INFLUENZA

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General Consideration

Season is from late November to late March

- Acute viral respiratory illnesses are among the most common of human diseases, accounting for one-half or more of all acute illnesses.
- Influenza is an acute respiratory illness caused by infection with influenza viruses.
- One of the most important Emerging and Reemerging infectious diseases.
- The illness affects the upper and/or lower respiratory tract and is often accompanied by systemic signs and symptoms such as fever, headache, myalgia, and weakness.
- Outbreaks of illness of variable extent and severity occur nearly every year. Such outbreaks result in significant morbidity rates in the general population and in increased mortality rates among certain high-risk patients, mainly as a result of pulmonary complications.

Influenza Mainly affects upper respiratory tract, rarely involve lungs (The respiratory tract) exception to this is H5N1 (avian influenza) affects mainly lower respiratory tract and it's a severe disease, not effectively transmitted between humans

Myxoviruses

Remember (octo) which means 8.

Orthomyxo viruses

This virus has 8 segments (RNA)

- ***Smaller***
- ***Segmented RNA genome*** (very imp)
- ***Liable to Agic variation***

Paramyxo viruses

- ***Larger***
- ***Single piece of RNA***
- ***Not liable to Agic variation***

Influenza viruses

- **Parainfluenza**
- **Mumps vairus**
- **Measles virus**
- **Respiratory syncytial virus** → Most common cause of bronchiolitis

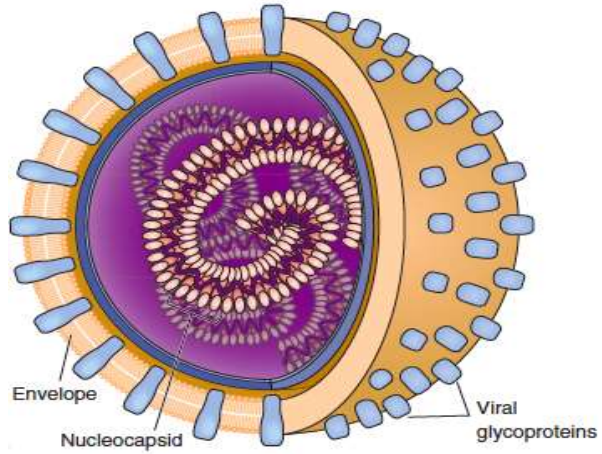
Myxo = affinity to mucin

Characteristics of Influenza Virus

- Pleomorphic
- Types (A, B, C), (D)
- Diameter 80 - 120 nm
- Pleomorphic, spherical, filamentous particles
- Single-stranded RNA
- Segmented genome, 8 segments in A and B
- Hemagglutinin and Neuraminidase on surface of

Affect Humans ← Types (A, B, C), (D) → Doesn't affect Humans

Typing based on:
1)Nucleocapsid(ribonucleoprotein)
2)Matrix protein



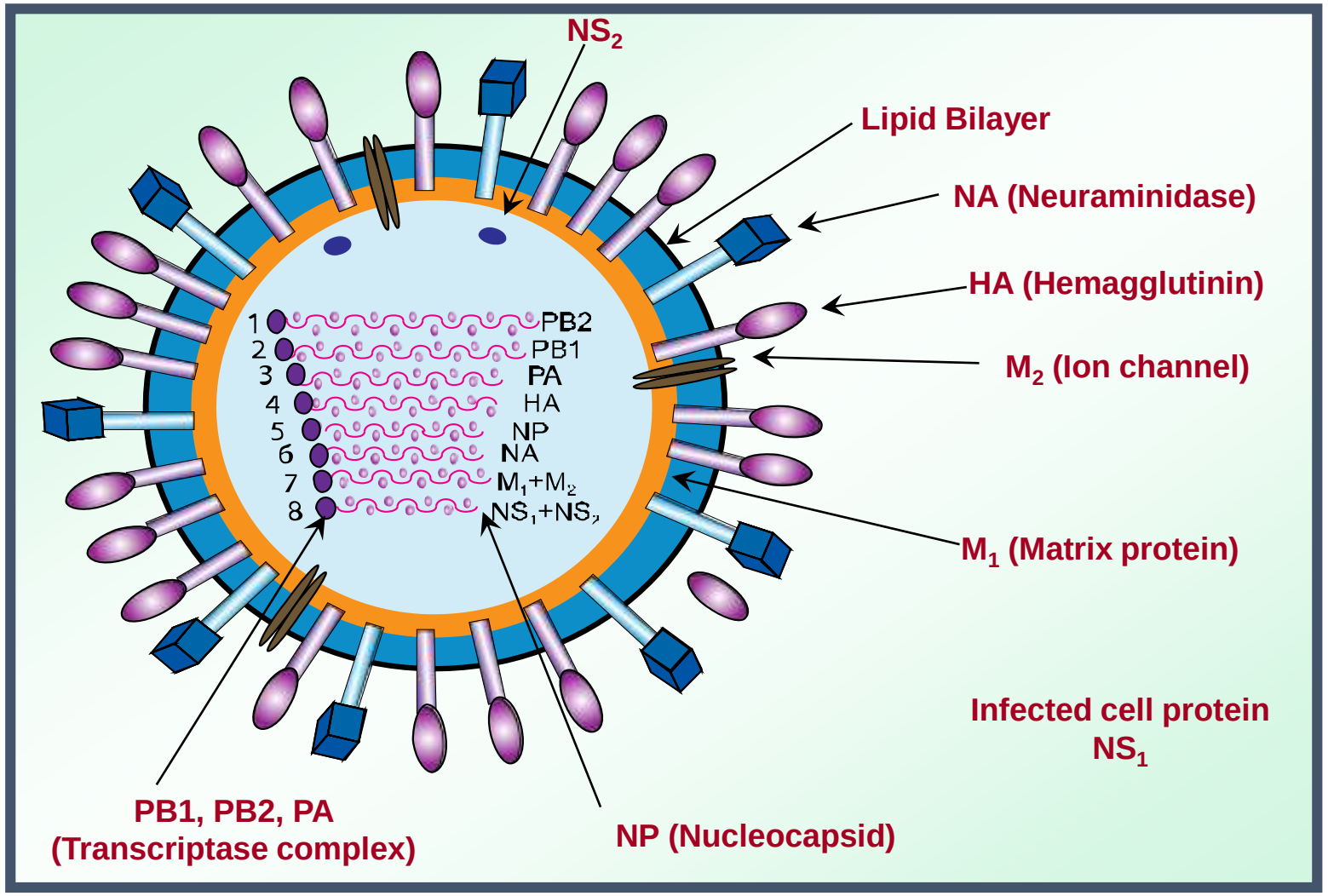
the virion

Influenza Structure

- 8 segments of single-stranded RNA
- Segments combine with nucleoprotein (NP) to form the ribonucleoprotein core
- M1 matrix protein surrounds the core
- Lipid coat surrounds the matrix
- Embedded in the lipid membrane are 2 important viral proteins: hemaglutinin (HA) and neuraminidase (NA)
- RNA segments + nucleocapsid = a nucleocapsid with helical symmetry

Influenza A Virus Structure

8 RNA segments



Antigenic structure& Classification

I- Type Specific Ag (core Ag):

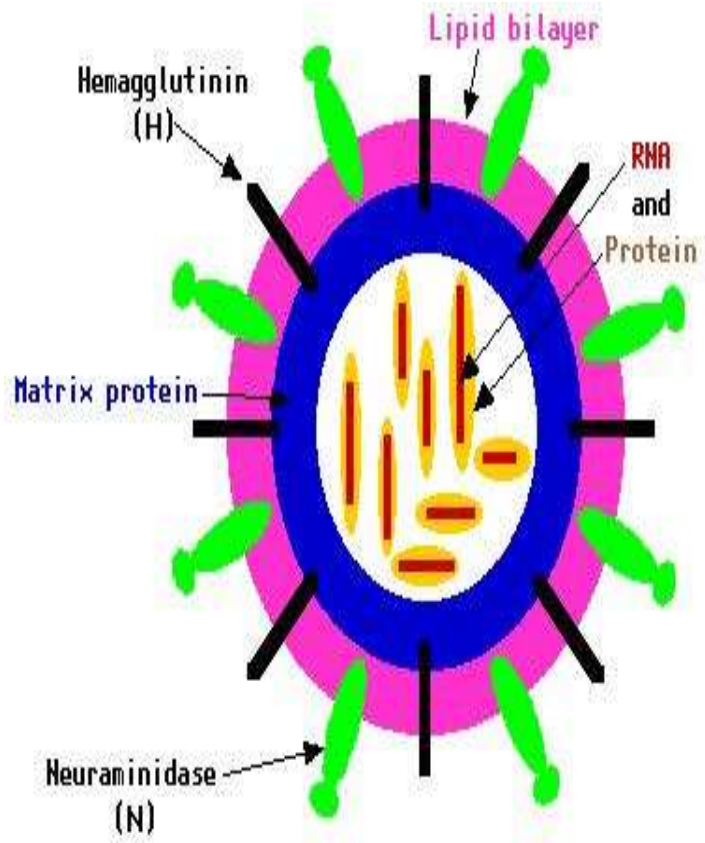
Most common

- Three serotypes: A,B & C according to internal structure ptns (nucleocapsid & matrix). These ptns don't cross react

