Viral Respiratory Tract Infections (A)

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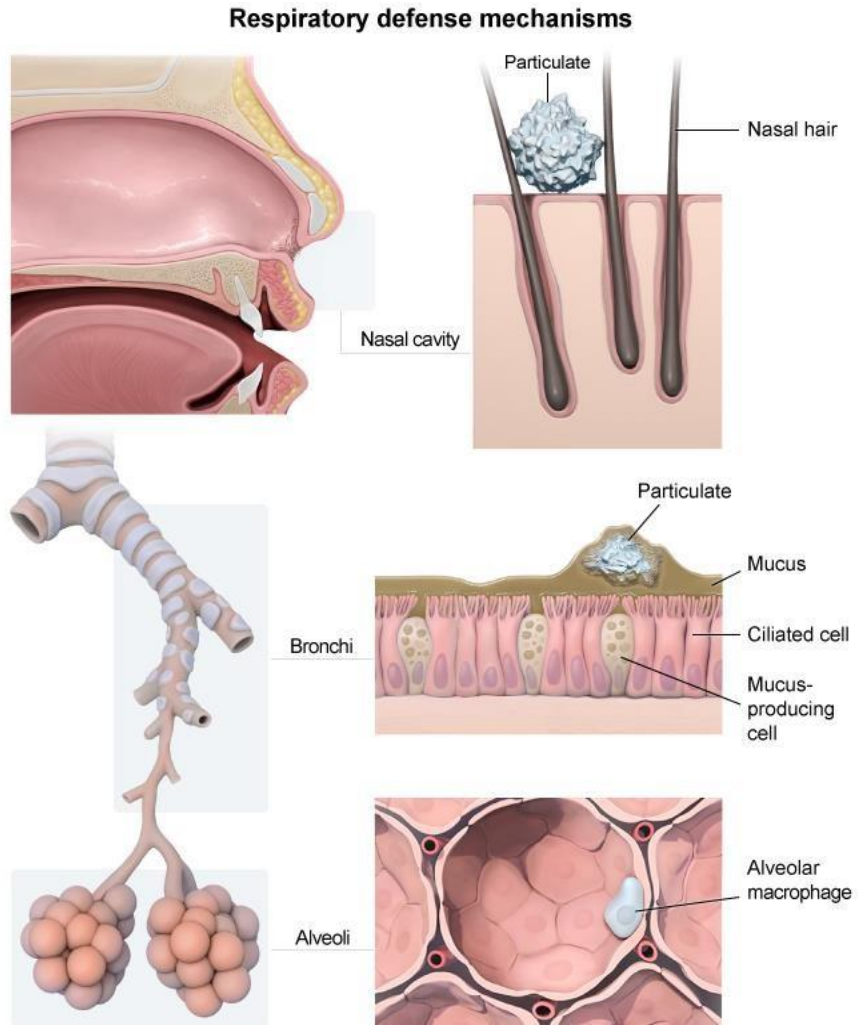
Respiratory Tract Defenses

- 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
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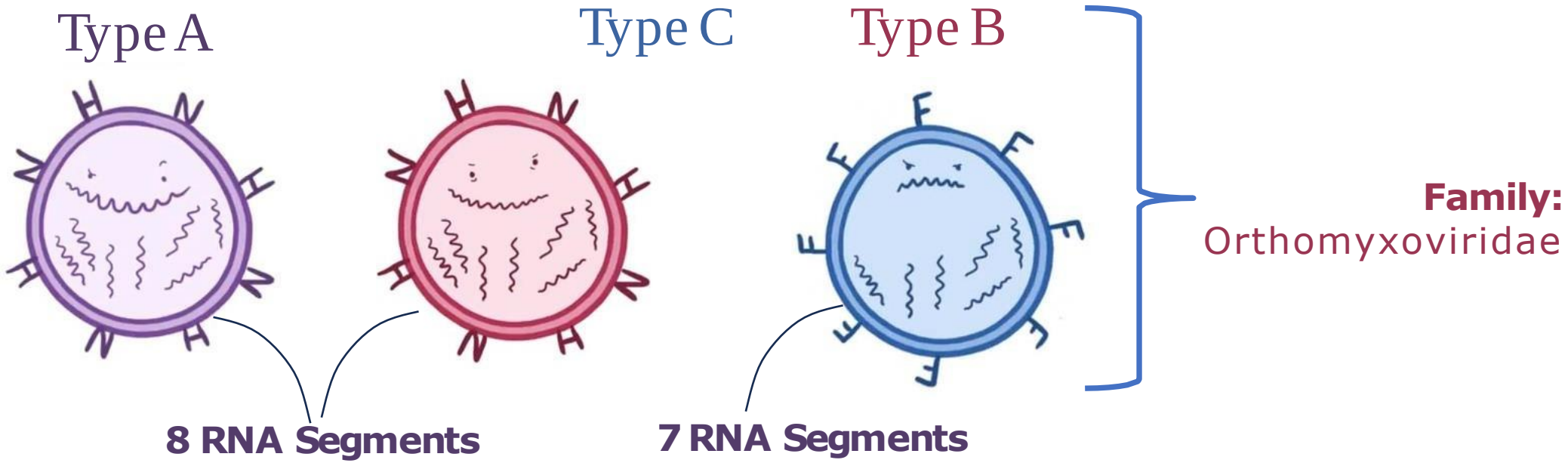
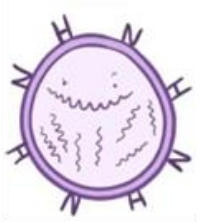
Introduction

