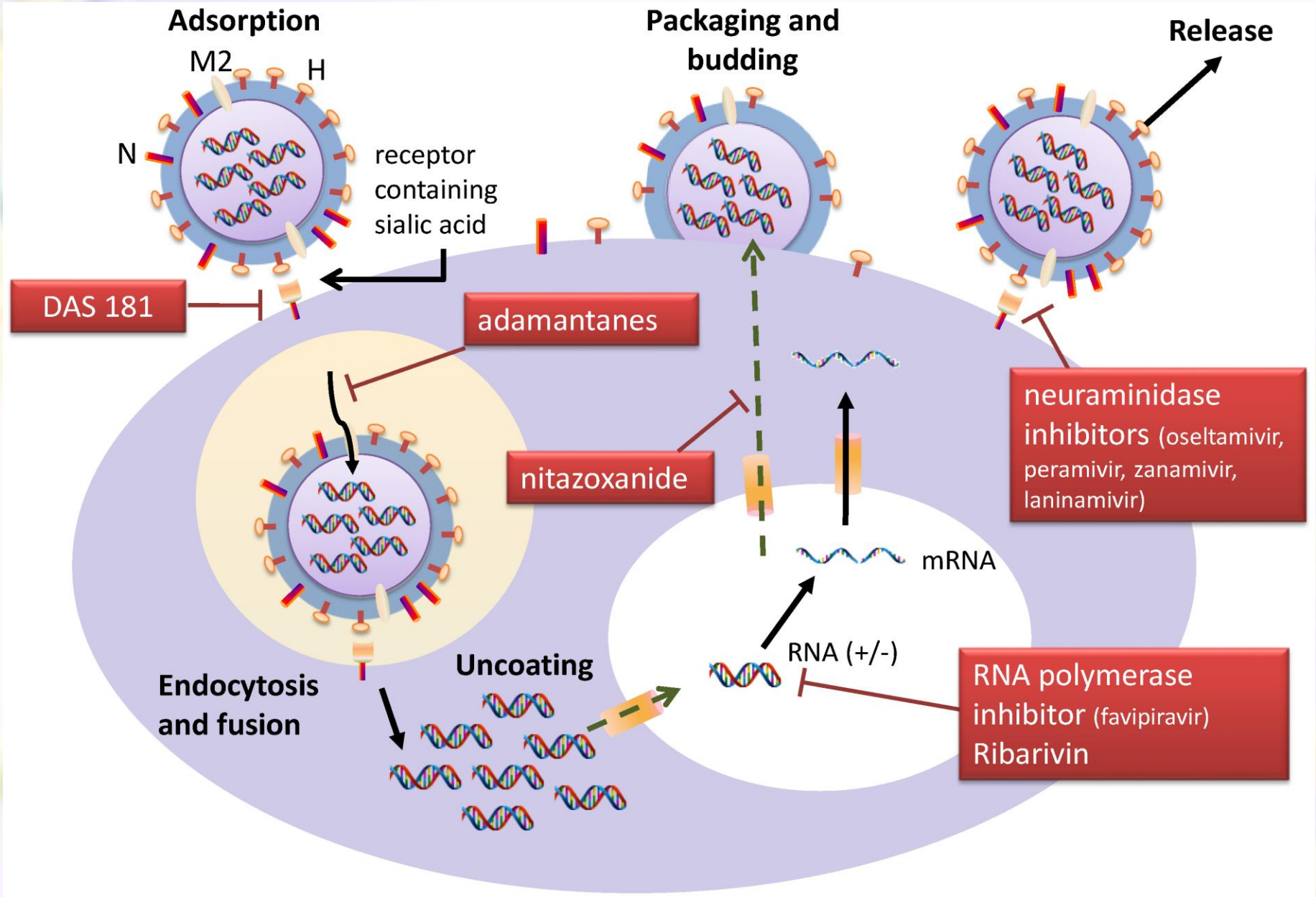
Ralenza (inhaled)

Amantadine (Older drugs)
Rimantadine

(Viral resistance to these is more common)

The action neuraminidase in replication of virions in influenza infection.




Adsorption
M2
H
N
receptor containing sialic acid
DAS 181
adamantanes
nitazoxanide
Packaging and budding
Release
neuraminidase inhibitors (oseltamivir, peramivir, zanamivir, laninamivir)
mRNA
RNA (+/-)
RNA polymerase inhibitor (favipiravir) Ribarivin
Endocytosis and fusion
Uncoating