II- Strain (subtype) specific Ag:

- Two surface glycoptns, HA & NA are used to subtype the virus
- Influenza strains are named after their types of HA & NA surface ptns e.g. H1N1

Circulating Now between Humans H1N1 H2N3

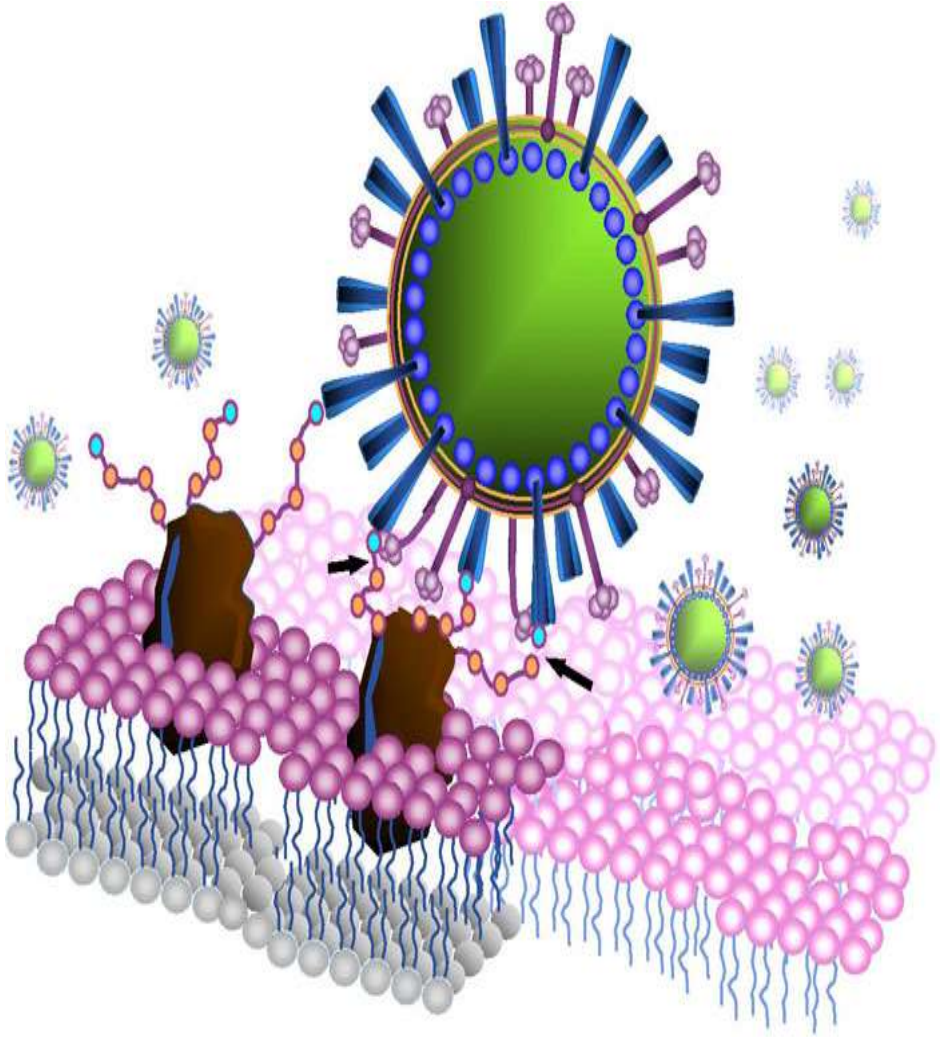


Works on neuraminic acid a component of the mucus

Neuraminidase (N)

Cleavage and spreading of the infection

Cleaves neuraminic acid to release virus progeny from infected cells

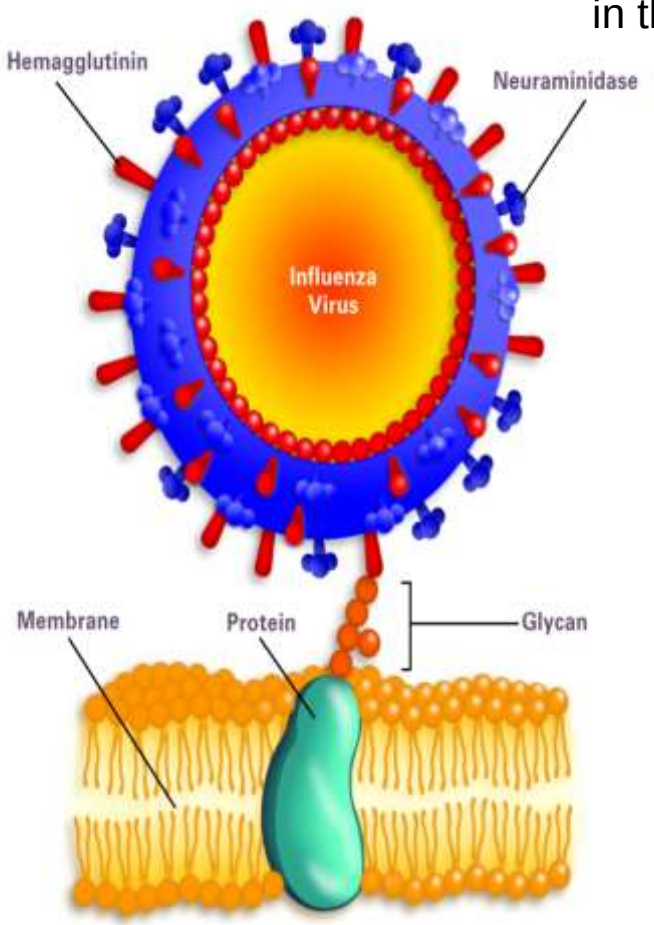


Has the ability to agglutinate RBCs of different species

Haemagglutinin (H)

Binds to host cell surface receptor

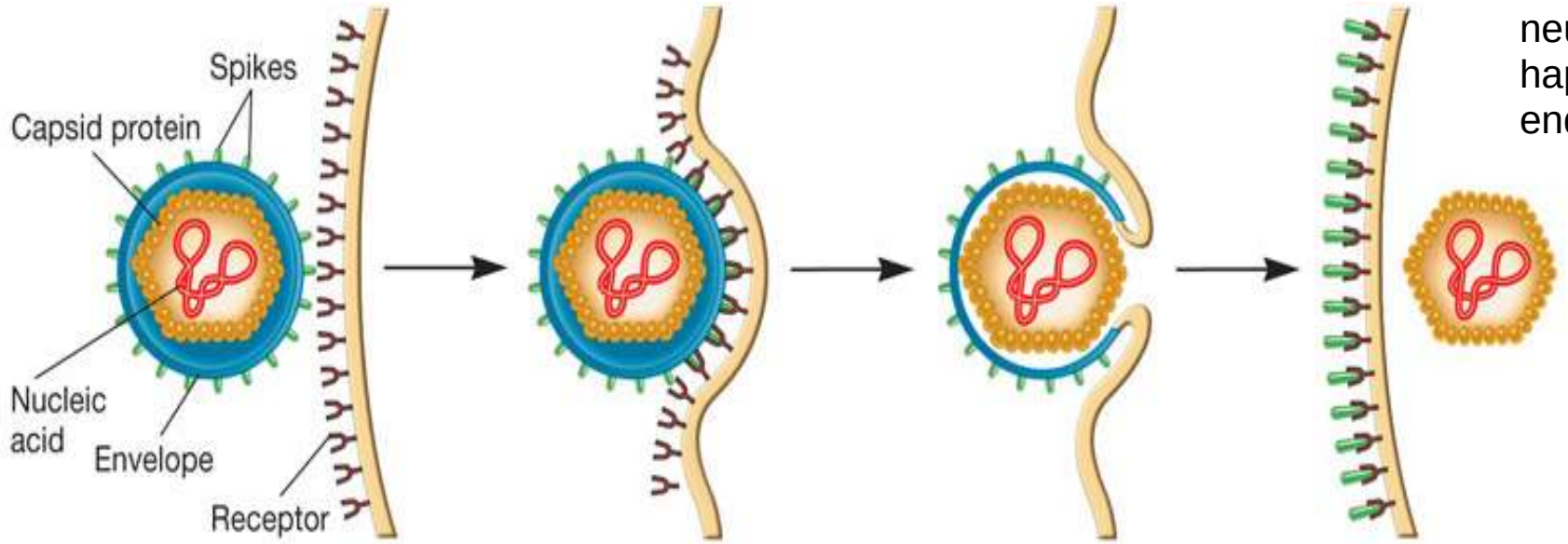
Initiation of infection, binds to sialic acid found in mucus secreting cells in the respiratory tract