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

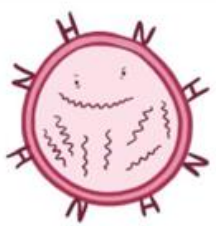


Orthomyxoviruses

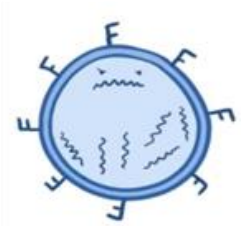
- **Family**: Orthomyxoviridae
- **Genera**: Total 7 Genera in Orthomyxoviridae
- The following are main genera:
  - Alpha influenza virus
    - Species: Influenza A virus
  - Beta influenza virus
    - Species: Influenza B virus
  - Gamma influenza virus
    - Species: Influenza C virus



Type A



Type B



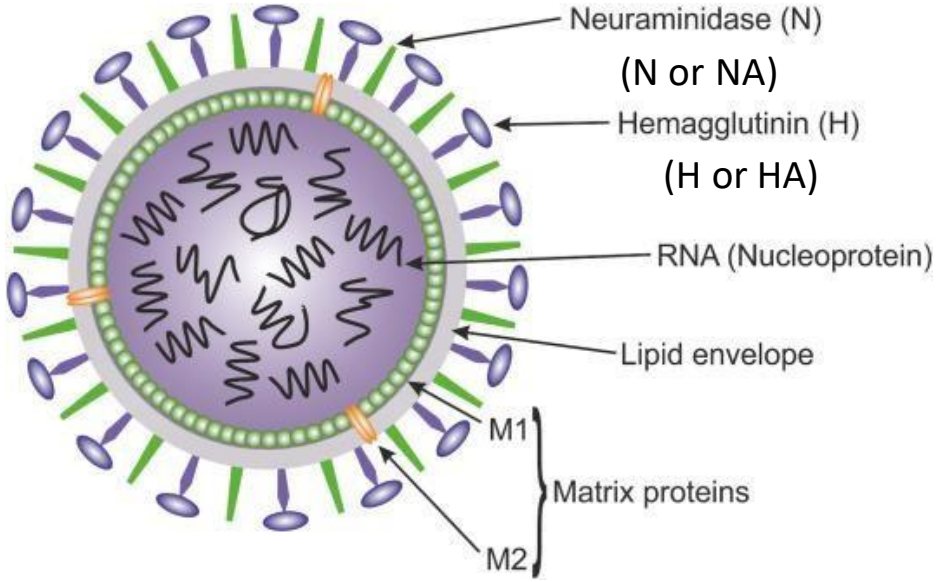
Type C

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

Structure and basic features (continue)

- **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)



Type A, B, C: NP, M1 protein

Sub-types: HA or NA protein

Orthomyxoviruses – Antigenicity

Influenza viruses have two types of antigens:

1. **Group specific antigens**:
   - Determined by Ribonucleoproteins and M1.
   - Distinguish types A, B and C.
2. **Type specific antigens**:
   - The HA, NA
   - Determine the subtype; e.g., H1N1, H3N2, H5N1…
   - HA antibodies are neutralising (protect) while NA antibodies are not.
   - Only **H1**, **H2**, **H3**, **N1**, **N2**, and **N8** have been associated with epidemics of disease in humans

Orthomyxoviruses – Antigenicity cont.

