# Viral Respiratory Tract Infections (A)

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Dr. Sulaiman Mahmoud Bani Abdel-Rahman

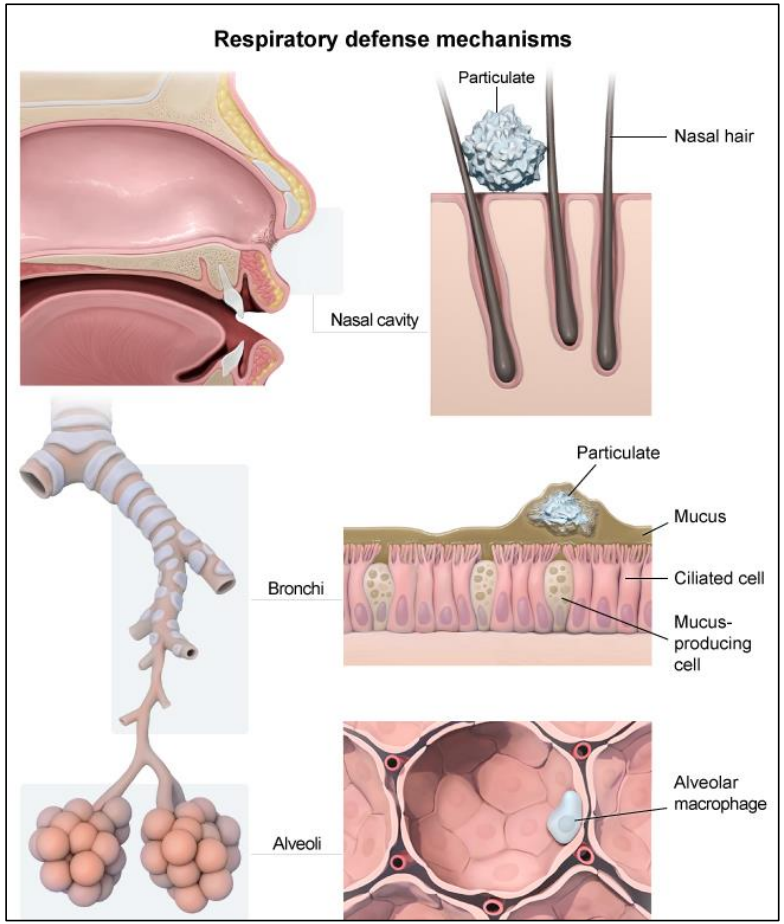
MBBS, Mutah university

MSC Medical Microbiology – University of Manchester

PhD Medical Virology - University of Manchester

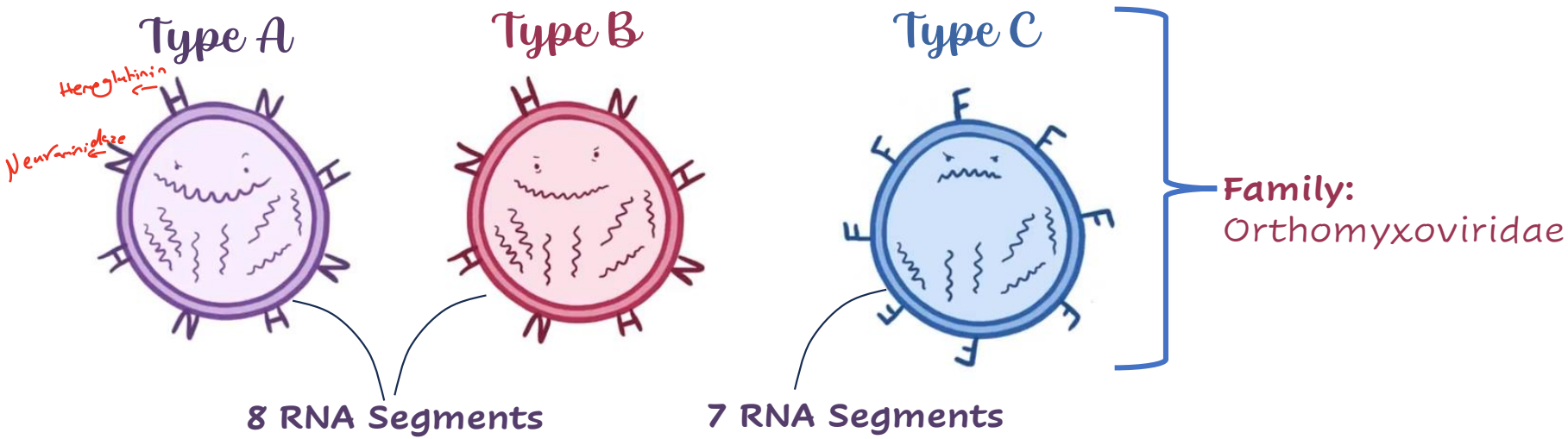
# Respiratory Tract Defenses

- Structural
  - Mucus
  - Ciliated epithelium
- Mechanical
  - Glottal reflex
  - Coughing
- Cellular
  - Alveolar macrophages (lower)
  - Neutrophils - with inflammation
- Fluid
  - IgA (upper)
  - IgG and complement transudation from blood (lower)



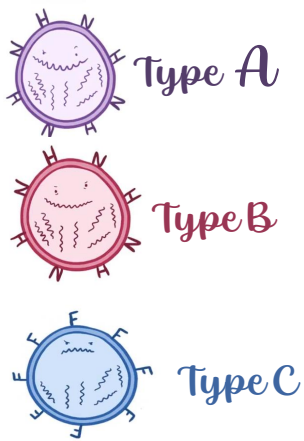
# Influenza virus (Introduction)

- **Definition:** Influenza, commonly called "the flu," is a contagious respiratory illness caused by influenza viruses.
- **Types:** Influenza A, B, and C



# Orthomyxoviruses

- **Family:** Orthomyxoviridae
- **Genera:** Total 7 Genera in Orthomyxoviridae - the following are main genera:
  - Alphainfluenzavirus
    - Species: Influenza A virus
  - Betainfluenzavirus
    - Species: Influenza B virus
  - Gammainfluenzavirus
    - Species: Influenza C virus