Fusion with Host Membrane

Receptor(sialic acid)-mediated endocytosis

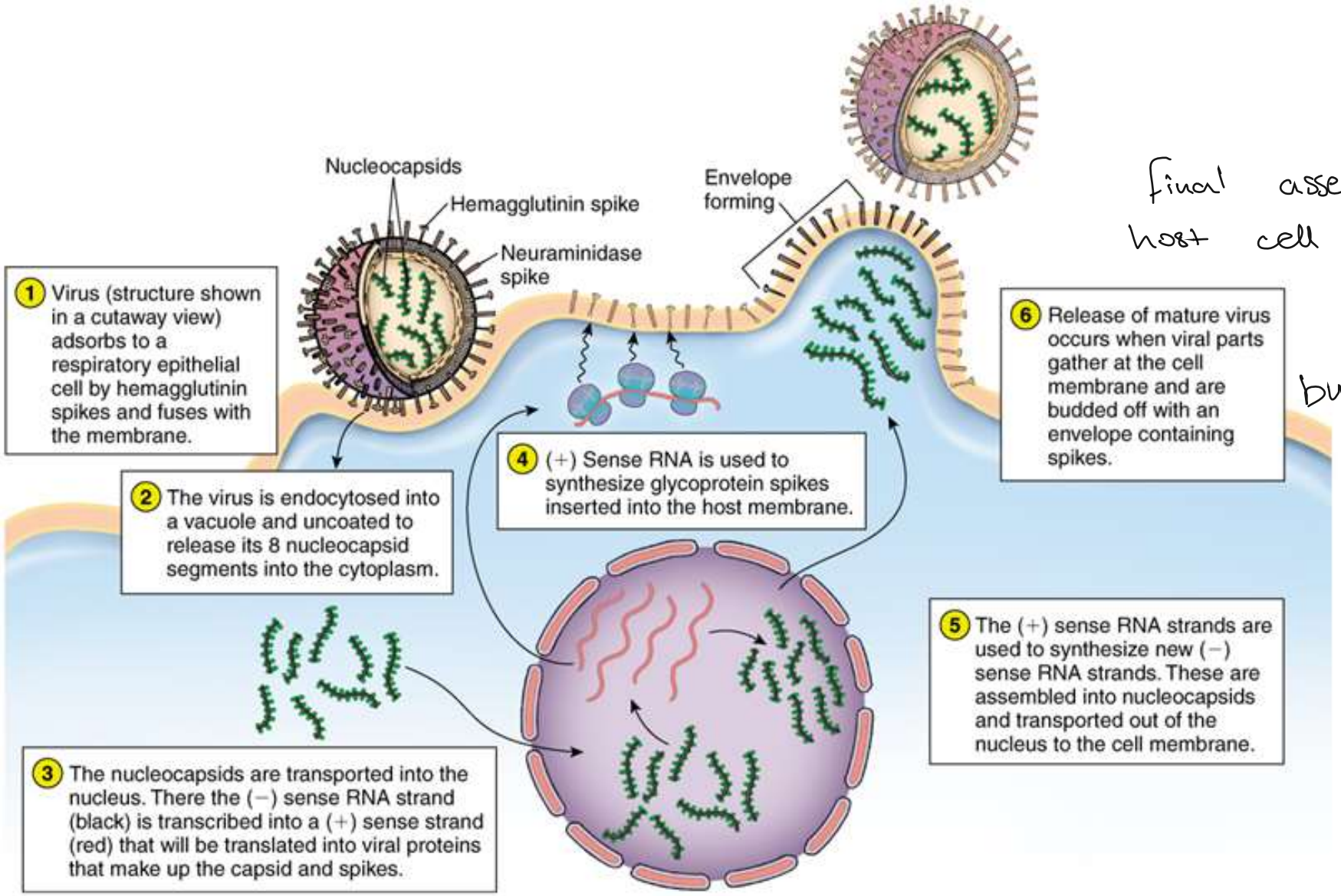
Replication in the nucleus and the synthesis of haemagglutinin and neuraminidase happens in the endoplasmic reticulum



(a) Entry of enveloped virus by fusing with plasma membrane

The flu virus binds onto sugars on the surfaces of epithelial cells such as nose, throat, and lungs of mammals and intestines of birds.

Influenza virus Replication cycle



final assembly at the host cell membrane.

budding

Types of Influenza virus

Result in epidemic outbreaks pandemic

I- Type A virus: Most common + Most severe

- Infects humans as well as animals
- Undergoes continuous Antigenic variations (shift) because The host Reservoir is very wild.
- Many animal species have their own influenza A virus
- Pigs & birds are the reservoirs playing a role in occurrence of influenza epidemics

Swine ←

Type B+C
only Humans

type A
Humans + Animals

Severity:
A > B > C

Antigenic stability
C > B > A
Most Stable

Types of Influenza virus

II- Type B virus: Minor outbreaks/epidemics-No pandemics

- **Causes milder disease**
- **Infects human only**
- **Only undergo antigenic drift**
- **Not known to undergo antigenic shift**

→ only sporadic cases.

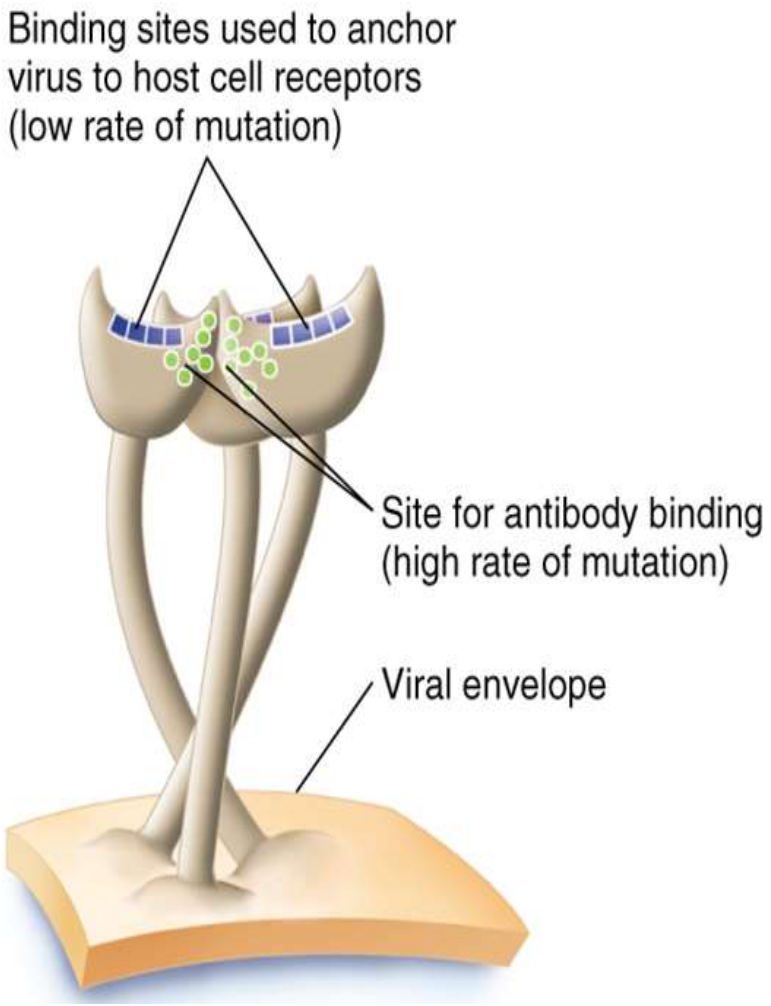
III- Type C virus: 7 segments (lacks Neuraminidase)

- **Agntigenically stable**
- **Known to cause only minor respiratory disease; probably not involved in epidemics**

Hemagglutinin

→ Mediate fusion (initiation of infection).

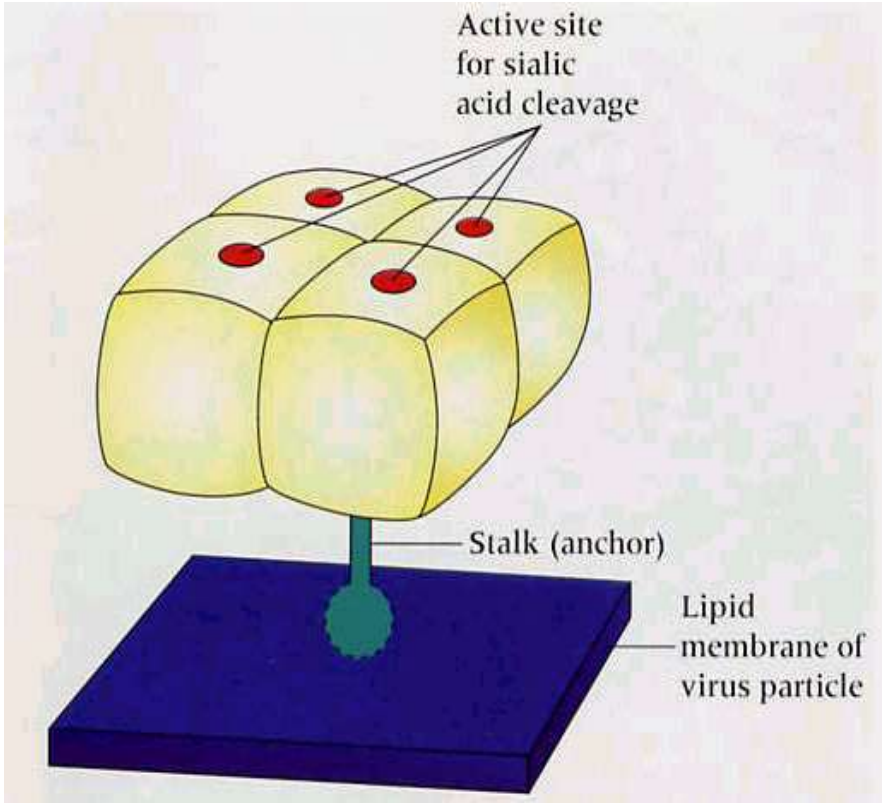
Of identical dimers (HA1-HA2)



- **Structure**: trimer of "lollipops" with fibrous stem anchored in the membrane and globular protein sphere containing the sialic acid receptor site
- **Function:** Sialic acid receptor sites bind to host cell's glycoproteins allowing for infection to occur

Neuraminidase → Spreading of infection

With identical monomers



- **Structure**: Box-shaped tetramer with stalk that anchors it to the cellular membrane
- **Function:** Cleaves off sialic acid molecules from the surface of cells thereby preventing infected cells from "recapturing" budding virus molecules .