- **Haemagglutinin (17 subtypes)**
  - H or HA.
  - Allows the virus to adhere 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 of erythrocytes.
- **Neuraminidase (9 serotypes)**
  - N or NA.
  - Allows the release of newly formed viruses within the host.
  - Cleaves newly formed virions off the sialic acid-containing receptor, allowing the virus to exit cells
  - Determinant of disease severity.
- **M proteins (1 & 2)**
  - Found between the capsid and the envelope (only in type A)
  - Act as an ion channel to mainly change the endosomal pH

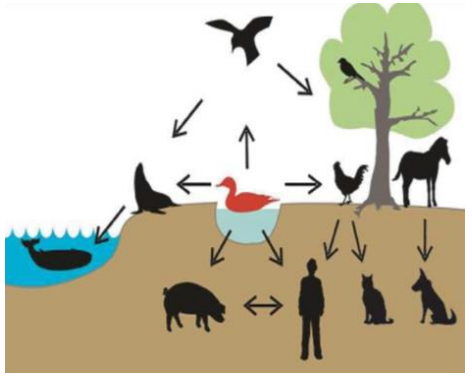
Influenza A

❖Reservoir

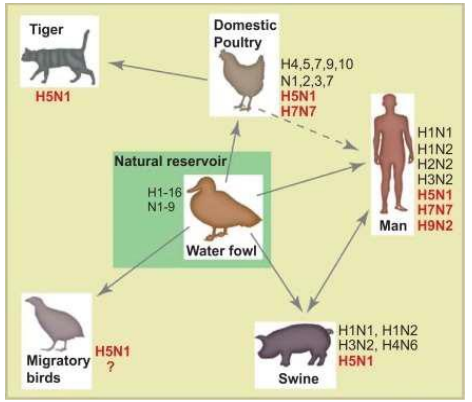
- **Wild aquatic birds** are the main reservoir of influenza A viruses.
- Virus transmission has been reported from wild waterfowl to poultry, sea mammals, pigs, horses, and humans.
- Viruses are also transmitted between pigs and humans, and from poultry to humans.
- Equine influenza viruses have recently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

❖Burden of influenza virus

- Acute febrile illness with variable degrees of systemic symptoms, ranging from mild fatigue to respiratory failure and death.
- WHO estimated that 3-5 million cases of severe illness and about 250,000 to 500,000 deaths occur annually.

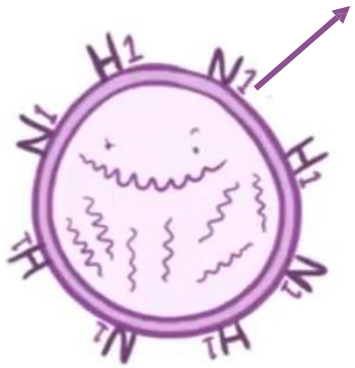


influenza A subtypes



Orthomyxoviruses – 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.
- **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

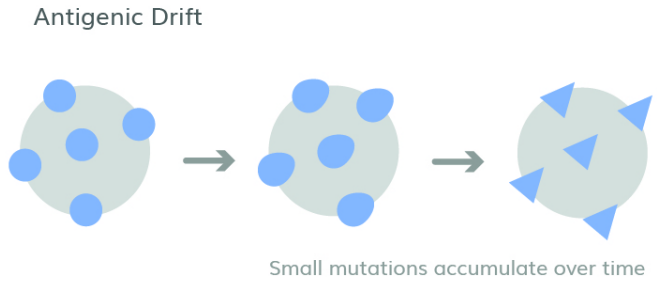
A / Duck / Alberta/ 35 / 76 (H1N1)

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.

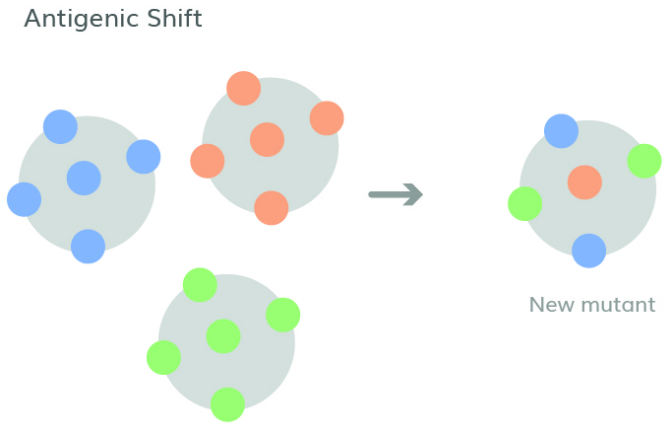
Antigenic Drift

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 important?	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.