# Orthomyxoviruses - Structure and basic features

- Capsid: large (~ 80-120 nm in diameter), enveloped, helical
- Genome:
  - Single stranded RNA (ssRNA)
    - Linear
    - Negative sense
    - Segmented: 8 segments (types A and B), 7 segments in type C.
  - Has RNA-dependent RNA polymerase (RDRP) → (important for infectivity/has transcription errors ~ 1: 10kb of the genome).
- Replicates within the nucleus

# Orthomyxoviruses - Structure and basic features (continue)

الاسماء+تفاصيل HA+NA

- Viral proteins:
  - Virulent envelope glycoproteins:
    - **Hemagglutinin (HA):** attaches to sialic acid-containing receptors on respiratory epithelial cells
    - **Neuraminidase (NA):** cleaves newly formed virions off the sialic acid-containing receptor, allowing the virus to exit cells
  - **M1 protein:** virion assembly
  - **M2 protein:** involved in viral uncoating within the respiratory epithelial cells
  - **Nucleoprotein:** helps distinguish between the 3 types of influenza viruses (A, B, and C)

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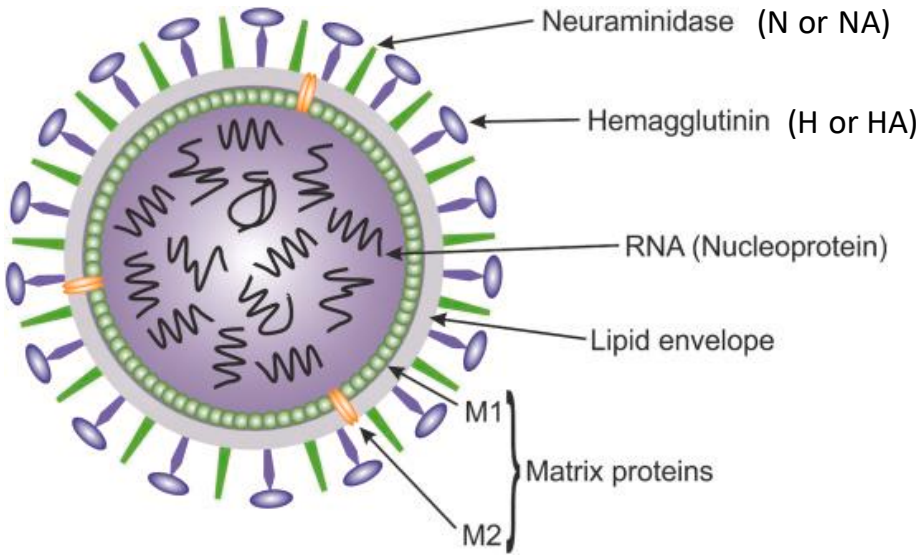



type A, B, C : NP, M1 protein مهم

sub-types: HA or NA protein

# Orthomyxoviruses / Antigenicity

- Influenza viruses have two types of antigens: group-specific antigens and type-specific antigens.
  1. Group specific antigens:
     A. Determined by Ribonucleoproteins and M1.
     B. Distinguish types A, B and C.

  2. Type specific antigens:
     A. The HA and NA.
     B. Used for serotyping.
     C. HA is the main determinant of immunity and stimulates the production of neutralizing antibodies.

     - HA antibodies are neutralising (protect) while NA antibodies are not.

# Viral proteins

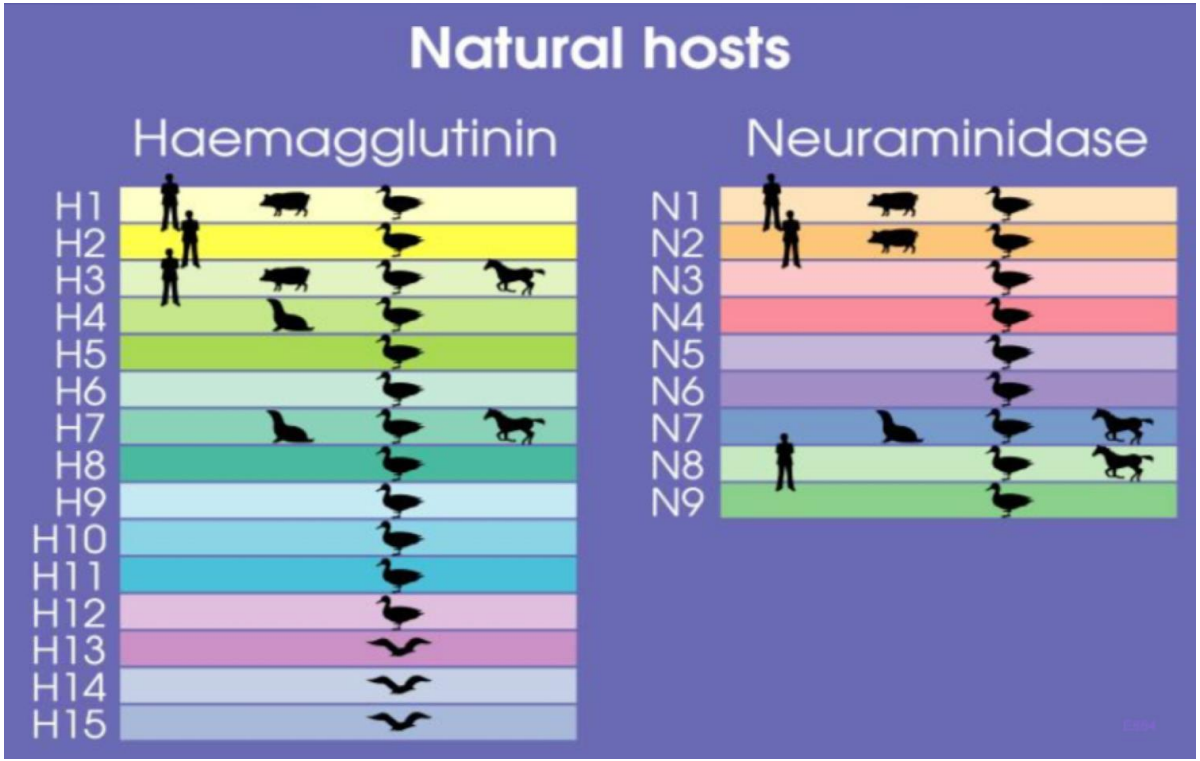
- **Hemagglutinin (HA) (17 subtypes):**
  - H or HA.
  - Allows virus to attach to endothelial cells in the respiratory tract (binding to sialic acid containing receptors).
  - Main determinant of immunity (stimulates the production of neutralizing antibodies).
  - Agglutinates certain species erythrocytes.
- **Neuraminidase (9 serotypes) (Not in type C):**
  - N or NA.
  - Allows release of newly formed viruses within host.
  - Cleaves newly formed virions off the sialic acid-containing receptor, allowing the virus to exit cells
  - Determinant of disease severity.