Surface Antigens

Haemagglutinin

- Binds to host cell surface receptor
- The target of neutralizing Abs
- Haemagglutinates RBCs from various animal species

Neuraminidase

- Cleaves neuraminic acid to release virus progeny from infected cells
- Degrades the protective layer of mucin in the respiratory tract
- Plays a minimal role in immunity to influenza

Antigenic Variation

- Ag Variations occurs only in infuenza A because it has a *wide host range*, giving influenza A the opportunity for a major reorganization of its genome & hence its surface Ags

- Pigs are susceptible to avian, human & swine influenza viruses and they potentially may be infected with influenza viruses from different species. If this happens, it is possible for the genes of these viruses to mix and create a new virus

Antigenic Variation

1- antigenic shift

Type A
Antigenic shift or Drift

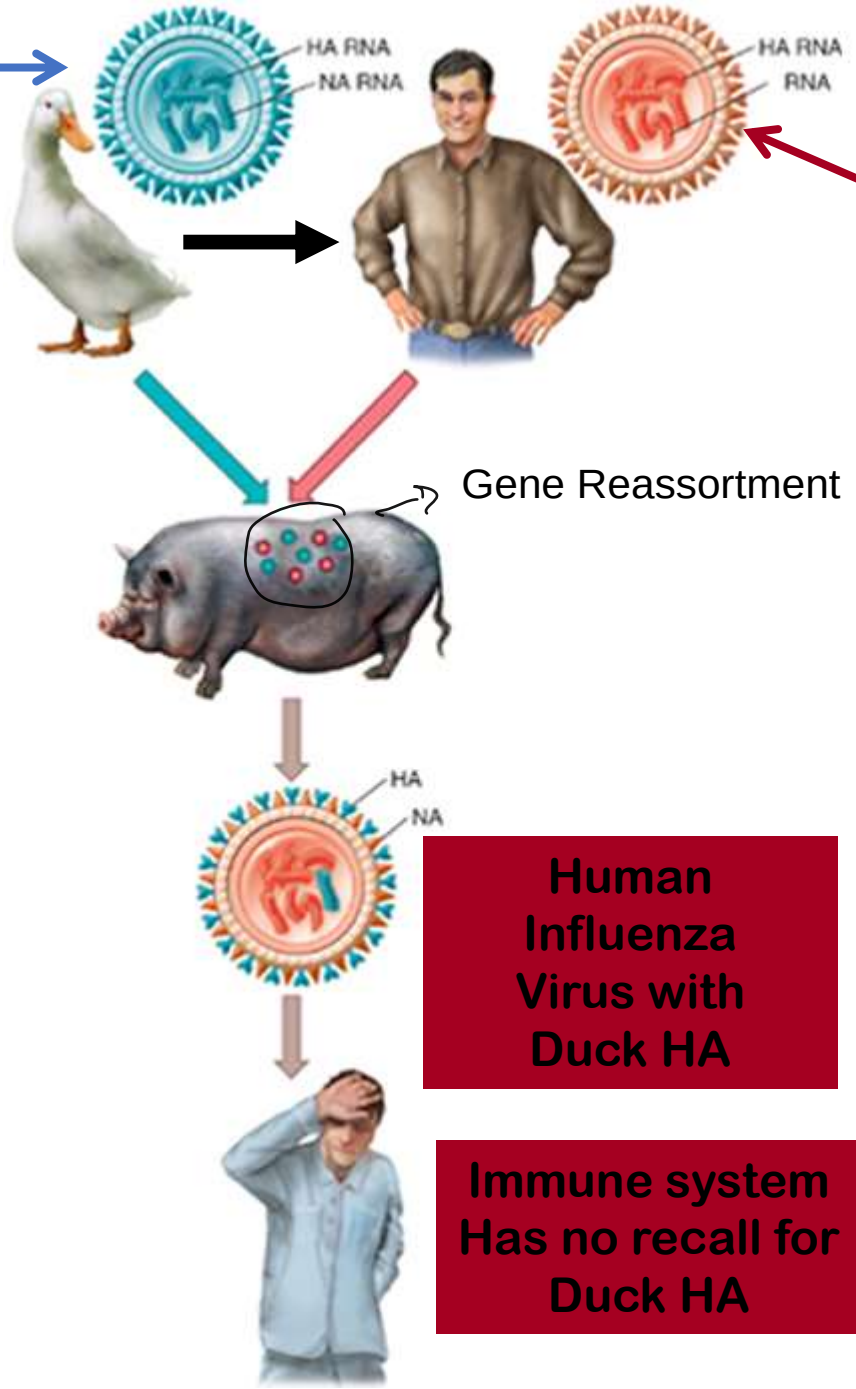
Type B+C
only Drift

- It is the process in which the genetic segment encoding for envelope glycoproteins (HA&NA) is replaced by another one from a different strain through genetic reassortment causing replacement of the original HA or NA by a new one
- **Major** change, new subtype, May result in pandemic.
- **Genetic reassortment:** the exchange of genetic material between viruses inside a host cell

Antigenic Shift event

Sudden + Major

Duck Influenza Virus



Human Influenza Virus

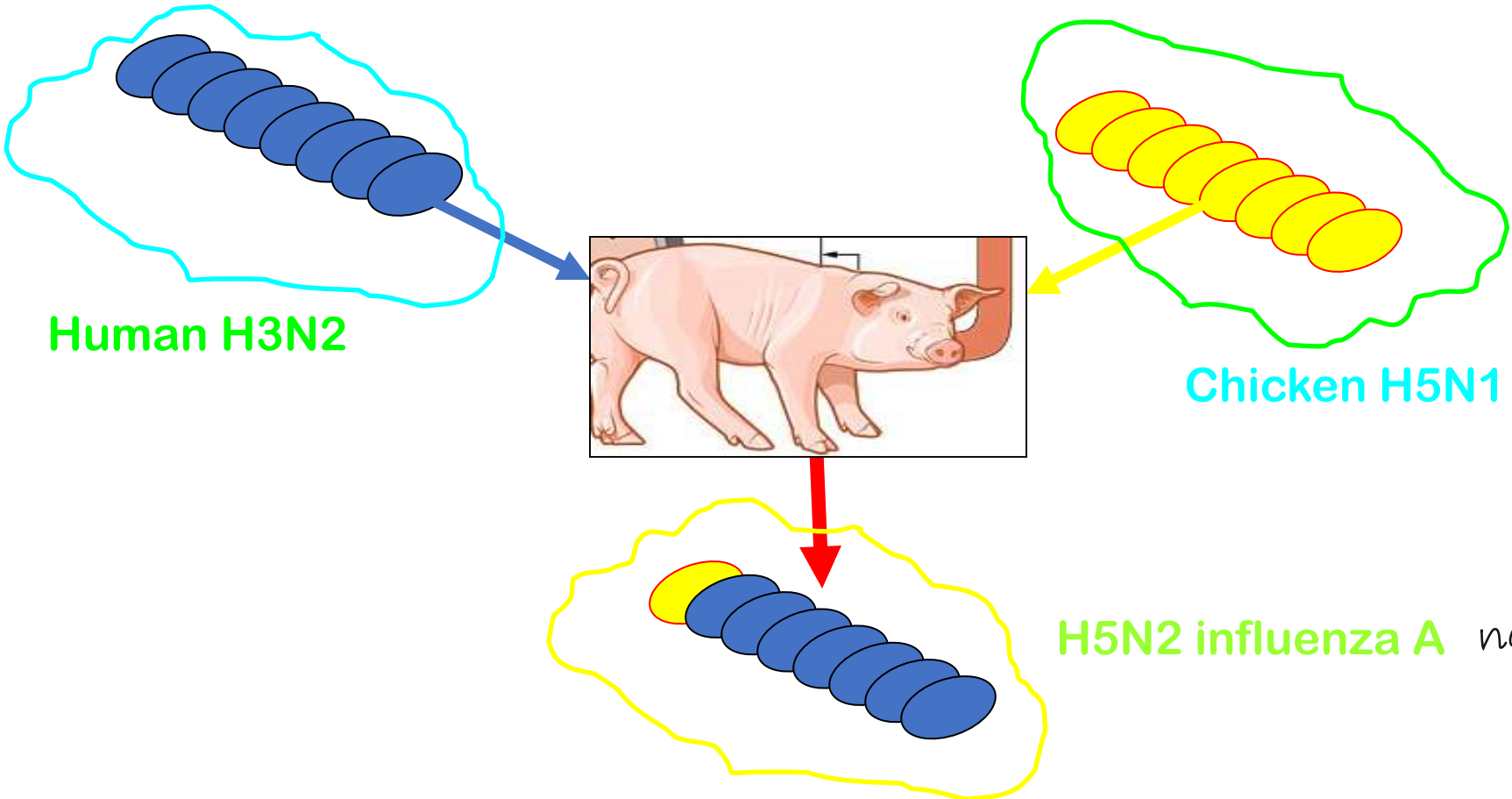
Human Influenza Virus with Duck HA

Immune system Has no recall for Duck HA

This is responsible for appearance of completely new strains to which no one is immune & not covered by annual vaccinations