Antigenic Drift Vs Shift

❖Why Do Flu Viruses Keep Changing?

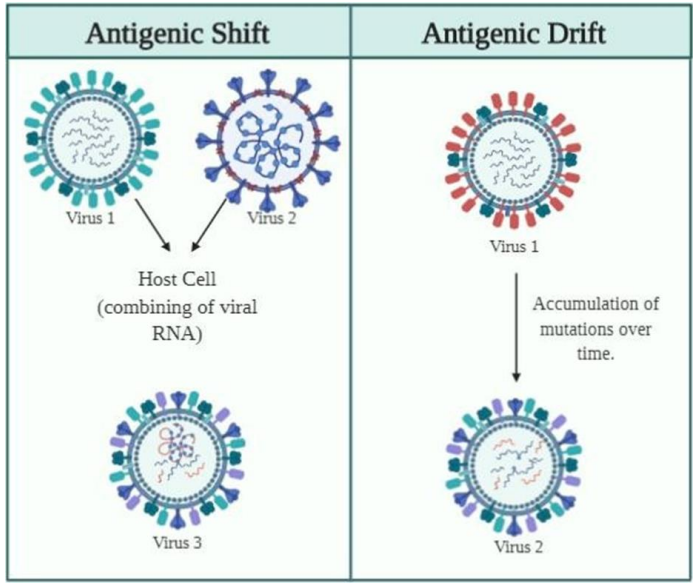
- Due to antigenic drift and shift

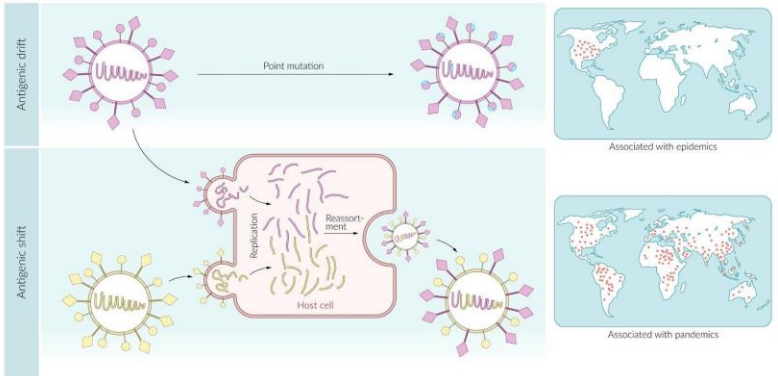
❖Why do we need a new flu vaccine every year?

- **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.

❖What causes pandemics?

- **Antigenic Shift**: Can cause major pandemics by creating entirely new viruses that can spread rapidly due to a lack of immunity in the population





Antigenic Drift Vs Shift

❖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.

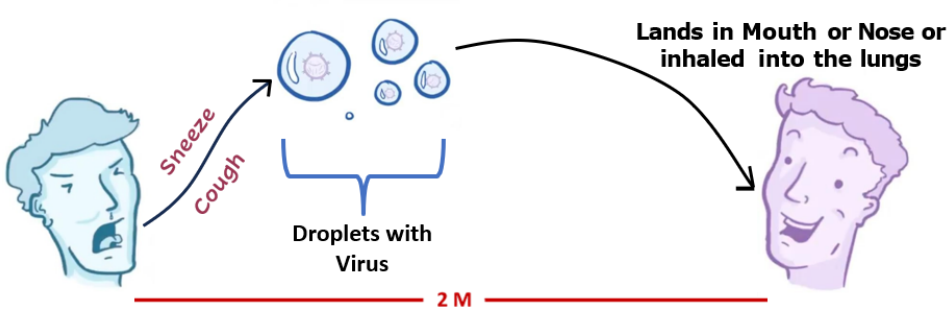
Orthomyxoviruses

❖Physical & biological characteristics

1. Can survive in cold sea water for several weeks.
2. Can stay in dust for more than 2 weeks/~1 week on human body.
3. Inactivated by:
   A. 30 minutes heat at 56°C.
   B. 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

- Directly via respiratory droplets (sneezing or coughing) or indirectly through contact with contaminated surfaces
- 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



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.