**Determine the subtype:**
E.g H1N1, H3N2, H5N1....

**Only H1, H2, H3, N1, N2, and N8 have been associated with epidemics of disease in humans**

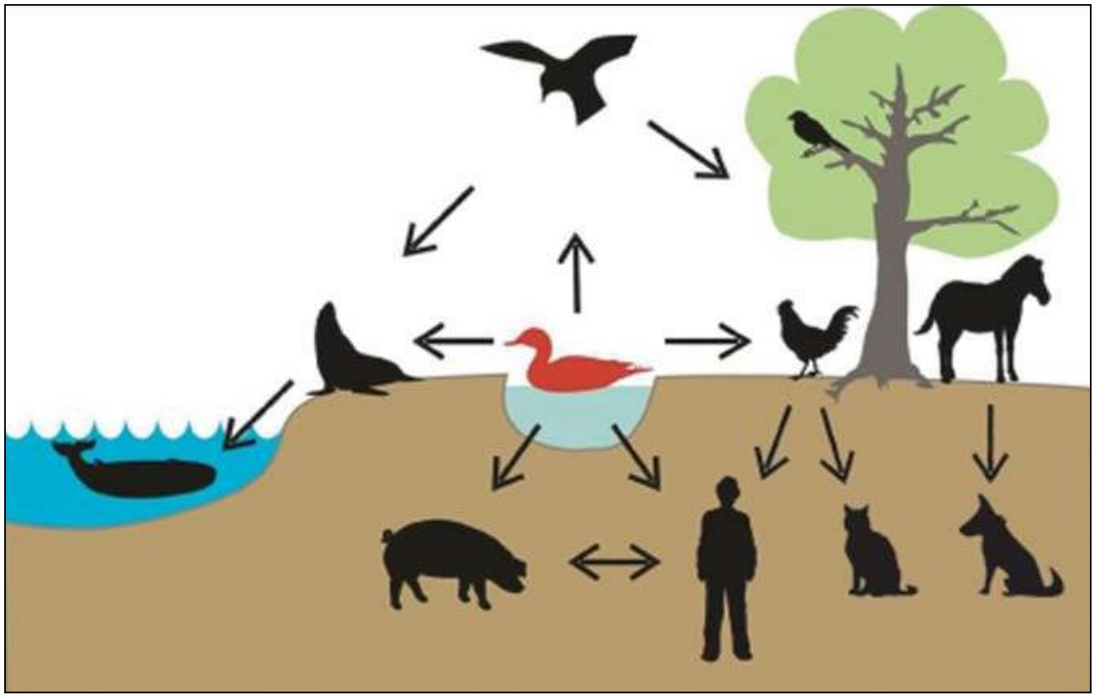
- **M proteins (1 & 2):** between the capsid and the envelop (only in type A):
  - Act as an ion channel to change the endosomal pH (M2 mainly).
  - M1 protein: virion assembly
  - M2 protein: involved in viral uncoating within the respiratory epithelial cells

# Natural hosts



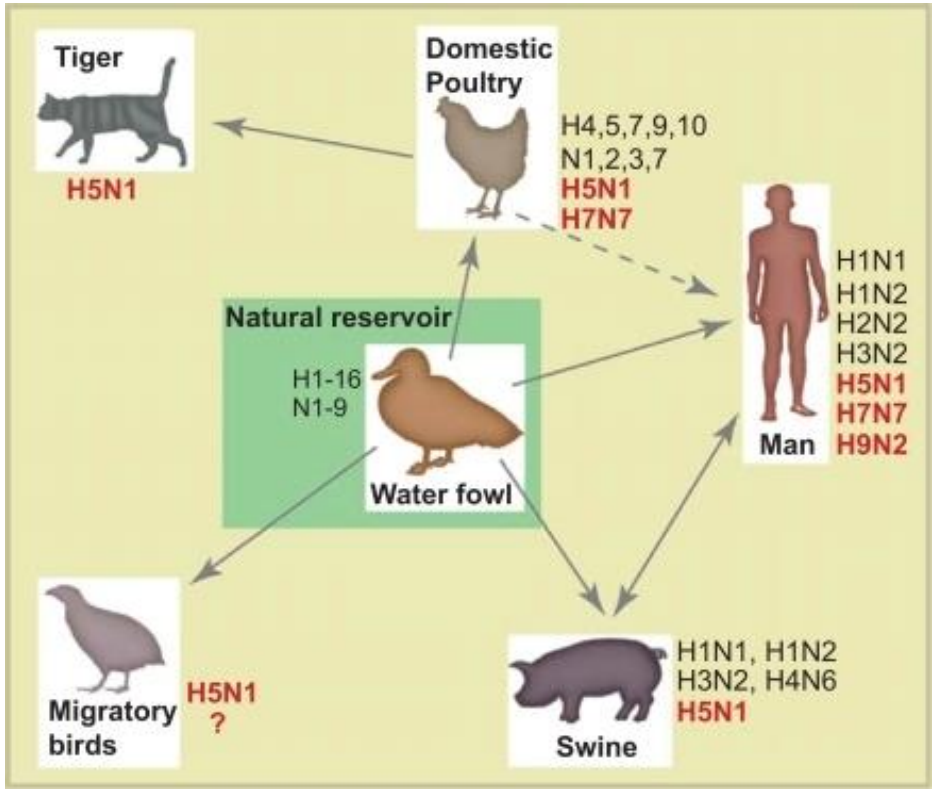

**Note:** Only memorize which proteins are found in humans.

# Influenza A reservoir



**Wild aquatic birds are the main reservoir of influenza A viruses.** Virus transmission has been reported from wild waterfowl to poultry, sea mammals, pigs, horses, and humans. Viruses are also transmitted between pigs and humans, and from poultry to humans. Equine influenza viruses have recently been transmitted to dogs.

