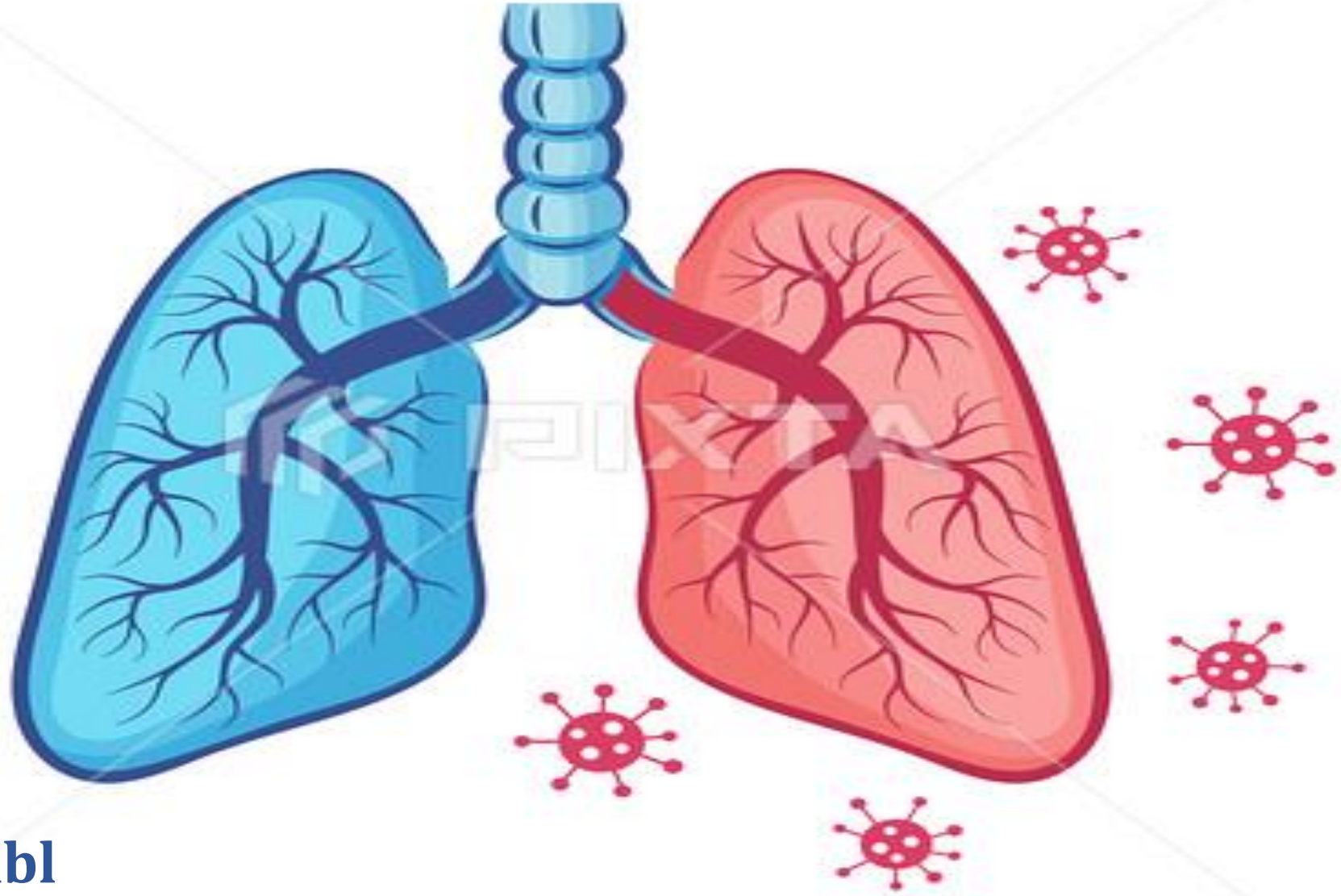
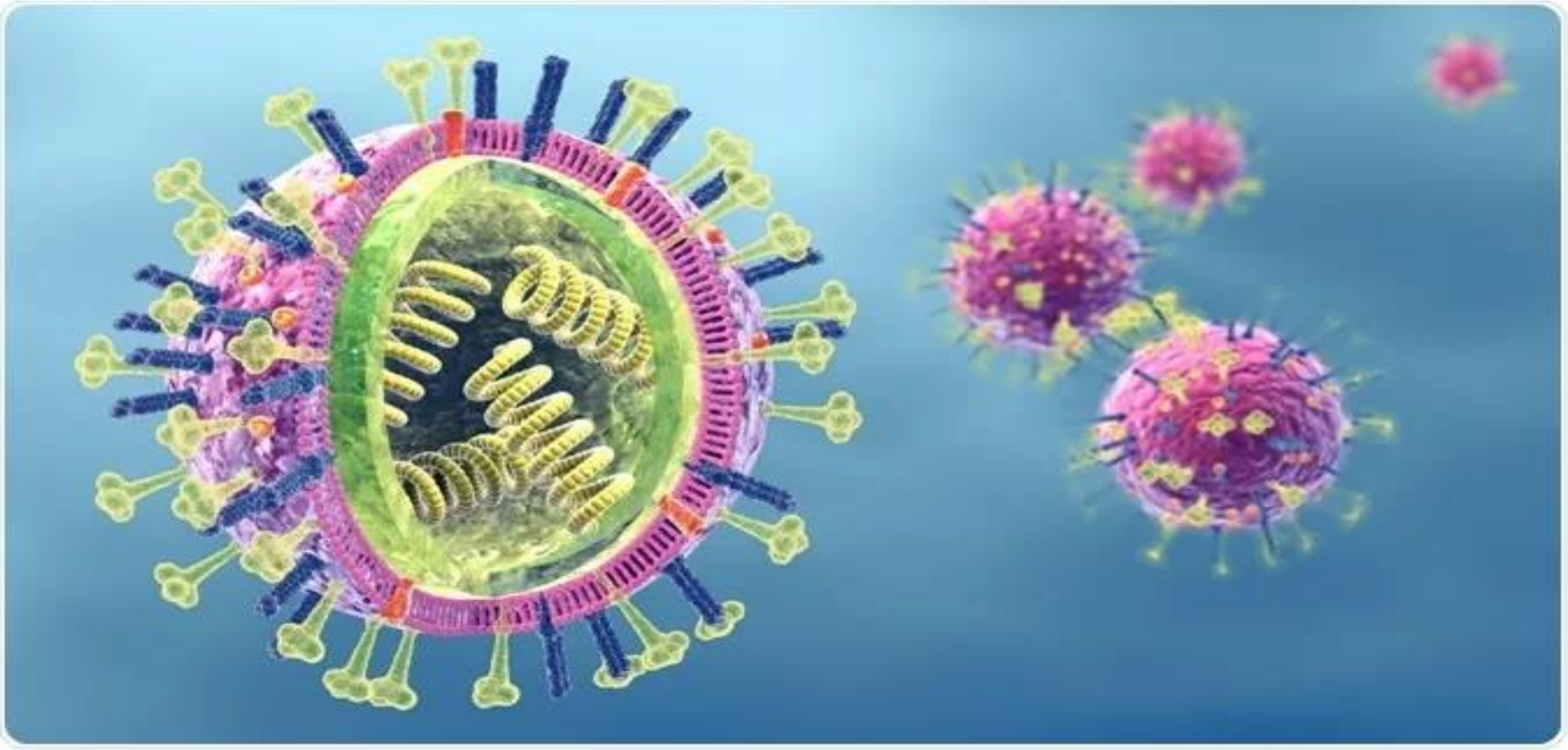
RESPIRATORY TRACT INFECTIONS -VI



By
Prof. Hala Tabl

MYXOVIRUSES



- They are **RNA viruses** which infect the respiratory tract.
- The term “myxo” refers to the affinity of these viruses to mucins (glycoproteins on the host cell surface).
- They are classified into:

A- Orthomyxoviruses: Influenza viruses types A, B, C.