Example of antigenic shift → can Happen inside Humans.

H2N2 virus circulated in 1957-1967
H3N2 virus appeared in 1968 and completely replaced H2N2 virus



Antigenic Variation

Minor changes (point mutations) or Amino acid substitutions

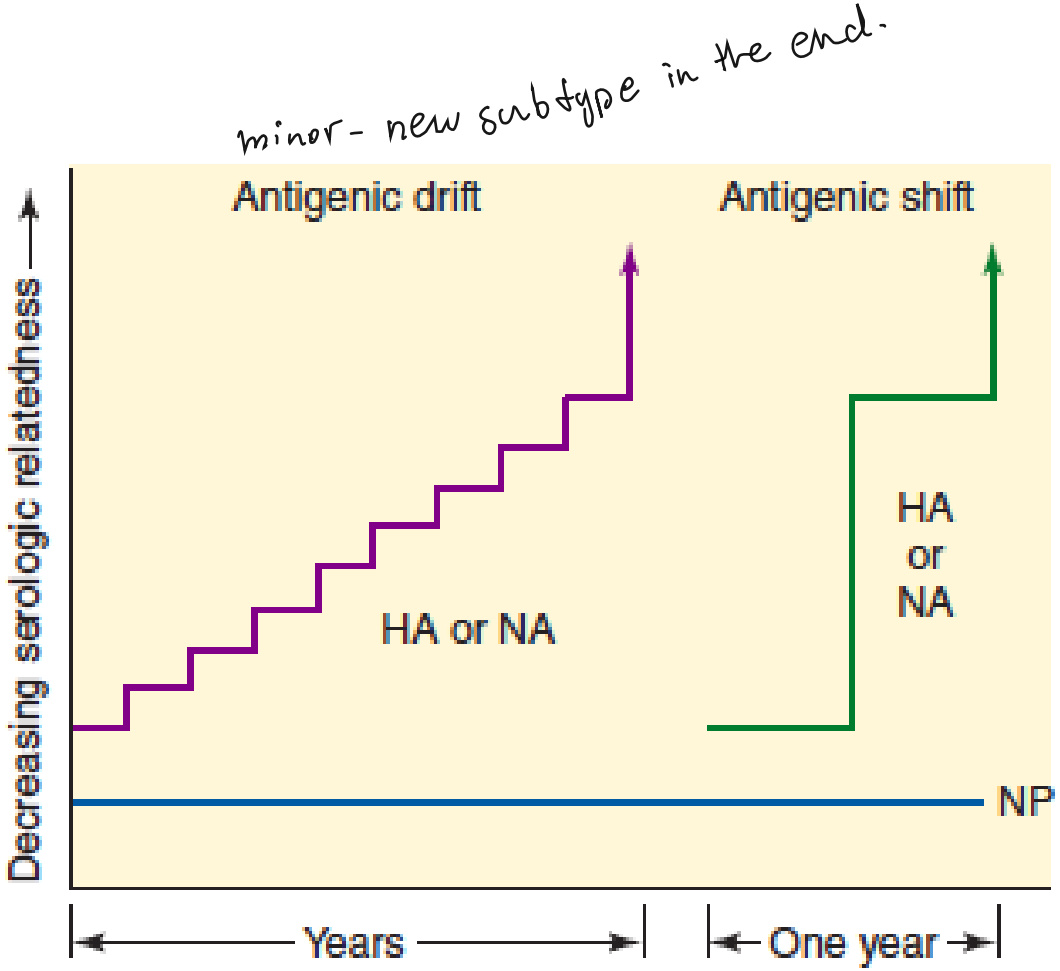
2) Antigenic Drift

- Minor change, same subtype

- Caused by point mutations in gene, minor change of an amino acid sequence of HA or NA. Occurs in influenza A & B produce new strains are referred to as antigenic shifts
  - May result in epidemic

- **Example of antigenic drift**
  - In 2003-2004, A/Fujian/411/2002-like (H3N2) virus was dominant
  - A/California/7/2004 (H3N2) began to circulate and became the dominant virus in 2005

minor - new subtype in the end.



Classification and Nomenclature

Origin is from Avian influenza except
HA(17-18)+NA(10+11) from bats

- The standard nomenclature system for influenza virus isolates includes the following information: type, host of origin, geographic origin, strain number, and year of isolation. Antigenic descriptions of the HA and the NA are given in parentheses for type A.
- The host of origin is not indicated for human isolates, such as A/Hong Kong/03/68(H3N2), but it is indicated for others, such as A/swine/Iowa/15/30(H1N1).
- So far, 18 subtypes of HA (H1–H15) and eleven subtypes of NA (N1–N9), in many different combinations, have been recovered from birds, animals, or humans. Four HA (H1–H3, H5) and two NA (N1, N2) subtypes have been recovered from humans.

influenza

↓

Sudden+ common complaints (fever/athralgia/chills...) +minor respiratory symptoms (cough/ runny nose/...)

common cold

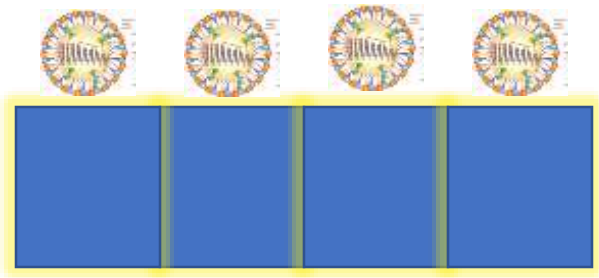
↓

Gradual, patient complains of respiratory problems and no systemic signs (fever/chills/...)

Pathogenesis

In influezna no viremia

Viral NA degrades the protective mucin layer
Allowing the virus to enter the cells