# Influenza A subtypes



# Nomenclature

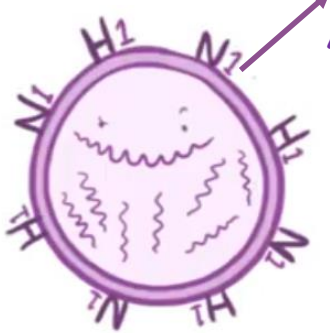
- Influenza A has 16 distinct H subtypes and 9 distinct N subtypes, of which only H1, H2, H3, N1, and N2 have been associated with epidemics of disease in humans.

- Influenza B viruses have both H and N antigens but do not receive subtype designations because intratypic variations are less extensive than in influenza A viruses.

- Influenza C viruses, on the other hand, have a hemagglutinin-esterase-fusion (HEF) protein instead of separate H and N antigens, and they do not have subtypes.

# Nomenclature / WHO (for type A)

**NAMING:** [Type] / [Original Host] / [Location] / [Strain #] / [Year of Origin] / ([subtype])




E.G → **H1N1 Type A** flu virus of **Duck** Origin from **Alberta, CA**, **35th Strain** discovered in **1976**

A / Duck / Alberta/ 35 / 76 (H1N1)

**Note1:** if isolated from human host, the origin is not given

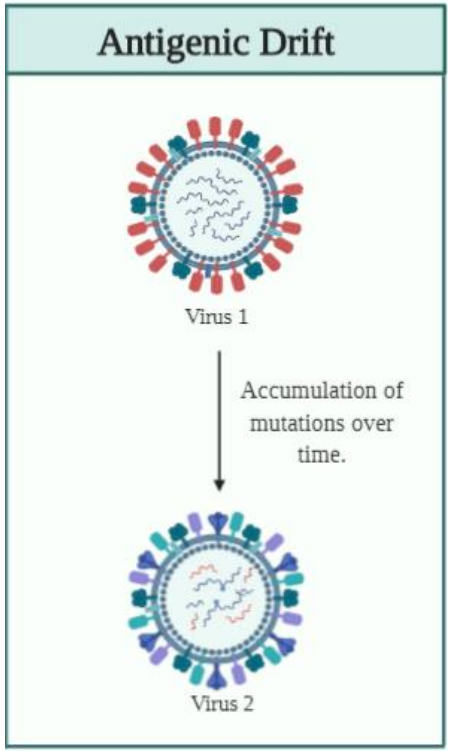
**Note 2:** For types B and C, the same naming conventions apply, except the subtype is not included.

# Why Do Flu Viruses Keep Changing?

Why do we need a new flu vaccine every year?

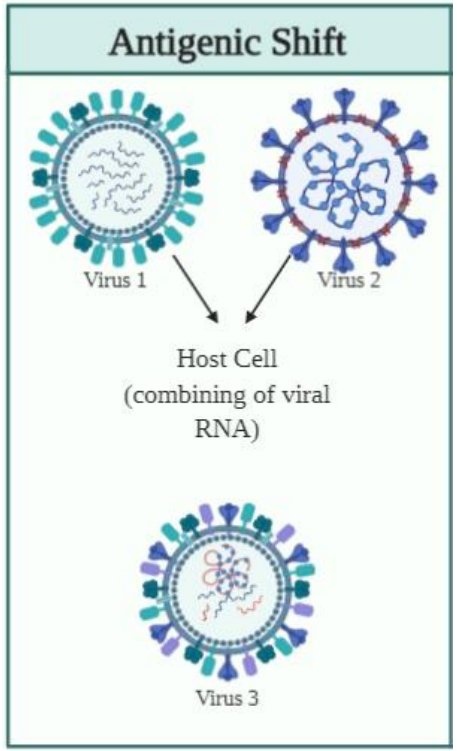
# Antigenic Drift

- **What is it?**
  - Gradual Changes Over Time
  - Antigenic drift refers to small, gradual changes that occur in the genetic material of the influenza virus over time, particularly in the genes that code for its surface proteins like **hemagglutinin (H)** and **neuraminidase (N)**. These changes lead to new viral strains that are just different enough to escape immune recognition.
- **How does it happen?**
  - The influenza virus uses an enzyme called **RNA-dependent RNA polymerase (RdRp)** to replicate its RNA genome. However, **RdRp lacks a proofreading mechanism**, meaning that every time the virus replicates, it makes small copying errors or mutations. These errors accumulate over time, leading to gradual changes in the virus's surface proteins.
- **Why is it important?**
  - These small mutations can alter the virus's **H** and **N** proteins, allowing the virus to evade the immune system's memory of previous infections or vaccinations.
- **Example:**
  - **Seasonal Flu:** Antigenic drift is the main reason why we experience seasonal flu outbreaks every year and need to update flu vaccines annually. As the virus slowly changes through drift, previously effective immune responses become less effective.