B- Paramyxoviruses:

- Parainfluenza viruses.
- Respiratory syncytial virus.
- Mumps virus.
- Measles virus.

Property	Orthomyxoviruses	Paramyxoviruses
Viruses	Influenza A, B, and C viruses	Measles, mumps, respiratory syncytial, and parainfluenza viruses
Genome	Segmented (eight pieces) single-stranded RNA of negative polarity	Nonsegmented single-stranded RNA of negative polarity
Virion RNA polymerase	Yes	Yes
Capsid	Helical	Helical
Envelope	Yes	Yes
Size	Smaller (110 nm)	Larger (150 nm)
Surface spikes	Hemagglutinin and neuraminidase on different spikes	Hemagglutinin and neuraminidase on the same spike[1]
Giant cell formation	No	Yes

ORTHOMYXOVIRUSES

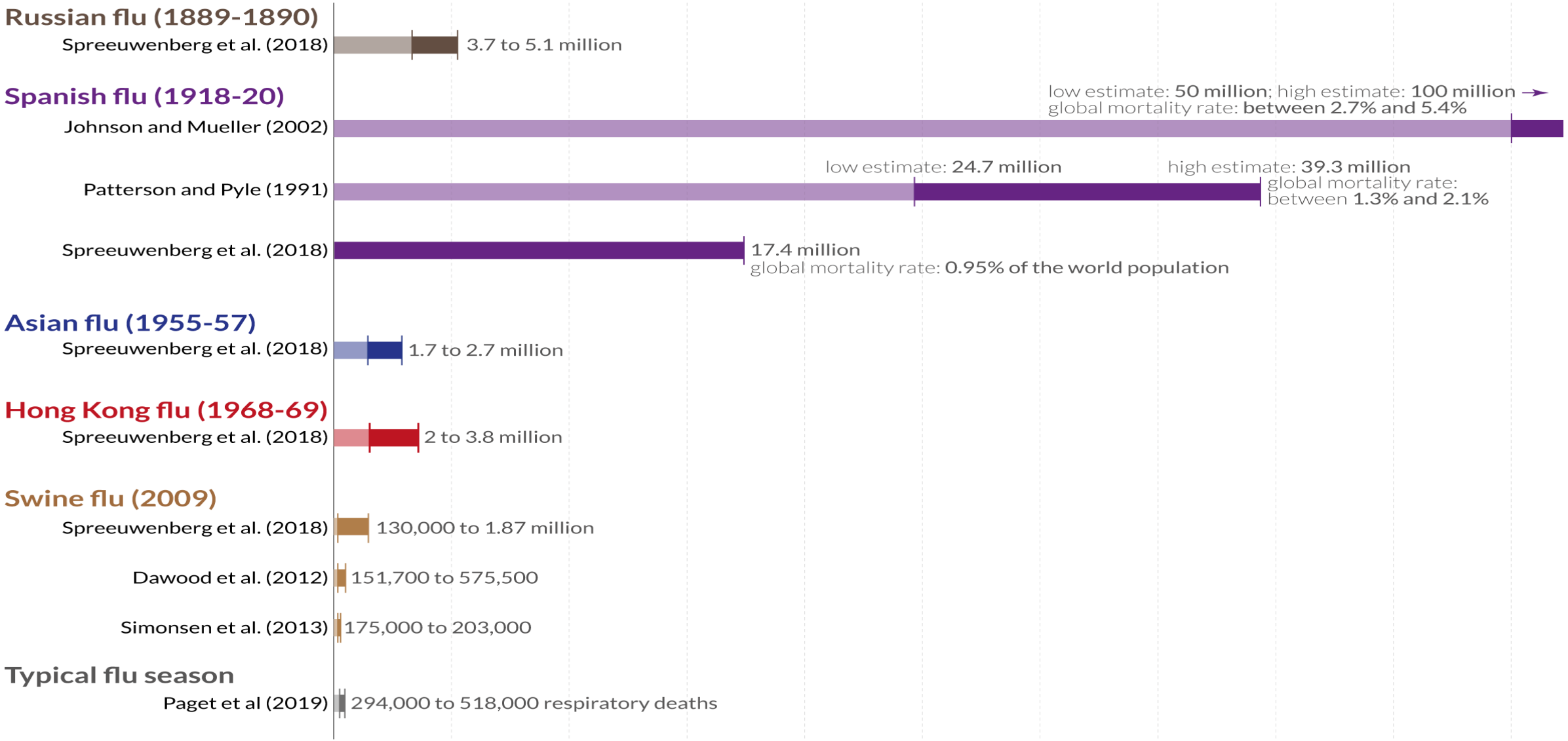
"INFLUENZA VIRUSES"

Influenza viruses are important human pathogens because they cause both outbreaks of influenza that sicken and kill thousands of people each year as well as infrequent but devastating worldwide epidemics (pandemics).

Global death toll from influenza pandemics

Shown are global mortality estimates from different research publications

Our World in Data

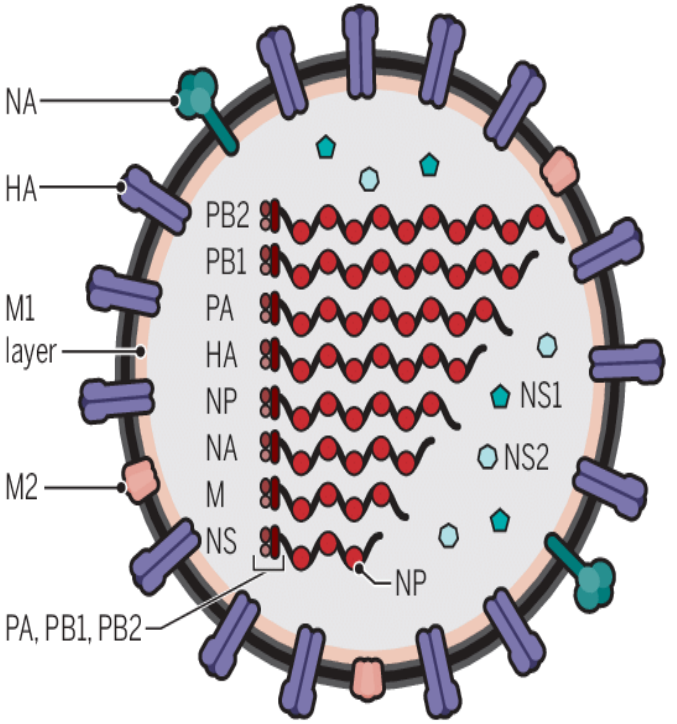


Morphological characters:

- Medium sized, Spherical.
- Structure:

1) Genome:

- Single-stranded RNA.
- **Segmented,** eight segments, each segments encode a certain viral protein.
- **Negative-polarity** (contains RNA-dependent RNA polymerase).