Epithelial cells of respiratory tract

Replication inside the cells
Cilia damage
Epithelial desquamation

The infection is limited to the respiratory tract → Might cause Metaplasia

There are *proteases* there essential for HA to be active

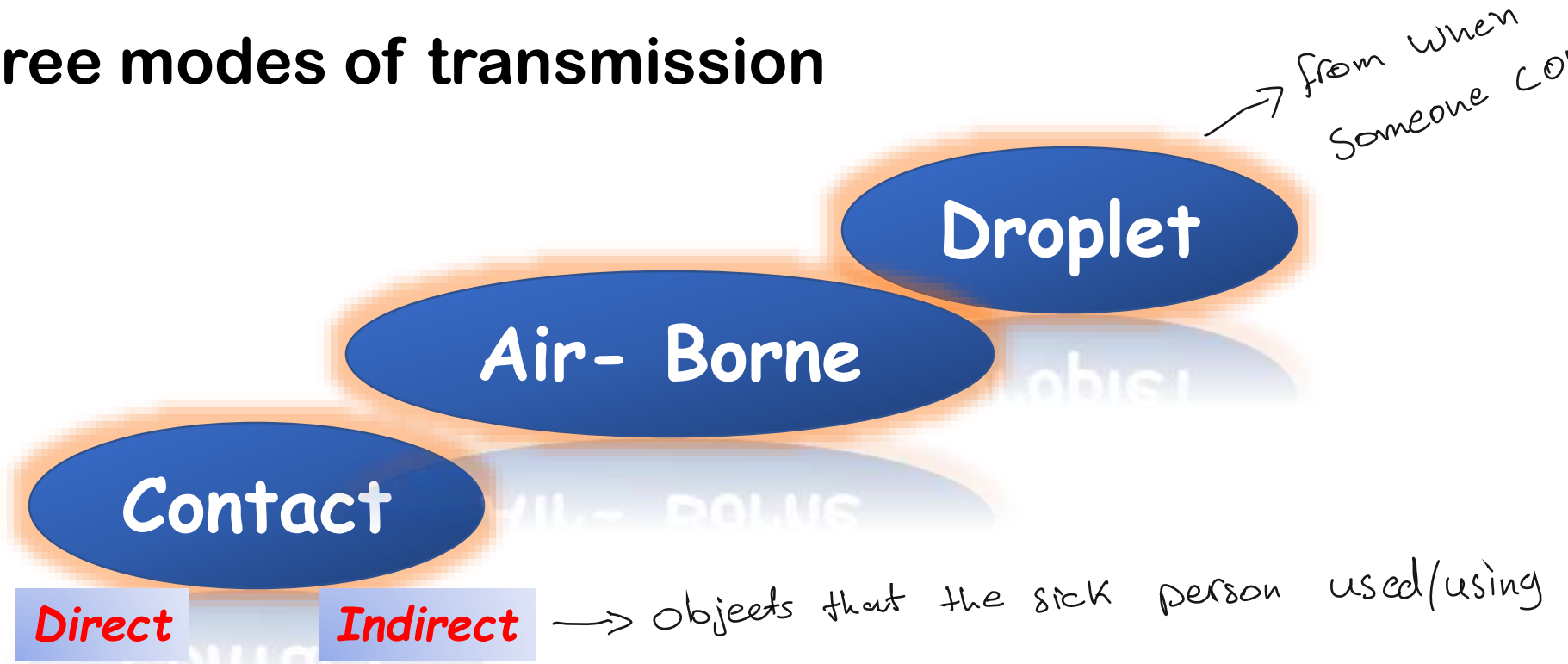
Despite systemic symptoms, no viremia

Those symptoms are due to *cytokines production*

Recovery takes a few months

Mode of transmission

- Highly contagious disease with person to person transmission
- Three modes of transmission



Short Incubation Period 1-3 days

Duration of shedding

Patient is contagious a day before he shows signs and till the 10th day of showing signs

- In otherwise healthy adults with influenza infection, viral shedding can be detected 24 to 48 hours before illness onset, but is generally at much lower titers than during the symptomatic period
- In a review of 56 studies of 1280 healthy adults who were experimentally challenged with influenza virus, shedding of influenza virus increased sharply one-half to one day following exposure, peaked on the second day, and then rapidly declined
- The average duration of shedding was 4.8 days Shedding ceased after six or seven days in most studies but occurred for up to 10 days in some. Studies of natural infection in healthy adults have shown similar results

Clinical Findings

↳ major signs are systemic

- High fever
- Non-productive as well as productive cough usually / still might be with spetum
- Shortness of breath
- Dyspnoea
- Hypoxia
- Evidence of lower respiratory tract disease with opacities, consolidation, and infiltrates noted on chest imaging
- More severe infections (i.e. pneumonia) are sometimes associated with Influenza because of the increased susceptibility to other infections as a result of a damaged airway

Risk group: Age > 65

Pulmonary complications → they kill (Not the influenza it self).

❖Primary influenza pneumonia

- Primary influenza pneumonia occurs when influenza virus infection directly involves the lung, typically producing a severe pneumonia.
- Clinical suspicion for primary influenza pneumonia should be raised when symptoms persist and increase instead of resolving in a patient with acute influenza.
- High fever, dyspnea, and even progression to cyanosis can be seen.

❖Secondary bacterial pneumonia (*Streptococcus pneumoniae, Staphylococcus aureus, and Haemophilus influenzae*).

Most common cause of superimposed infection pneumonia post influenza is staph aureus

❖Mixed viral and bacterial pneumonia

Complications of pneumonia

- **Septic shock,**
- **Respiratory failure,**
- **Acute respiratory distress syndrome,**
- **Refractory hypoxemia,**
- **Acute renal dysfunction,**
- **Multiple organ dysfunction,**
- **Rhabdomyolysis,**
- **Encephalopathy (Reye syndrome)**
- **Bacterial and fungal infections such as ventilator-associated pneumonia and blood-stream infection sometimes by multi-drug resistant bacteria**

→ edema liver + brain

Dont give children who have Flu like syndrome (salicylic drugs like aspirin)

Groups at high risk for influenza complication

- Children <2 years*
- Adults ≥65 years of age
- Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematologic (including sickle cell disease), metabolic (including diabetes mellitus), neurologic, neuromuscular, and neurodevelopmental disorders (including disorders of the brain, spinal cord, peripheral nerve and muscle such as cerebral palsy, epilepsy, stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury)
- Immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus)
- Women who are pregnant or postpartum (within 2 weeks after delivery)
- Children <19 years of age and receiving long-term aspirin therapy
- Native Americans and Alaskan Natives
- Morbidly obese (body mass index [BMI] ≥40 for adults or BMI >2.33 standard deviations above the mean for children)
- Residents of nursing homes and other chronic care facilities

Laboratory Diagnosis

Diagnosis in epidemic is easy, all patients complaining of the same symptoms

A. Polymerase Chain Reaction → in jordan and most of the countries

- Rapid tests based on detection of influenza RNA in clinical specimens using reverse transcription polymerase chain reaction (RT-PCR) are preferred for diagnosis of influenza. RT-PCR is rapid (<1 day), sensitive, and specific.

B. Isolation and Identification of Virus

- Viral culture procedures take 3–10 days. Classically, embryonated eggs and primary monkey kidney cells have been the isolation methods of choice for influenza viruses, although some continuous cell lines may be used. in the presence of trypsin, which cleaves and activates the HA so that replicating virus will spread throughout the culture. Cell cultures can be tested for the presence of virus by hemadsorption 3–5 days after inoculation, or the culture fluid can be examined for virus after 5–7 days by hemagglutination.

C. Serology needs time

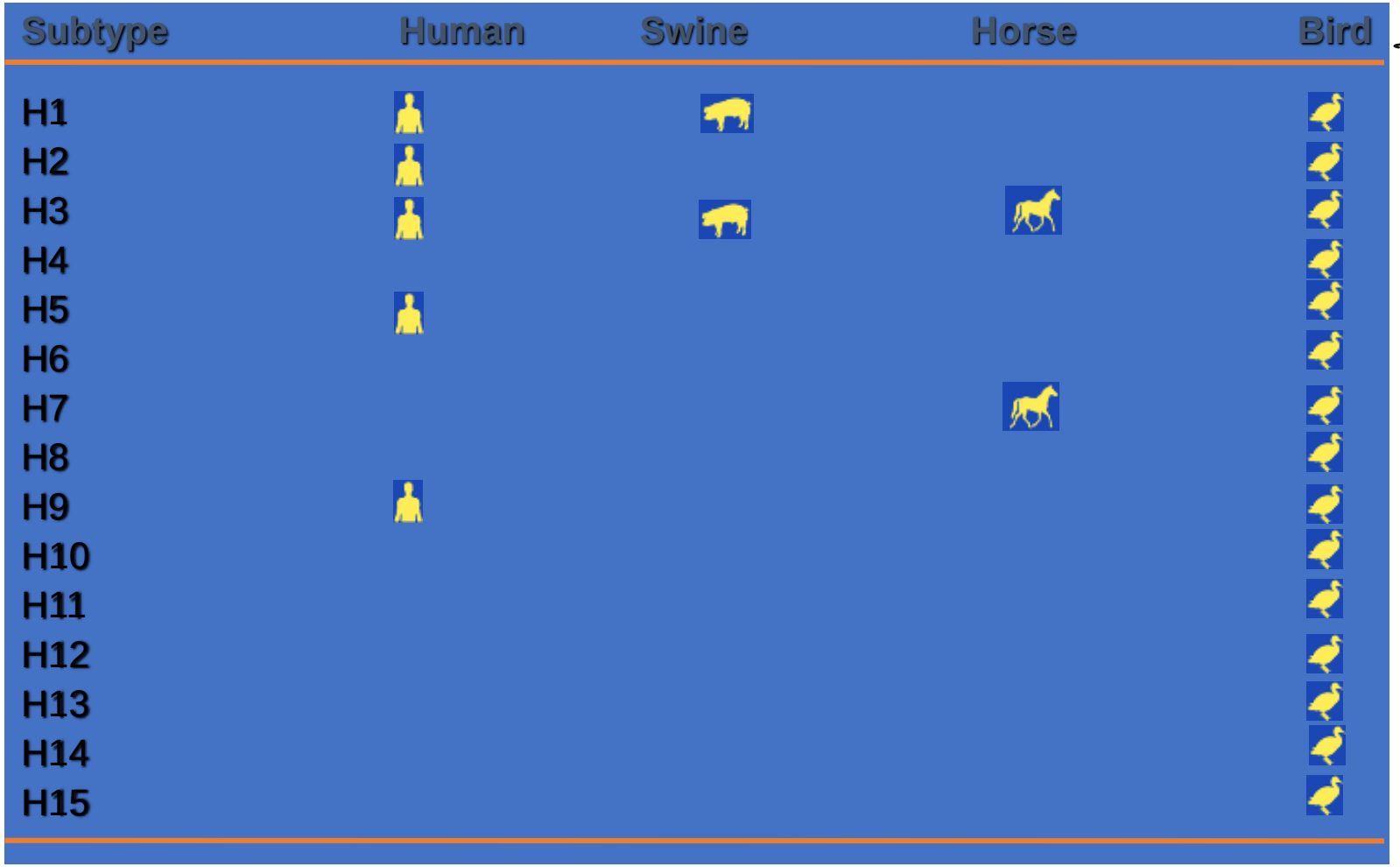
- Antibodies to several viral proteins (hemagglutinin, neuraminidase, nucleoprotein, and matrix) are produced during infection with influenza virus. The immune response against the HA glycoprotein is associated with resistance to infection.
- Routine serodiagnostic tests in use are based on haemagglutination inhibition (HI) and enzyme-linked immunosorbent assay. Paired acute and convalescent sera are necessary because normal individuals usually have influenza antibodies. A fourfold or greater increase in titer must occur to indicate influenza infection. Human sera often contain nonspecific mucoprotein inhibitors that must be destroyed before testing by HI.