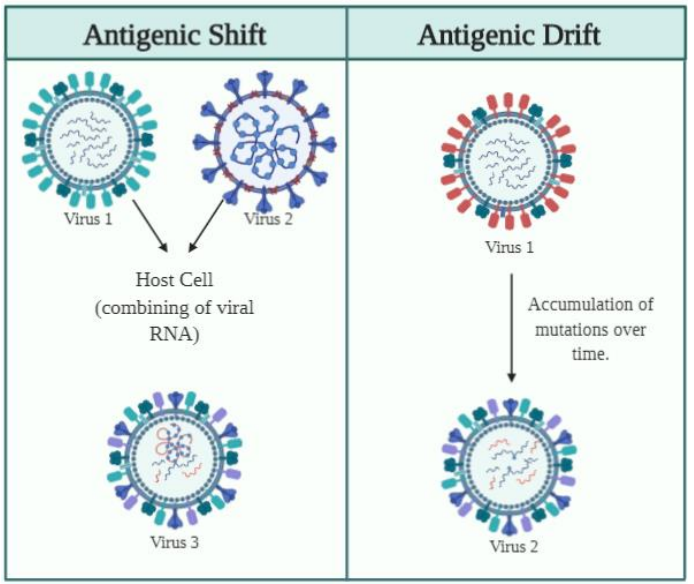
# Antigenic Shift

- **What is it?**
  - Major Changes Leading to New Viruses
  - Antigenic shift is a dramatic and sudden change in the influenza virus's genetic material, resulting from the reassortment of gene segments between two different strains of influenza viruses. This typically happens when an animal strain (like avian or swine flu) mixes with a human strain.
- **How does it happen?**
  - When two different influenza viruses infect the same host cell, they can exchange segments of their genetic material, creating a new virus with surface proteins that are entirely different from any strain that humans have previously encountered. → **new HA and NA**
- **Why is it dangerous?**
  - Since the new virus is so different from any previous strain, the human population generally has no pre-existing immunity, which can lead to rapid and widespread transmission, causing pandemics.
- **Example:**
  - H1N1 "Swine Flu" Pandemic of 2009: This virus emerged from antigenic shift, when a virus from pigs reassorted with human flu viruses, creating a new strain that spread quickly across the globe.



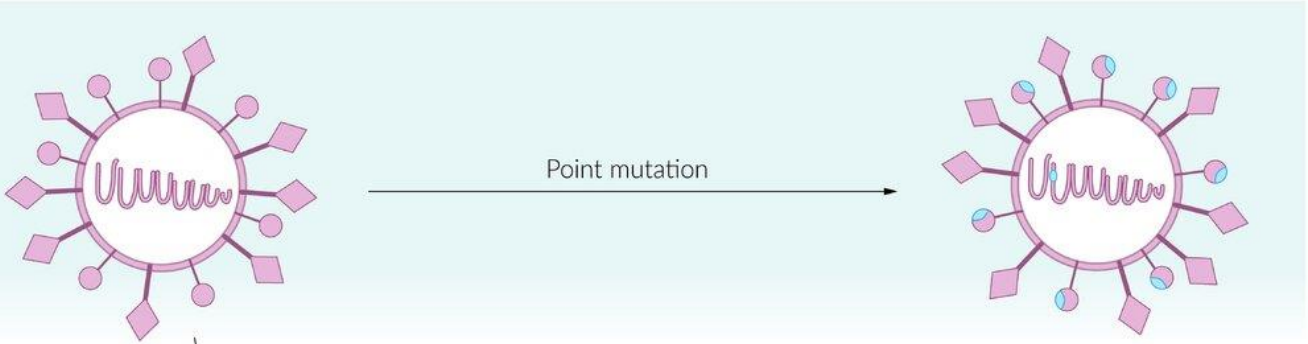
# Shift vs Drift

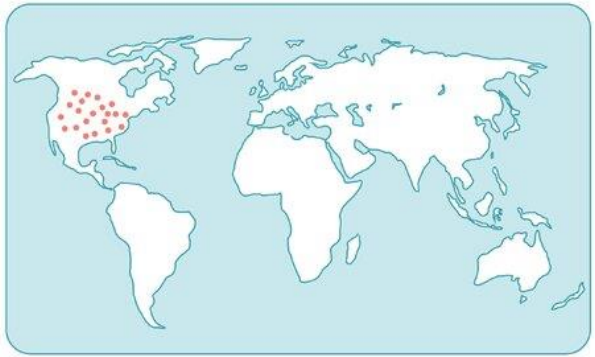
- **Why Does It Matter?**
  - **Antigenic Drift**: Causes gradual mutations, leading to seasonal flu outbreaks/epidemics and necessitating annual vaccine updates. The lack of proofreading by the virus's **RdRp** enzyme makes antigenic drift more frequent.
  - **Antigenic Shift**: Can cause major pandemics by creating entirely new viruses that can spread rapidly due to a lack of immunity in the population.




- **Questions?**
  - Why does Shift happen only in Influenza A? Because it's not only in human
  - Why Does Antigenic Drift Occur in Influenza A, B, and C?
  - What is the epidemiological outcome for each case?

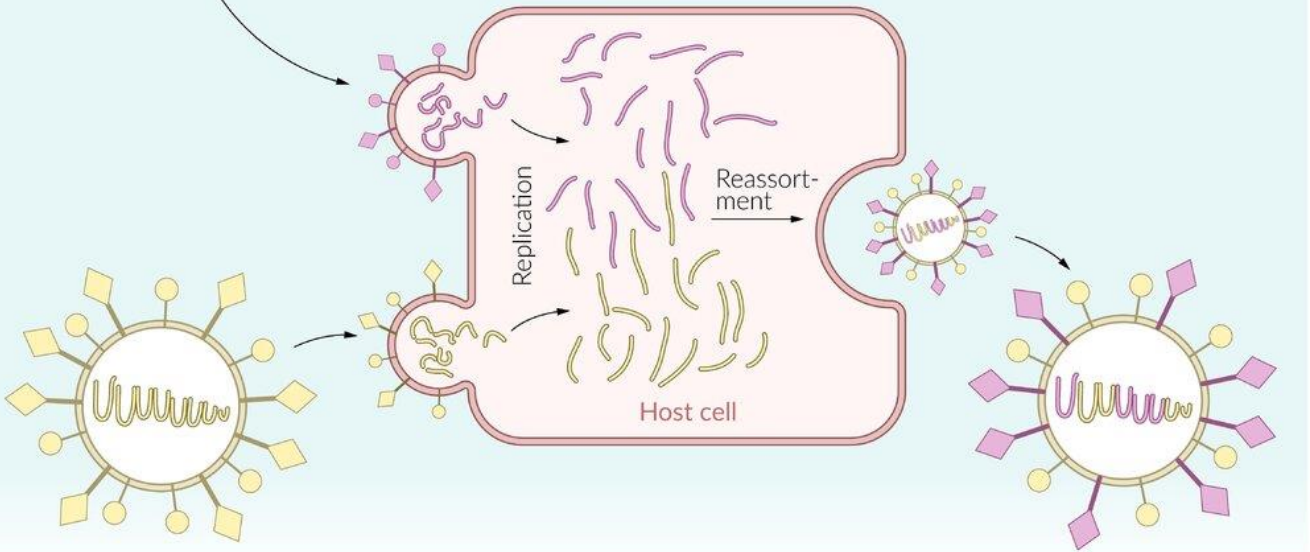
Antigenic drift



Associated with epidemics

Antigenic shift




Associated with pandemics

# Why does Shift happen only in Influenza A?

- Influenza A infects a variety of species: humans, birds, pigs, horses, and more. This creates opportunities for reassortment (genetic mixing) when different strains infect the same host. Strains from different species (e.g., bird and human flu) can swap RNA segments, creating new viruses with different surface proteins (H & N).