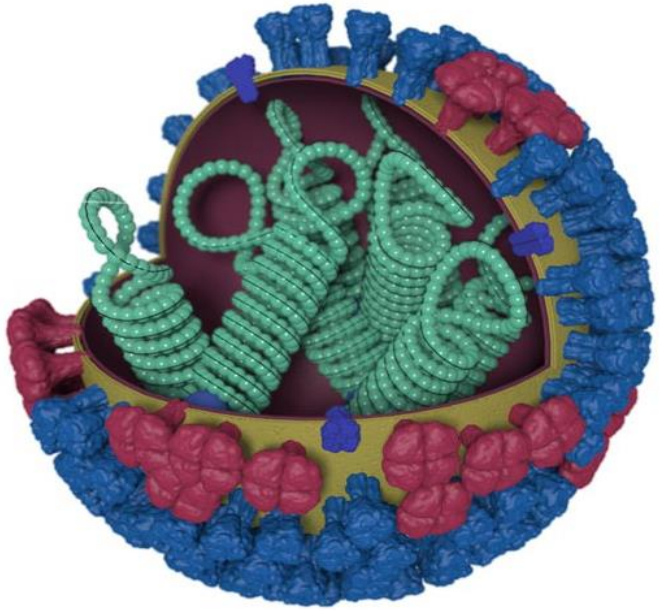
2) Helical capsid symmetry.

3) Enveloped:

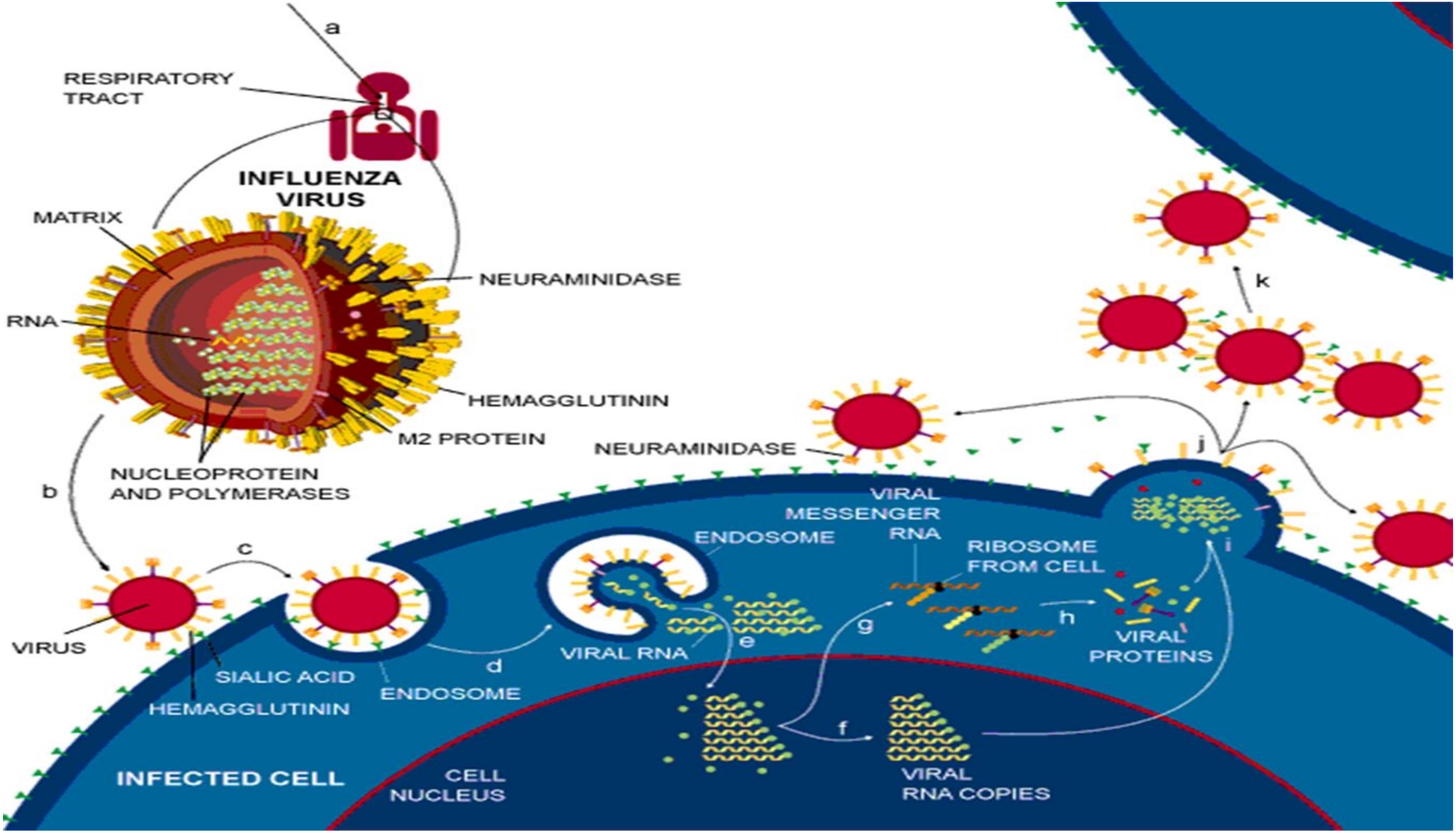
The envelope carries 2 types of projections:

Hemagglutinin spikes (HA) & Neuraminidase spikes (NA).

- Influenza virus (and retroviruses) are the only RNA viruses that have an important stage of their replication takes place in the **nucleus**.



Haemagglutinin spikes (HA)	Neuraminidase spikes (NA)
➢ Bind to the cell surface receptor (**neuraminic acid, sialic acid**) to initiate (**entry**) of the cell.	➢ Degrades the protective layer of mucus in the respiratory tract.
➢ Cleaved by cellular proteases to mediates **fusion** with endosomal membrane.	➢ Cleaves neuraminic acid (sialic acid) to **release** progeny virus from the cell.
	➢ Inactivate the **free receptor.**
➢ HA functions **at the beginning** of the life cycle.	➢ NA function **at the end** of the life cycle.
➢ It is the target of **neutralizing antibody** (i.e., antibody against the hemagglutinin **inhibits infection** of the cell).	➢ Antibody against the neuraminidase **NOT prevent infection**, it reduce amount of virus released, reducing spread of virus.
➢ **Agglutinates** red blood cells.	
➢ Encoded by segment 4.	➢ Encoded by segment 6.


a
RESPIRATORY TRACT
INFLUENZA VIRUS
MATRIX
NEURAMINIDASE
RNA
HEMAGGLUTININ
M2 PROTEIN
NUCLEOPROTEIN AND POLYMERASES
b
NEURAMINIDASE
k
j
i
VIRAL MESSENGER RNA
ENDOSOME
RIBOSOME FROM CELL
c
VIRUS
SIALIC ACID
HEMAGGLUTININ
ENDOSOME
d
VIRAL RNA
e
g
h
VIRAL PROTEINS
f
INFECTED CELL
CELL NUCLEUS
VIRAL RNA COPIES

Genetic variations of Influenza viruses:

Influenza viruses have two types of antigens:

(1) The internal ribonucleoprotein:

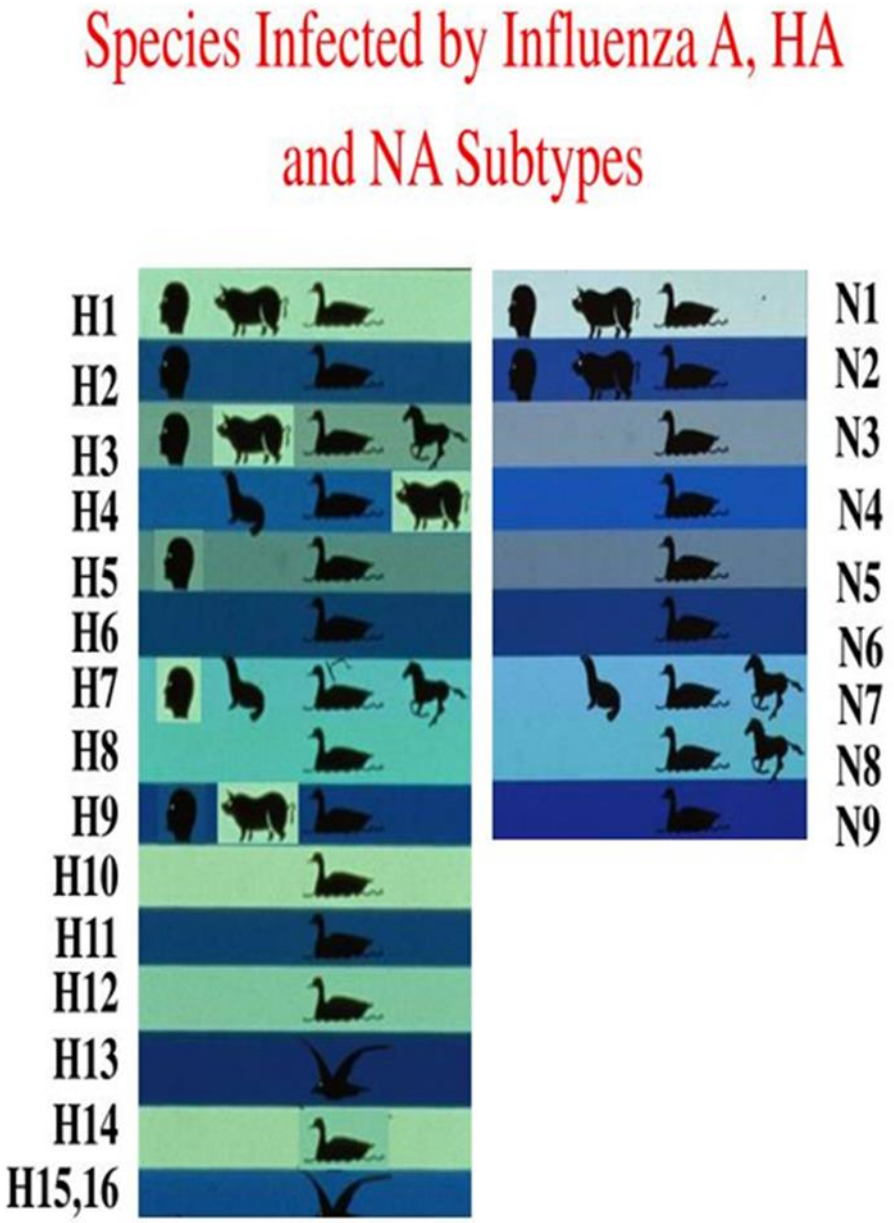
distinguishes influenza into three types; A, B, and C.

(2) The surface HA & NA:

- **Influenza A** virus has **16** antigenically distinct types of HA and **9** antigenically distinct types of NA.

  Some of these types cause diseases in humans, but most of them typically cause diseases in other **animal** species such as birds, horses, and pigs.

- **Influenza B** virus **almost exclusively infects humans**.