Hemagglutinin Subtypes of Influenza A Virus

Seasonal flu now adays (H1N1 - H3N2)

(H5N1 + H7N9) → from Avian

Not efficient in Humans.



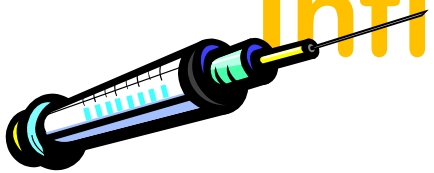
→ origin of all influenza viruses

History: Known Flu Pandemics

Name of pandemic	Date	Deaths
Spanish Flu	1918-1920	40 -100 million
Asian Flu	1957-1958	1 - 1.5 million
Hong Kong Flu	1968-1969	0.75 - 1 million
Swine Flu	2009-2010	0.15-0.6 million

Treatment and Prevention

Influenza Vaccines important for prevention.

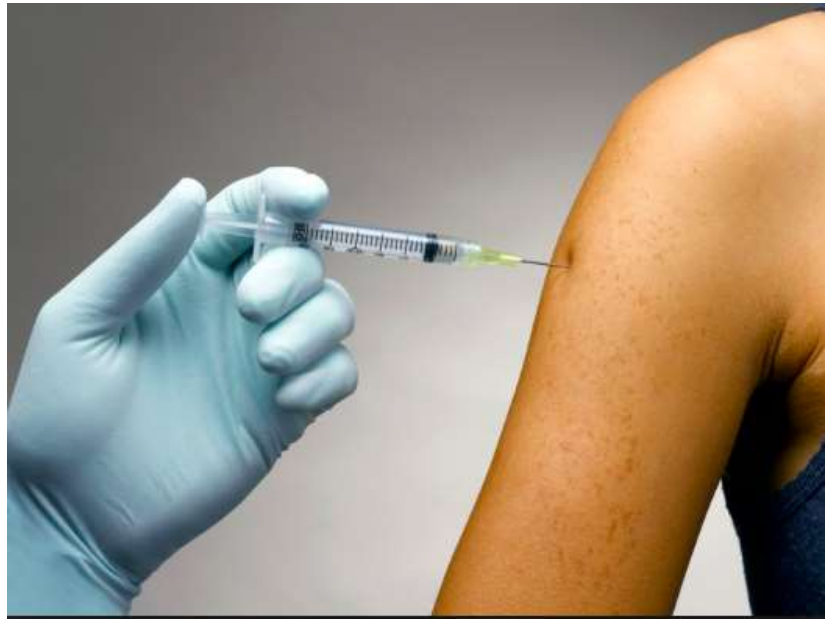


- Whole virus vaccines: inactivated forms of virus with the predicted HA, are grown in embryonated eggs
- Subunit vaccine: uses both HA and NA subunits extracted from recomibinant virus forms
- Split-virus vaccines: purified HA (lessens the side-effects)
- Recommended for health care workers, elderly/ people in nursing homes, asthmatics, chronic lung disease patients, some pregnant women, and anyone who is susceptible to infection

Influenza Vaccines

Flu shot= killed
Trivalent (in Jordan)= 2 subtypes of A and 1 Subtype of B
quadrivalent vaccine (In USA)= 2subtypes of A and 2 Subtypes of B

- Inactivated subunit (TIV)
  - Intramuscular
  - Trivalent
  - Annual



Contraindicated in pregnancy

- Live attenuated vaccine (LAIV) — FLUMIST
  - Intranasal
  - Trivalent
  - Annual

WHO recommends annual vaccination for (in order of priority)

- Nursing-home residents (the elderly or disabled)
- Elderly individuals
- People with chronic medical conditions
- Other groups such as pregnant women, health care workers, those with essential functions in society, as well as children from ages six months to five years

- Medical personnel

Specially for old people because you cant vaccinate them

Antiviral Treatment Recommendations

neuramidase inhibitors.

- Treatment with oseltamivir (Tamiflu) or zanamivir is recommended for:
  - All patients requiring hospitalization
  - Patients at increased risk of complications
    - Children 0-4 years
    - Pregnant women
    - Persons with immune suppression, chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological (including sickle cell disease), neurologic, neuromuscular, or metabolic disorders (including diabetes mellitus) or > 65 years
- Early treatment is the key
- Clinicians should not wait for confirmatory tests to treat
- Postexposure prophylaxis should generally not be used
  - Consider for high-risk person with close unprotected exposure
  - Do not use if more than 48 hours after exposure

Healthy Habits

- **When Healthy:**
  - Avoid close contact with those who are sick
  - Wash your hands often
  - Avoid touching your eyes, nose and mouth to decrease the spread of germs
- **When Ill:**
  - Cover your mouth and nose with a tissue (or upper sleeve) when you sneeze or cough
  - Stay home from work or school when you are sick

Key facts

- Influenza is an acute viral infection that spreads easily from person to person.
- Influenza circulates worldwide and can affect anybody in any age group.
- Influenza causes annual epidemics that peak during winter in temperate regions.
- Influenza is a serious public health problem that causes severe illnesses and deaths for higher risk populations.
- An epidemic can take an economic toll through lost workforce productivity, and strain health services.
- Vaccination is the most effective way to prevent infection.

Avian Influenza

In wild birds, silent infection
If Domestic (ducks and chickens) are affected they cause a disease in them, chickens are used to predict the next circulating strains

- A contagious viral infection and/or disease of many avian species including poultry, wild and exotic birds, ratites, shore birds and migratory waterfowl.

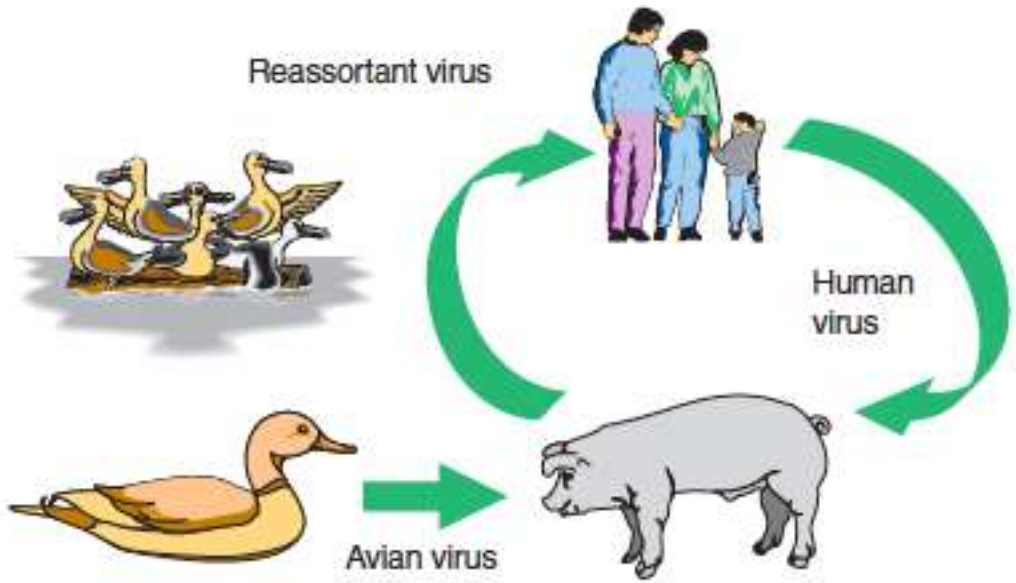
- The highly pathogenic form of the disease is characterized by severe depression, decrease in egg production, high mortality, edema, hemorrhage, and frank necrosis.

- All H5 and H7 infections are reportable to the World Organization for Animal Health (OIE).

Where does AI virus come from?

- All known subtypes of influenza A viruses circulate among wild birds, especially migratory waterfowl (e.g. ducks and geese) which are considered natural reservoirs for influenza A viruses
- Domestic poultry like chickens and turkeys are not natural reservoirs for AI virus and usually develop clinical disease when infected with AI virus

Mode of transmission contact, droplet (not sure/no studies)
Main route is their feces (the virus stays alive for 3 months)



How does AI virus spread?