- Influenza B and C primarily infect humans (C sometimes infects pigs). Since they don't infect as many species, they lack the opportunity for genetic mixing across species, so antigenic shift does not occur in these types.

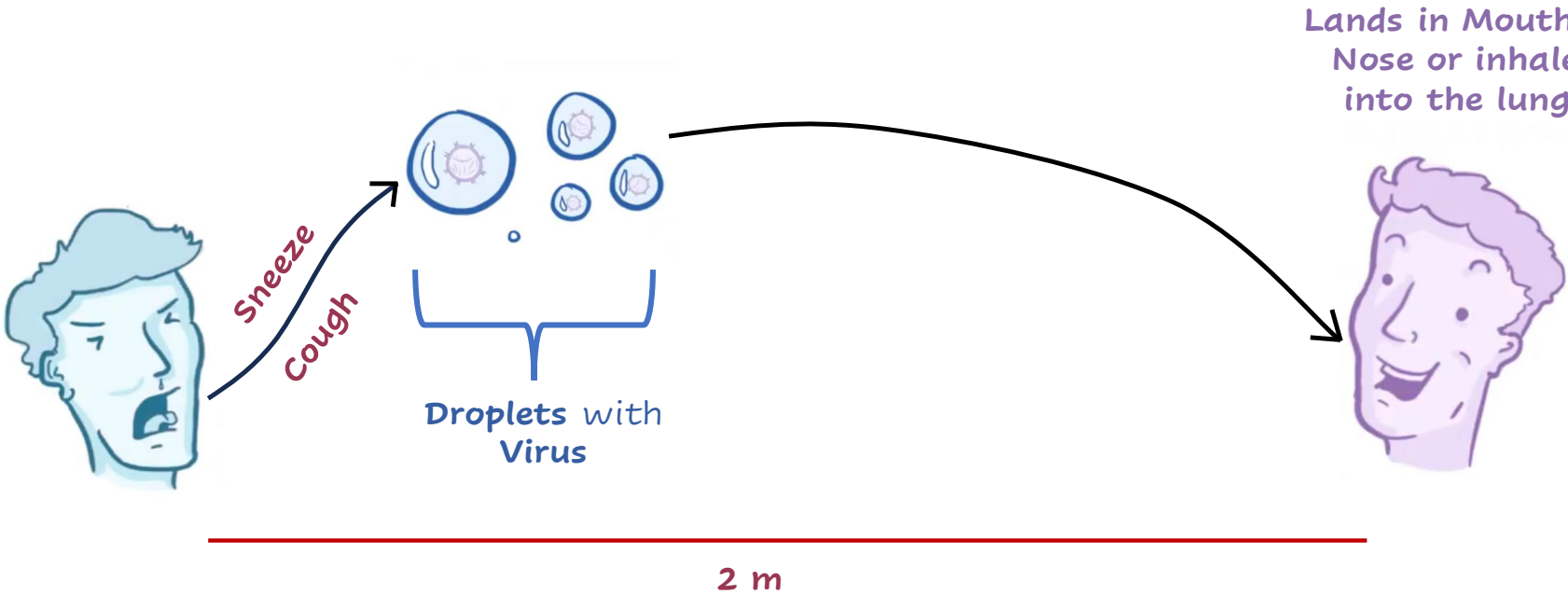
# Why Does Antigenic Drift Occur in Influenza A, B, and C?

- **RNA Polymerase Errors:** All influenza types (A, B, and C) rely on RNA-dependent RNA polymerase for replication. This enzyme lacks a proofreading mechanism, leading to frequent mutations.

# Orthomyxoviruses - Physical & biological characteristics

1. Can survive in cold sea water for several days.
2. Can stay in dust for more than 2 weeks/~1 week on human body.
3. Inactivated by:
    1. 30 minutes heat at 56°C.
    2. 20% Ether, Phenol, 70% Ethanol, Formaldehyde, soaps and many others.
4. Type A has many hosts, B infects human, C infects human and pigs.

# Mode of Transmission




**The virus can survive on surfaces for few hours, so it is possible to get the virus by touching a contaminated surface and then touching your nose or mouth**

→ *directly via respiratory droplets (sneezing or coughing) or indirectly through contact with contaminated surfaces*

# Orthomyxoviruses: Pathogenesis

- Usually no viremia.
- Multifactorial:
    1. Host factors
        - Immune status
        - Pre-existing conditions: Chronic diseases (e.g., COPD, asthma) worsen the course of infection
    2. Viral factors:
        - Infectious dose/droplet size
        - Viral-respiratory cells tropism (Influenza virus specifically targets respiratory epithelial cells due to its affinity for sialic acid receptors).
    3. Environmental:
        - Crowded environments: Close contact with infected individuals increases exposure.
        - Seasonality: Influenza is more prevalent in colder months due to factors like indoor crowding and longer virus survival in cool, dry air.