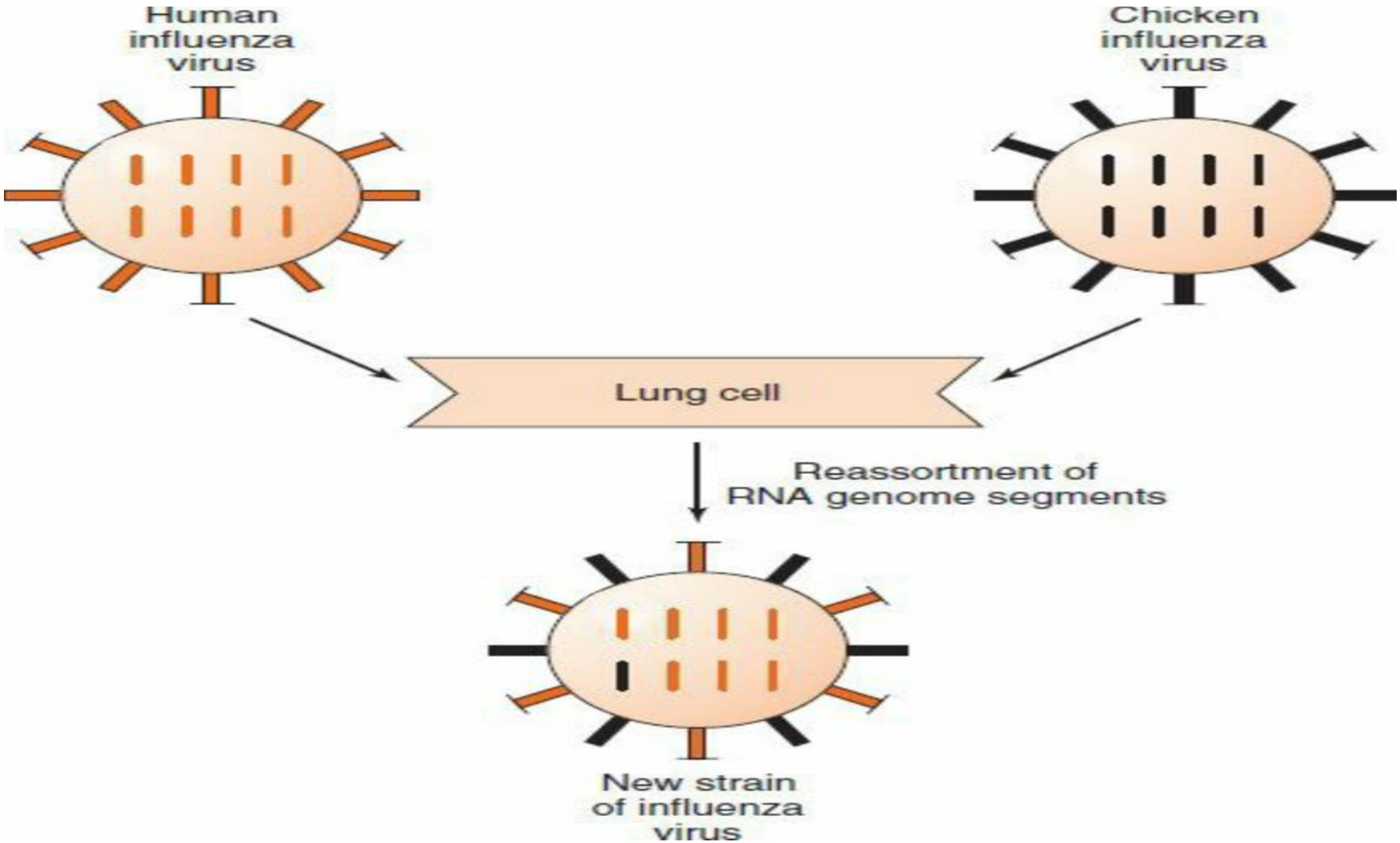


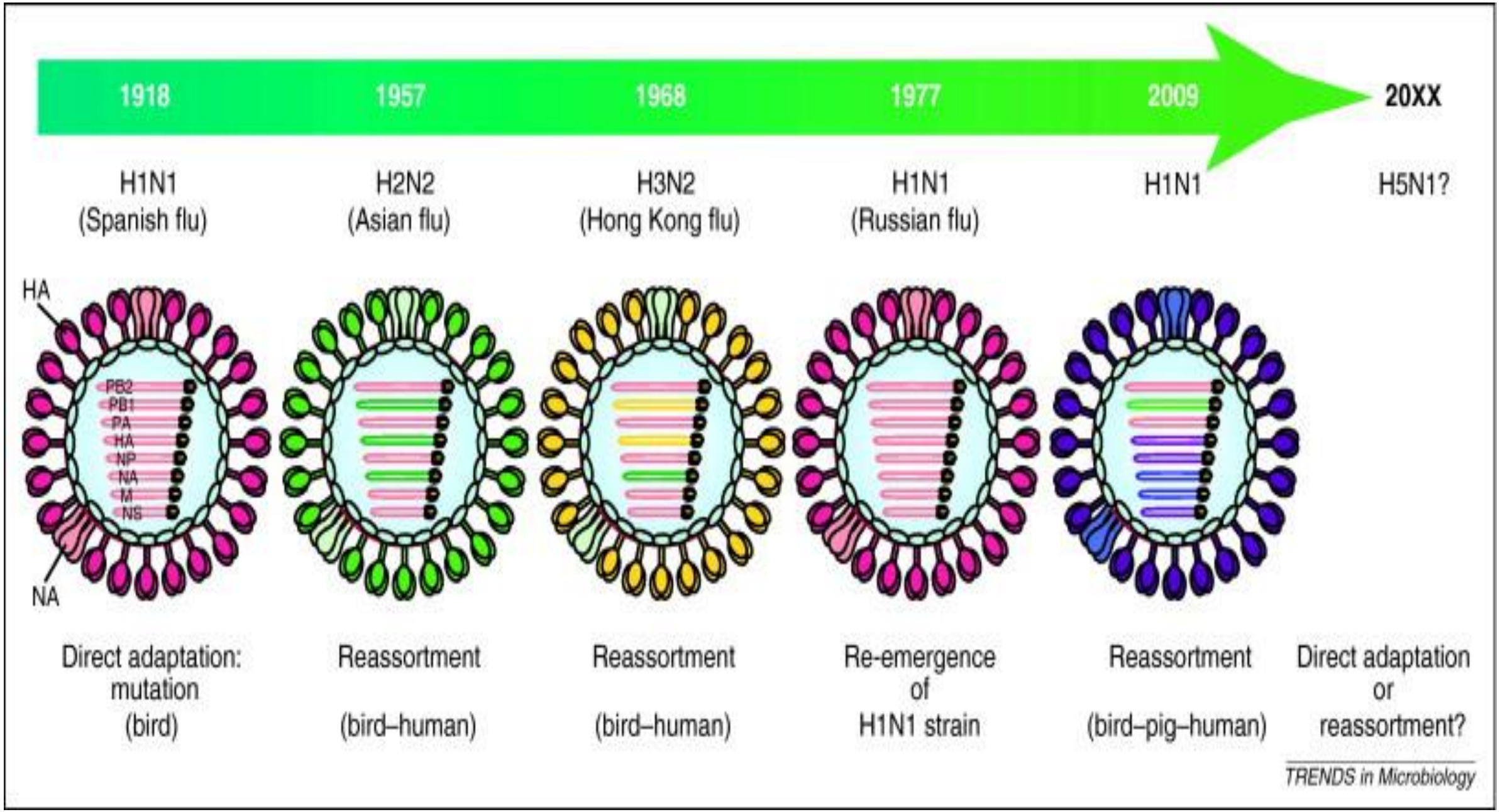
- **Influenza A & B,** are unique among viruses, that have the ability to change their surface antigens (HA and NA) from time to time. These genetic variations result in emergence of new strains and thus resulting in outbreaks, epidemics or pandemics.
- **Type C is almost antigenically stable,** does not cause major outbreaks.

  It can infect human and pigs.
- Two types of antigenic variations can occur **in type A & B**:
  - **Antigenic shift.**
  - **Antigenic drift.**

Antigenic shift:

- A **major change** in one or both of surface antigens of the virus.
- Results from **genetic reassortment** between two different virus strains (e.g. one of human and the other of animal origin; avian or swine), when a host cell is infected at "the same time" with both strains.
- In reassortment, **entire segments of RNA are exchanged**, each one of which codes for a single protein (e.g., hemagglutinin).
- Yielding a new strain showing **NO** serologic relationship with the parent strains, so that the preexisting immunity of population is **NO longer effective**.
- **Pigs** serve as important **"mixing vessel"** within which the human, avian, and swine viruses reassort.
- Occurs **only in type A** (Not in type B…..Why???)
- Responsible for influenza **pandemics (worldwide epidemics)**.
- Although occurs infrequently (10-40 years), it occurs suddenly, unpredictable and drastic devastating.


Human influenza virus
Chicken influenza virus
Lung cell
Reassortment of RNA genome segments
New strain of influenza virus


1918
1957
1968
1977
2009
20XX
H1N1
(Spanish flu)
H2N2
(Asian flu)
H3N2
(Hong Kong flu)
H1N1
(Russian flu)
H1N1
H5N1?
HA
PB2
PB1
PA
HA
NP
NA
M
NS
NA
Direct adaptation:
mutation
(bird)
Reassortment
(bird–human)
Reassortment
(bird–human)
Re-emergence
of
H1N1 strain
Reassortment
(bird–pig–human)
Direct adaptation
or
reassortment?
TRENDS in Microbiology

Antigenic drift:

- A **minor change** in the surface antigenic structure.
- Result from **single spontaneous mutations** in the genome RNA.
- Yielding a strain retaining **a degree of serologic relationship** with the circulating parent strain.
- Occurs in **both types, A and B.**
- Responsible for **yearly influenza outbreaks & epidemics**.