- Exposure of poultry to migratory waterfowl
- Exposure of commercial poultry to AI-infected backyard, game bird, or hobby flocks
- Contact with AI-infected live bird markets
- Bird to bird contact (through feces)
- Aerosol droplets
- Manure, equipment, vehicles, egg flats, crates, contaminated shoes and clothing
- Wildlife vectors/scavengers

What are the types of Avian Influenza in domestic poultry?

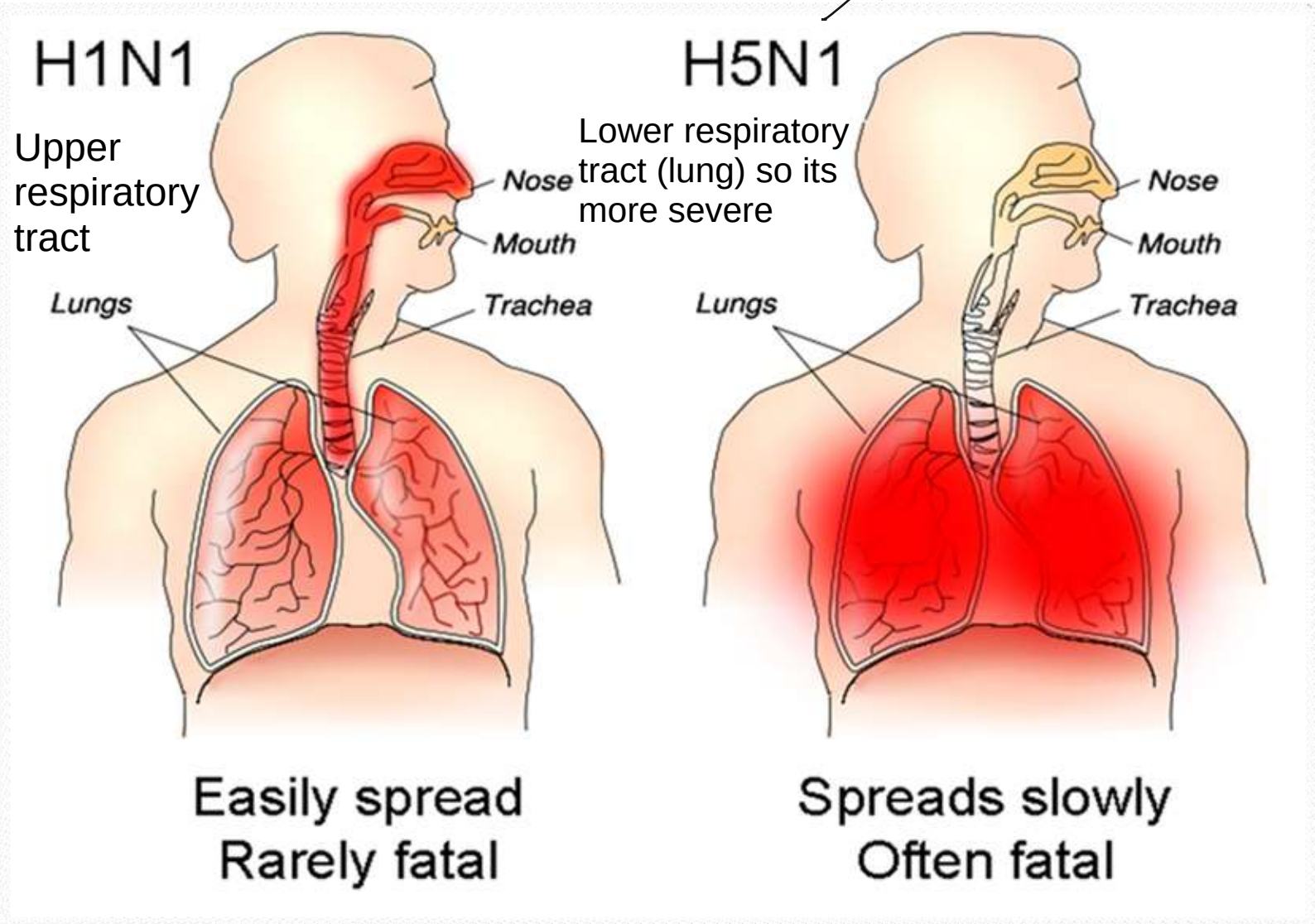
Both of them can affect humans

- **Low pathogenic avian influenza (LPAI)** → concered with birds
  - Mild or no clinical signs
  - Low to moderate mortality
  - However, the low pathogenic H5 and H7 strains are capable of mutating under field conditions into highly pathogenic strains
- **Highly pathogenic avian influenza (HPAI)**
  - Sudden onset
  - Severe clinical signs
  - High mortality

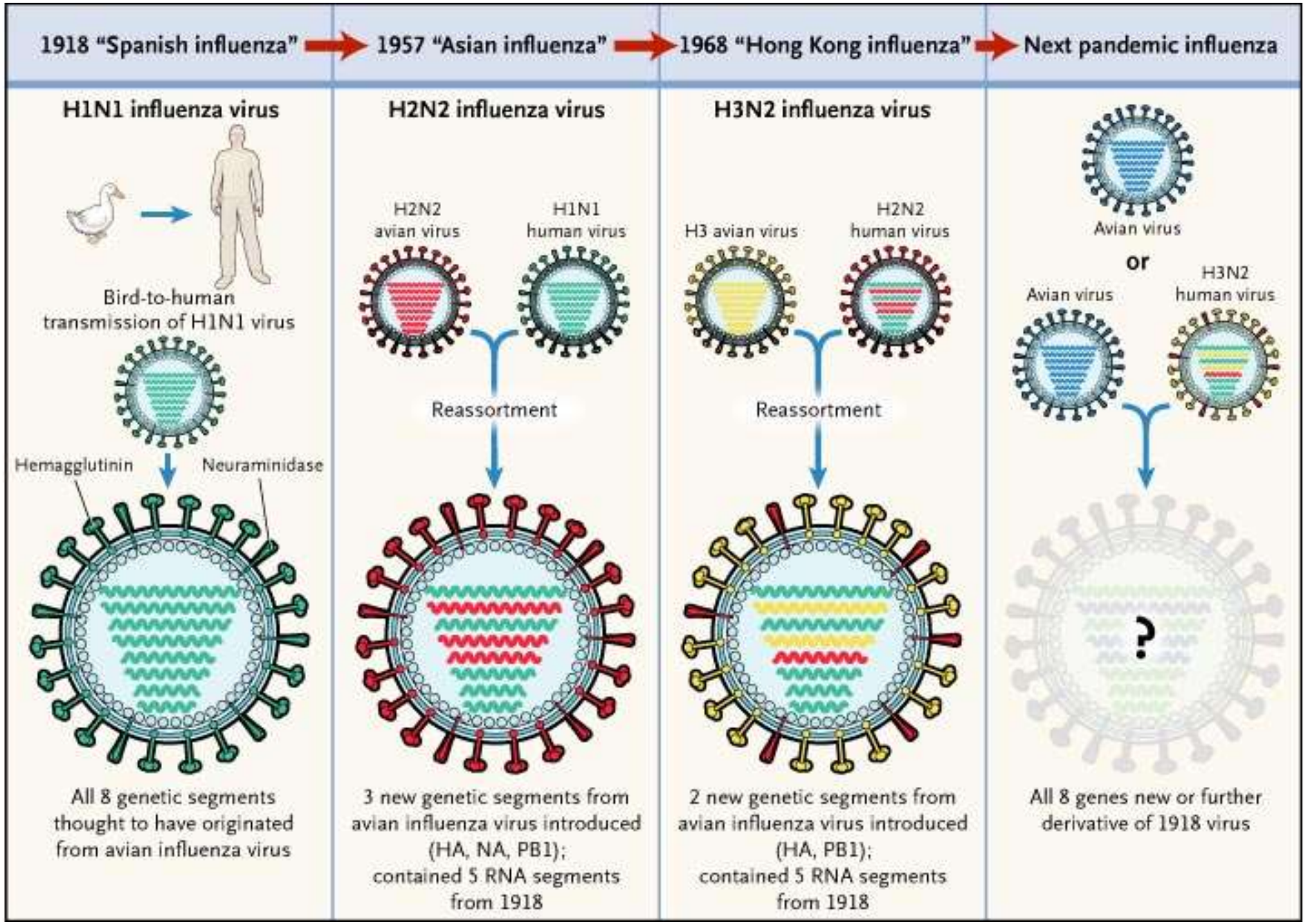
No effective transmission cycle between humans ← (H6N1+ H7N9 from birds)

H1N1/H5N1

→ from birds (most common in Avian).



Criteria for pandemic
1)New subtype (Antigenic shift)
2)Efficient human to human transmission
3)It produces a severe disease



No one can predict when the pandemic is going to happen or what it will be

WHAT IS SWINE FLU ?

Show signs and symptoms

Swine Influenza (swine flu) is a respiratory disease of pigs caused by type A influenza viruses (H1N1 subtype) that causes regular outbreaks in pigs.

People do not normally get swine flu, but human infections can and do happen

Swine flu viruses have been reported to spread from person-to-person, but in the past, this transmission was limited and not sustained beyond three people

The End