# Orthomyxoviruses: Pathogenesis (continue)

ال details مش حفظ

- Mechanisms of Damage
  - Respiratory Cell Damage:
    - The virus binds to **sialic acid receptors** on respiratory epithelial cells via **hemagglutinin (HA)** and enters through **endocytosis**.
    - After replication inside the cell, viral particles accumulate and cell lysis occurs, leading to **desquamation** (shedding of the epithelial cells).
  - Impaired Mucociliary Clearance:
    - Loss of epithelial cells impairs the mucociliary escalator, which normally clears pathogens and debris, making the lungs more susceptible to secondary infections.
  - Direct Tissue Toxicity:
    - The virus replicates within host cells, leading to **cell death** through lysis and **apoptosis**.
    - The immune response exacerbates tissue damage by releasing **cytokines**, increasing vascular permeability, and recruiting neutrophils that further damage tissues via enzymes and reactive oxygen species (ROS).
  - Increased Susceptibility to Bacterial Superinfection:
    - Damaged respiratory epithelial cells and impaired clearance mechanisms facilitate bacterial invasion, leading to superinfections (e.g., ***Streptococcus pneumoniae, Staphylococcus aureus***).

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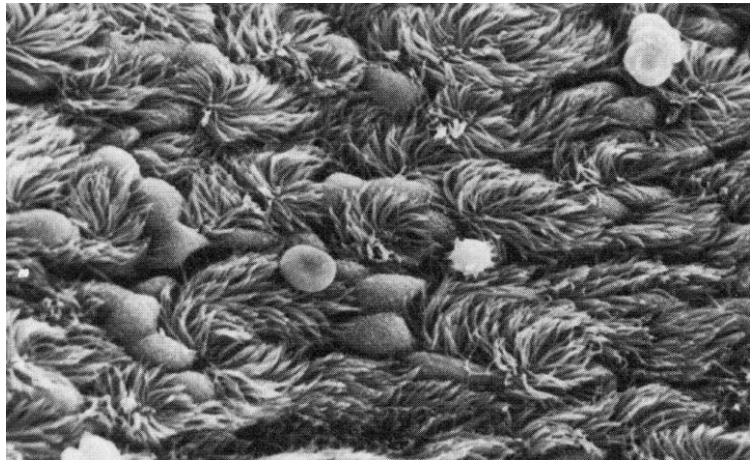
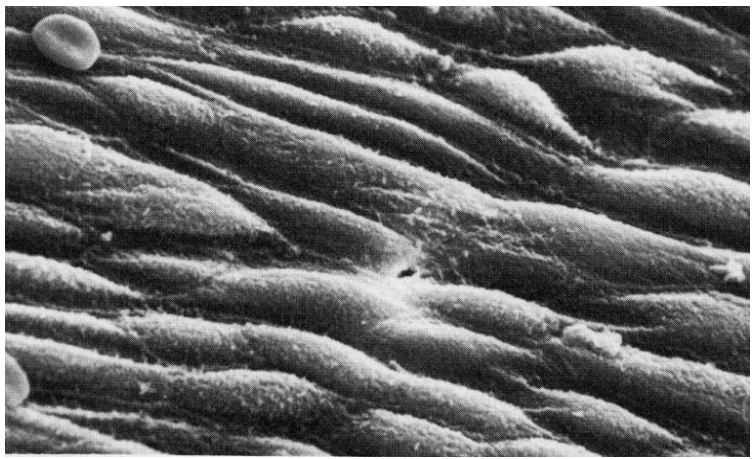


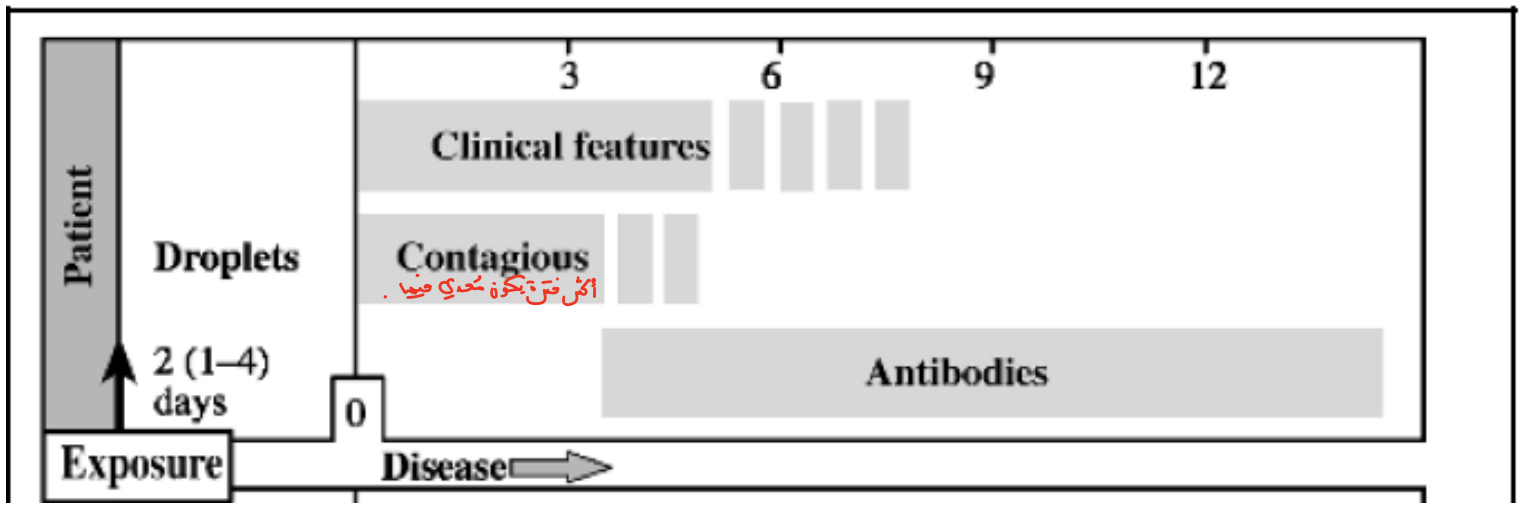
NORMAL TRACHEAL MUCOSA



3 DAYS POST-INFECTION

# Clinical Features

- Incubation period (I.P): 1-4 days.
- Symptoms may last 3-7 days on average.