Immunity against Influenza virus:

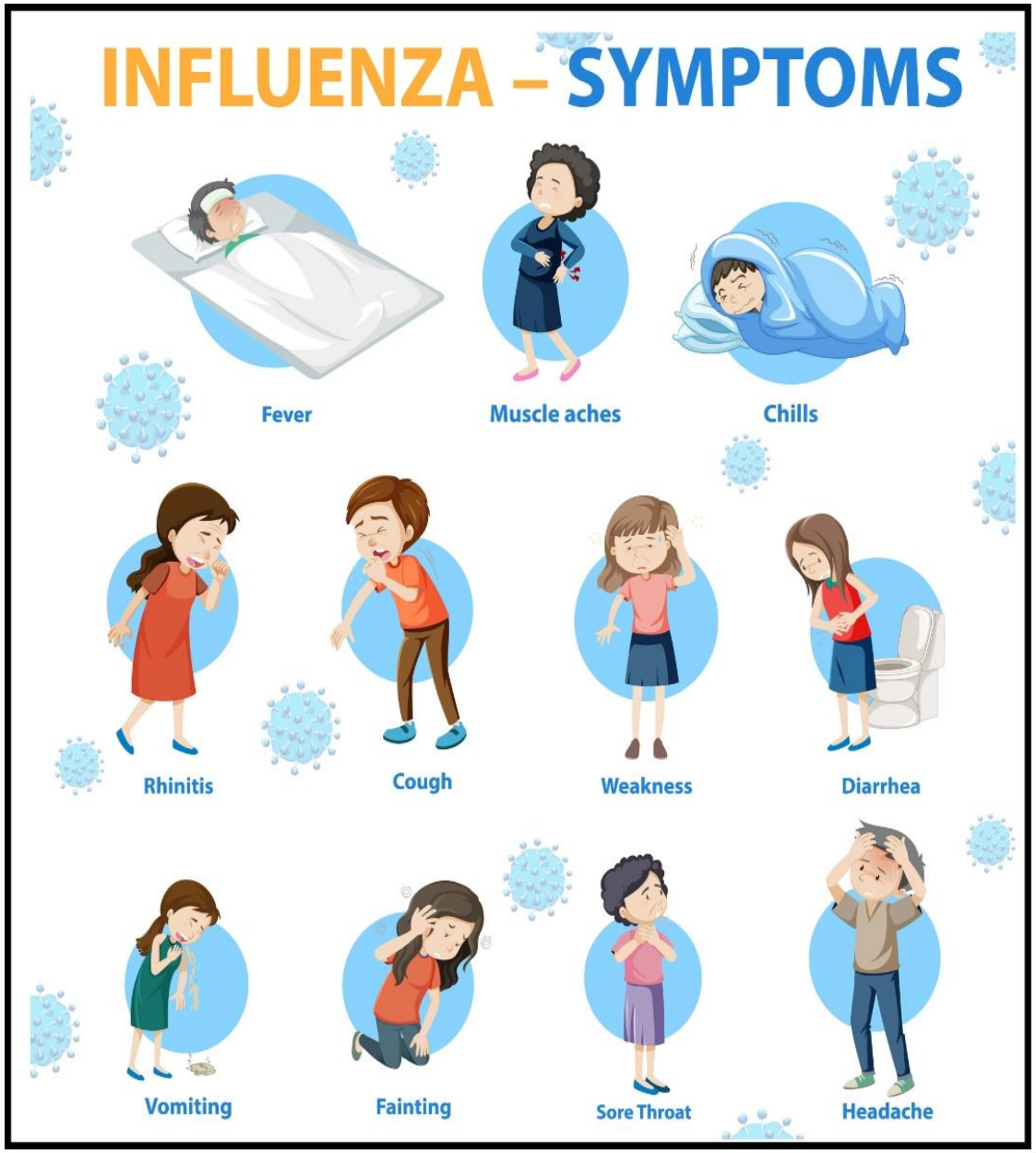
- Immunity depends mainly on **secretory IgA** in the respiratory tract.
- Cytotoxic T cells also play a protective role.
- Antibody against the **hemagglutinin neutralizes the infectivity** of the virus (**prevents disease**).
- Antibody against the **neuraminidase** does **NOT neutralize infectivity** but does reduce disease by decreasing the amount of virus released from the infected cell and thus **reducing spread** of the virus to adjacent cells.
- The disease is **NOT followed by long-lasting immunity** because the viruses undergo frequent antigenic variations.

Pathogenesis:

- Influenza occurs primarily in the **winter months**.
- The virus is transmitted by **airborne respiratory droplets**.
- It causes inflammation in pharynx, larynx, trachea, and bronchi. Pneumonia, may also occur.
- The infection is limited primarily to the respiratory tract because **the proteases that cleave the hemagglutinin are located in the respiratory tract.**
- Although **viremia rarely occurs**, influenza associated with systemic symptoms, e.g. severe myalgias. The systemic symptoms are attributed to **cytokines** circulating in the blood.

Clinical Findings:

- Incubation period: 24 to 48 hours.
- The symptoms usually resolve spontaneously in 4 to 7 days.
- “Severe myalgia coupled with respiratory symptoms are typical of influenza”.



Complications:

Very young, elderly, immunocompromised, those with heart or lung diseases are more prone.

- Influenzal pneumonia.
- Secondary bacterial pneumonia (*Streptococcus pneumonia*, *Hemophilus influenzae*, *Staphlyococcus aureus).*
- **Reye's syndrome:**
  - ✓ Characterized by encephalopathy and liver degeneration.
  - ✓ Is a rare, life-threatening complication in children following some **viral infections,** particularly influenza and chickenpox.
  - ✓ **Aspirin** given to reduce fever in viral infections has been implicated in the pathogenesis of Reye's syndrome.

Laboratory Diagnosis:

Specimens: nasal or throat washings, nasal or throat swabs, or sputum.

1. Detection of viral antigen: by **rapid** test as ELIZA or IF.

The rationale for using the rapid tests is that treatment with the neuraminidase inhibitors should be instituted within 48 hours of the onset of symptoms.

2. Serology: Detection of specific antibodies.

3. Virus isolation: Sample is inoculated in:

Monkey kidney tissue cultures or Amniotic cavity of chick embryo:

The virus is detected by hemagglutination or hemadsorption tests and typed by hemagglutination or hemadsorption inhibition with specific antisera.

Treatment:

1) Amantadine and its analogues, rimantadine (given orally):

- Effective **only against influenza A**, NOT against influenza B.
- These drugs act by inhibiting uncoating of the virus.

2) Neuraminidase inhibitors: Oseltamivir (Tamiflu, Oral) and zanamivir (Relenza, Inhalant):

- Effective against **both influenza A and B** viruses.
- Act by inhibiting the release of virus from infected cells, and therefore reduce the chance of spread from one cell to another.
- To be effective, these drugs must be given **within 48 hours of the onset** of symptoms. They reduce the duration of symptoms by 1 to 2 days.

Note that, theses drugs approved for both treatment and prevention of severe manifestations and complications and so, should be **considered in high risk groups.**

Prophylaxis: Influenza Vaccines

- Contains **both influenza A and B viruses**.
- The vaccine is usually **reformulated each year** to contain the current antigenic strains.
- These vaccines especially **recommended for those at high risk.** Yearly boosters are recommended and should be given shortly before the flu season (e.g., in October).
- **Types** of influenza vaccines:

1- Inactivated whole virus vaccine: given by injection

2- Subunit (subvirion) vaccine: contain purified HA and NA glycoproteins.

3- Live attenuated vaccine: given intranasally.

- The virus replicate in the cooler (33°C) nasal mucosa where they induce IgA.
- The live vaccine should not be given to pregnant women or to immunocompromised individuals.

Disadvantages of influenza vaccines:

1- Immunity is **NOT absolute &NOT long lasting** (moderate degree of protection 50-80%).

2- Immunity is only for the virus strain contained in the vaccine.

3- Because vaccine is **prepared in eggs**, the egg proteins may lead to **hypersensitivity**.

In 2012, Food and Drug Administration (FDA) approved two types of vaccines:

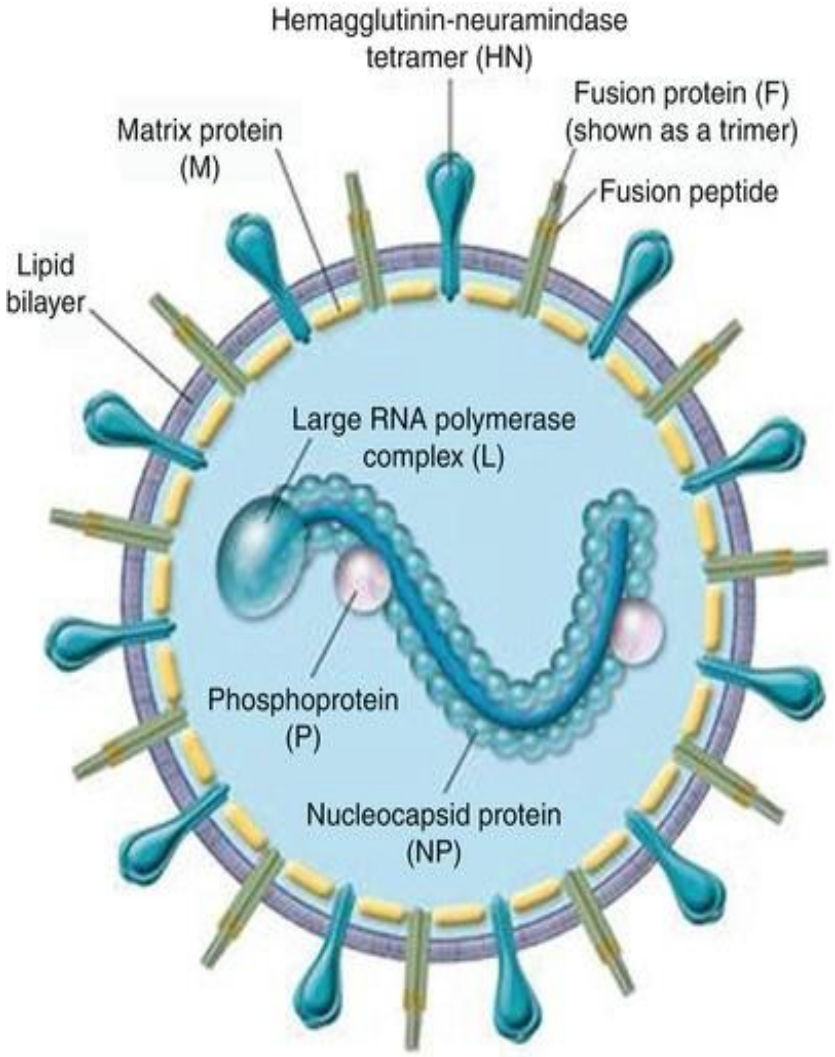
- A killed influenza vaccine (Flucelvax) made in calf kidney cell culture.
- A recombinant vaccine (Flublok) made by genetic engineering (contains purified hemagglutinin).

These vaccines can be given to those with egg allergy.

PARAINFLUENZA VIRUS

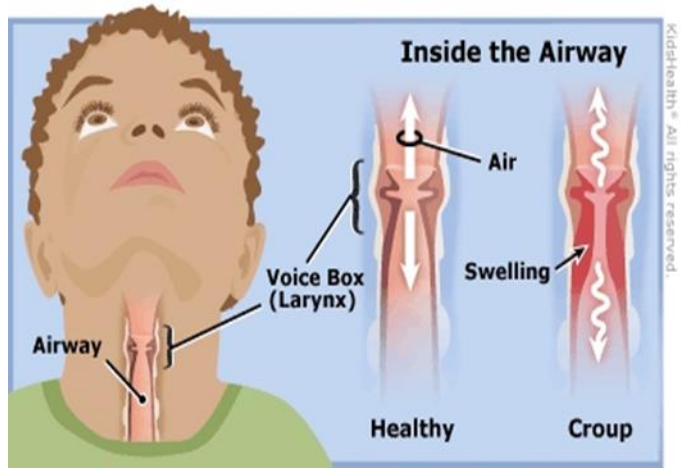
Morphological characters:

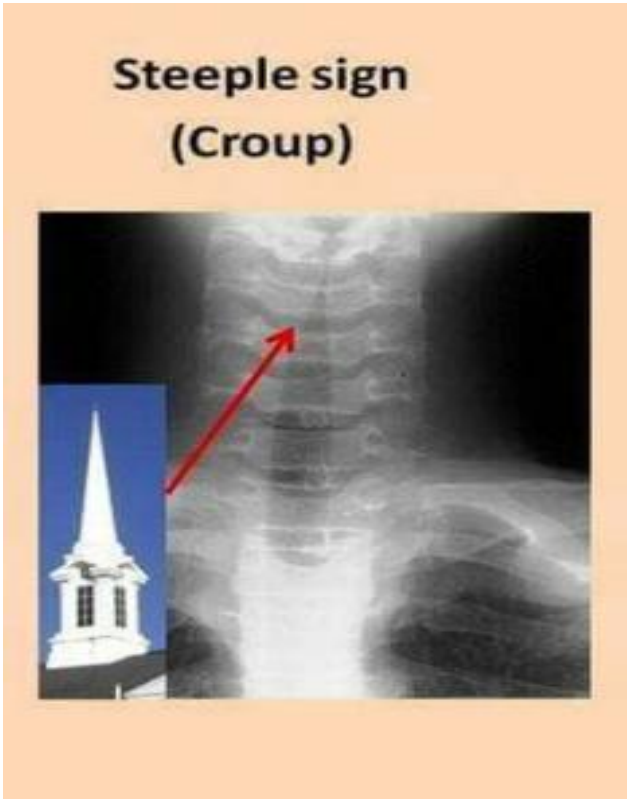
- Medium sized, Pleomorphic.
- **Genome:**
- **Non-segmented** single-stranded RNA genome.
- **Negative-polarity** (RNA-dependent RNA polymerase).
- **Helical capsid symmetry.**
- **Enveloped:**
- The envelope carries 2 types of spikes:
  Hemagglutinin-Neuraminidase (HN) on the same spike and **Fusion (F)** on a separate spike.
- F protein mediates the formation of multinucleated giant cells (syncytia).
- Replication takes place in the **cytoplasm**.



Pathogenesis & Clinical Findings:

- These viruses are transmitted via respiratory droplets.
- There are four types, 1, 2, 3, 4 and two subtypes 4a and 4b.
- Parainfluenza viruses (**type 1 and 2):** are **major causes of croup (acute laryngo-tracheobronchitis)** in children younger than 5 years of age. Clinically it presents with fever, barking cough, hoarseness of voice and inspiratory stridor due to mucosal edema.
- Parainfluenza viruses (**type 3):** Bronchiolitis and pneumonia in young children and infants.
- Parainfluenza virus (**type 4):** rarely causes disease, except for the common cold.





Inverted V sign

Laboratory Diagnosis:

1. Detection of viral antigen: in respiratory secretions by IF or ELISA.

2. Virus isolation: samples are inoculated in monkey kidney tissue cultures. The virus is detected by hemadsorption of human group O RBCs or by IF. Typing of the virus is done by hemadsorption inhibition test by standard antisera.