# Clinically

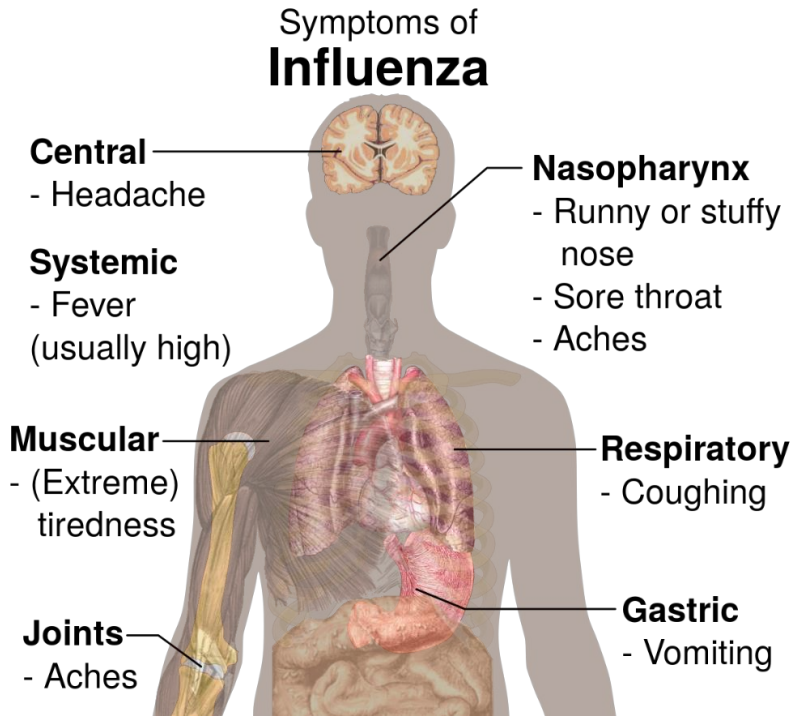
1. Main symptoms (mainly type A):
   - Symptoms appear 1 – 4 days after infection
   - Fever, Chills (1-5 Days) (Febrile Convulsions In Children).
   - Headache, Myalgia, Cough, Anorexia.
   - Rhinitis, Ocular Symptoms.
   - type B is somewhat milder, type C is usually afebrile.
   - Severity more in:
     1. Extreme ages and immunocompromised.
     2. Chronic lung and heart diseases.

here virus is just a trigger

نشنجات حرارية

# Clinically / cont'd

2. Pulmonary complications:
   - CROUP (YOUNG CHILDREN)
   - PRIMARY INFLUENZA VIRUS PNEUMONIA
   - SECONDARY BACTERIAL INFECTION
     - *Streptococcus pneumoniae*
     - *Staphlyococcus aureus*
     - *Hemophilus influenzae*
3. Non-pulmonary complications:
   - Cardiac: myositis (rare, > in children, > with type B).
   - liver and CNS.
     - Reye's syndrome
       - (encephalopathy + liver degeneration).
       - Precipitated by Aspirin.
       - Reye's also caused by parainfluenza and chickenpox.
   - Peripheral nervous system
   - Guillian-Barré syndrome/Ascending paralysis. (autoimmune disease)


Symptoms of
Influenza
Central
- Headache
Systemic
- Fever
(usually high)
Muscular
- (Extreme)
tiredness
Joints
- Aches
Nasopharynx
- Runny or stuffy
nose
- Sore throat
- Aches
Respiratory
- Coughing
Gastric
- Vomiting

# Pandemics

مش مطلوب ولا حفظ

- 1918 Spanish Flu H1N1: 20-40 million deaths
- 1957 Asian Flu H2N2: 1-4 million deaths
- 1968 H3N2 Hong Kong Flu 1-4 million deaths
- 1977 H1N1 again
- Recently in 2009, H1N1 (Swine) thousands of deaths
- (The 2009 H1N1 virus was a hybrid of swine, avian and human strains, Influenza A (H1N1)

# Diagnosis

1. Culturing the virus (in cells or eggs) from nasopharyngeal samples: takes long time (~ 7 days)
2. serology to detect at least a 4-fold increase in antibody titter
   - Needs 2 serum samples (paired) during the acute illness and 10-14 days later.
   - Good for epidemiology.
3. Immunofluorescent detection of viral antigens in respiratory samples, fast.
4. PCR to detect viral RNA: very sensitive but not widely available.

# Treatment and prevention

1. Symptomatic:
   - Fluids, analgesia BUT no ASPIRIN in children (<18).

2. Drugs (should be given early):
   A. Amantadine and rimantadine:
      - For type A
      - High resistance – not used any more
      - MOA: inhibit viral uncoating (M2 protein)

# Drugs (continue)

2. Drugs (continue):
   B. Neuroaminidase inhibitors
      - Zanamavir (Relenza/inhalation) and Oseltamivir (Tamiflu/orally), Permivir (Rapivab I.V).
      - Treatment of type A and B.
      - Mode of action: neuroaminidase inhibitors > inhibit viral release.

   C. Cap-dependent endonuclease inhibitor
      - Baloxavir marboxil
      - Active against both influenza A and B viruses
      - Acts by interfering with viral RNA transcription and blocks virus replication

# General prevention measures

1. Hand washing with soap, Alcohol-based handwipes or gel sanitizers are also effective.
2. Cover your nose and mouth with a tissue when you cough or sneeze. Throw the tissue in the trash after you use it.
3. Avoid touching your eyes, nose or mouth.
4. Germs spread this way.
5. Avoid contact with sick people.
6. Masks, social distancing

# Prevention / vaccine

- The aim is to produce HA antibody in the vaccines 2 weeks post vaccine.
- Should have the most 2 recent influenza A and 1-2 influenza B strains (determined by the WHO).
- Major vaccine types:
- Inactivated (formaldehyde), egg grown – I.M
- Life attenuated - Nasally
- 2. sub-unit vaccine for children.

# Vaccine

- Should be updated and given annually.
- Side effects: flu-like symptoms, localised injection site pain, GBS?
- Who should get it? Many, including
    1. Extreme ages
    2. Immunocompromised
    3. Patient with chronic illnesses, lung and heart problems.
    4. Pregnant women at any stage

# Vaccine C/I

- In general avoid in:
  - Severe Eggs allergy or previous vaccine allergy
  - Acute fever
  - In pregnant and people with immunosuppressant conditions; avoid life attenuated