3. Serology: Neutralization, HI, CF tests can be used.

Treatment & Prevention:

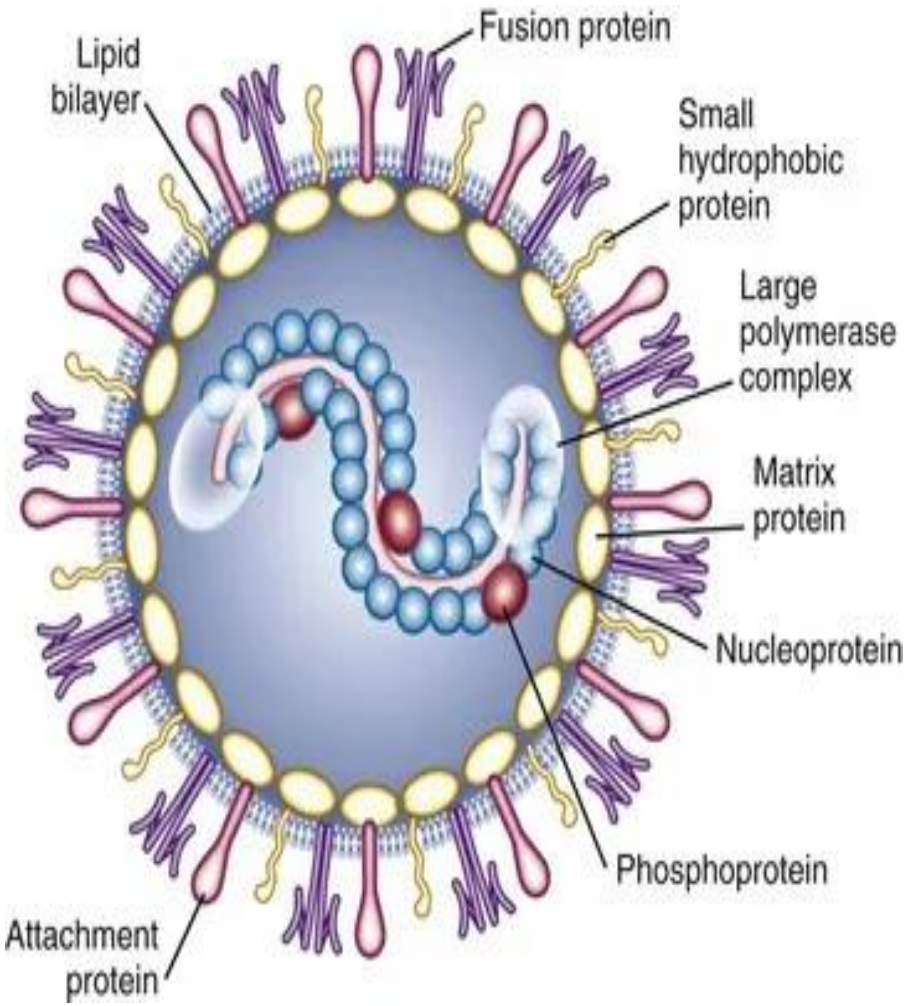
There is neither specific antiviral therapy. **NO vaccine.**

Management of croup.

RESPIRATORY SYNCYTIAL VIRUS

Morphological characters:

- Medium sized, Pleomorphic.
- **Genome:**
- **Non-segmented** single-stranded RNA genome.
- **Negative-polarity** (RNA-dependent RNA polymerase).
- **Helical capsid symmetry.**
- **Enveloped:**
- Its surface spikes are **fusion (F), attachment (G) NOT** hemagglutinins or neuraminidases
- The F protein causes cells to fuse, forming **multinucleated giant cells (syncytia)**, which give rise to the name of the virus.
- Replication takes place in the **cytoplasm**.



Epidemiology:

- RSV has two serotypes, designated subgroup A and subgroup B.
- Transmission occurs via respiratory droplets and by direct contact of contaminated hands with the nose or mouth.
- RSV causes outbreaks of respiratory infections every winter and also causes outbreaks of respiratory infections in hospitalized infants and in childcare nurseries.
- RSV occurs worldwide, and virtually everyone has been infected by the age of 3 years.
- Multiple infections can caused by RSV, indicating immunity is incomplete.

Clinical Findings:

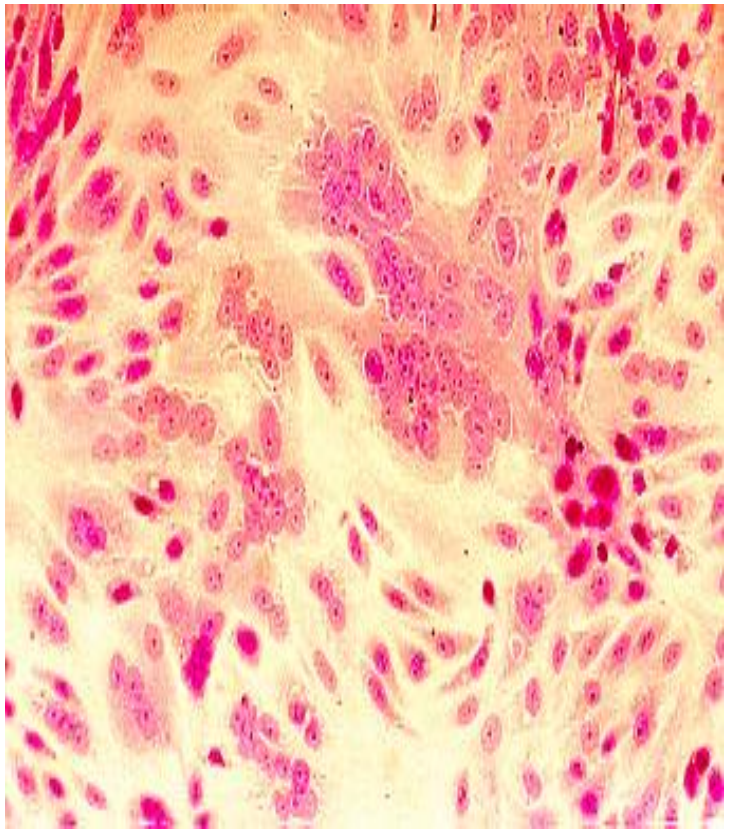
- RSV is **the most important** cause of lower respiratory tract diseases such as **bronchiolitis and pneumonia in infants < 1 year**.

  (Cough, wheezing and respiratory distress with hypoxia & hypercapnia).

  The disease is more severe in infants with congenital heart disease & congenital immunodeficiency disease.
- RSV is also an important cause of otitis media in young children.
- In older children and young, healthy adults, RSV causes respiratory tract infections such as the common cold and bronchitis.

Laboratory Diagnosis:

1. **Detection of viral antigen:** in respiratory secretions by IF or ELISA.
2. **Virus Isolation:** respiratory secretions are inoculated in the HeLa or HEP-2 cells. The characteristic CPE of **syncytia of multinucleated giant cells** can be seen. The presence of virus is confirmed by IF.
3. **Serology:** serum antibodies can be assayed by IF, ELISA, CF and neutralization tests.



Treatment & Prevention:

- Aerosolized ribavirin is recommended for severely ill hospitalized infants.
- Bronchodilators, corticosteroids and oxygenation in severe cases.
- **There is NO vaccine.**

Thank you