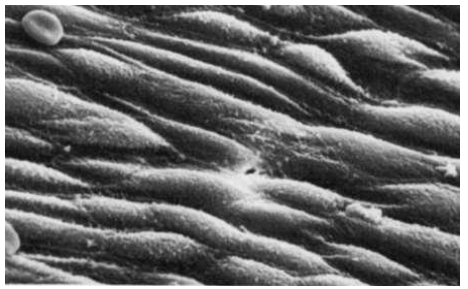
Pathogenesis – Mechanisms of Damage

- **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).0

Orthomyxoviruses – Clinically

- More in winter, crowded areas.
- Incubation period: 1-4 days.
- Symptoms may last 3-7 days on average
    1. Main symptoms (mainly type A):
        - Sudden onset:
            - 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.

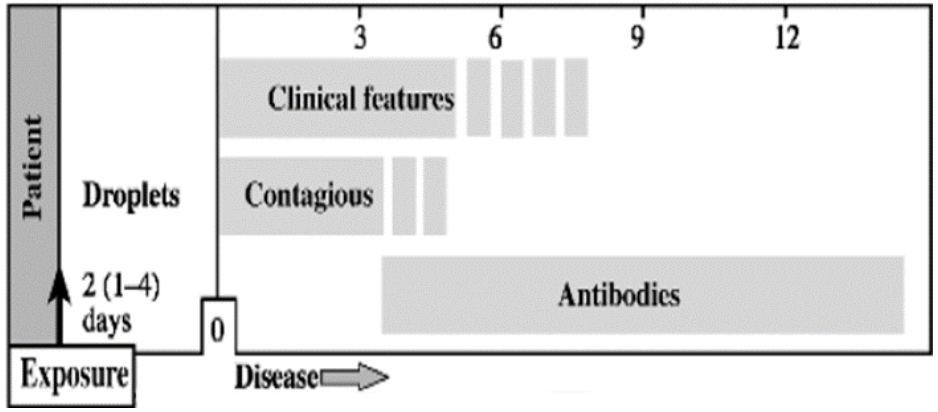
Normal tracheal mucosa



3 days post-infection

Orthomyxoviruses – Clinically cont.

2. **Pulmonary complications**
   - Croup (young children)
   - Primary influenza virus pneumonia
   - Secondary bacterial infection
     - Streptococcus pneumoniae
     - Staphylococcus 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)

Orthomyxoviruses – Pandemics

- 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
- In 2009, H1N1 (Swine) thousands of deaths (The 2009 H1N1 virus was a hybrid of swine, avian and human strains, Influenza A (H1N1)

Orthomyxoviruses – 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 titer
   - 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.

Orthomyxoviruses – Treatment & Prevention

❖**Symptomatic**
- Fluids, analgesia BUT no ASPIRIN in children (<18).

❖**Drugs** (should be given early)

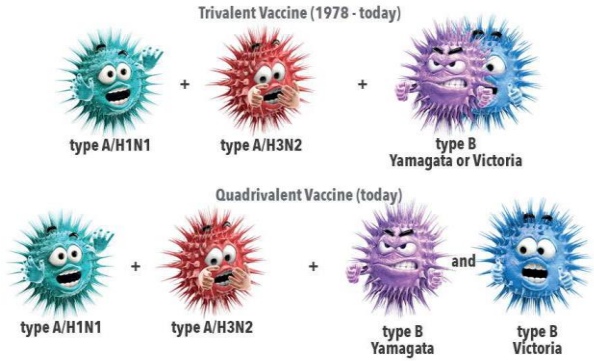
1. Amantadine and rimantadine:
   - For type A
   - High resistance – not used anymore
   - Mechanism of Action: inhibit viral uncoating (M2 protein)
2. **Neuroaminidase inhibitors**
   - Zanamavir (Relenza/inhalation) and Oseltamivir (Tamiflu/orally),
   - Permivir (Rapivab I.V).
   - Treatment of type A and B.
   - Mode of action: neuroaminidase inhibitors > inhibit viral release.
3. **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

Orthomyxoviruses – general prevention measures

1. Hand washing with soap, Alcohol-based hand wipes, 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. Avoid contact with sick people
5. Masks, social distancing

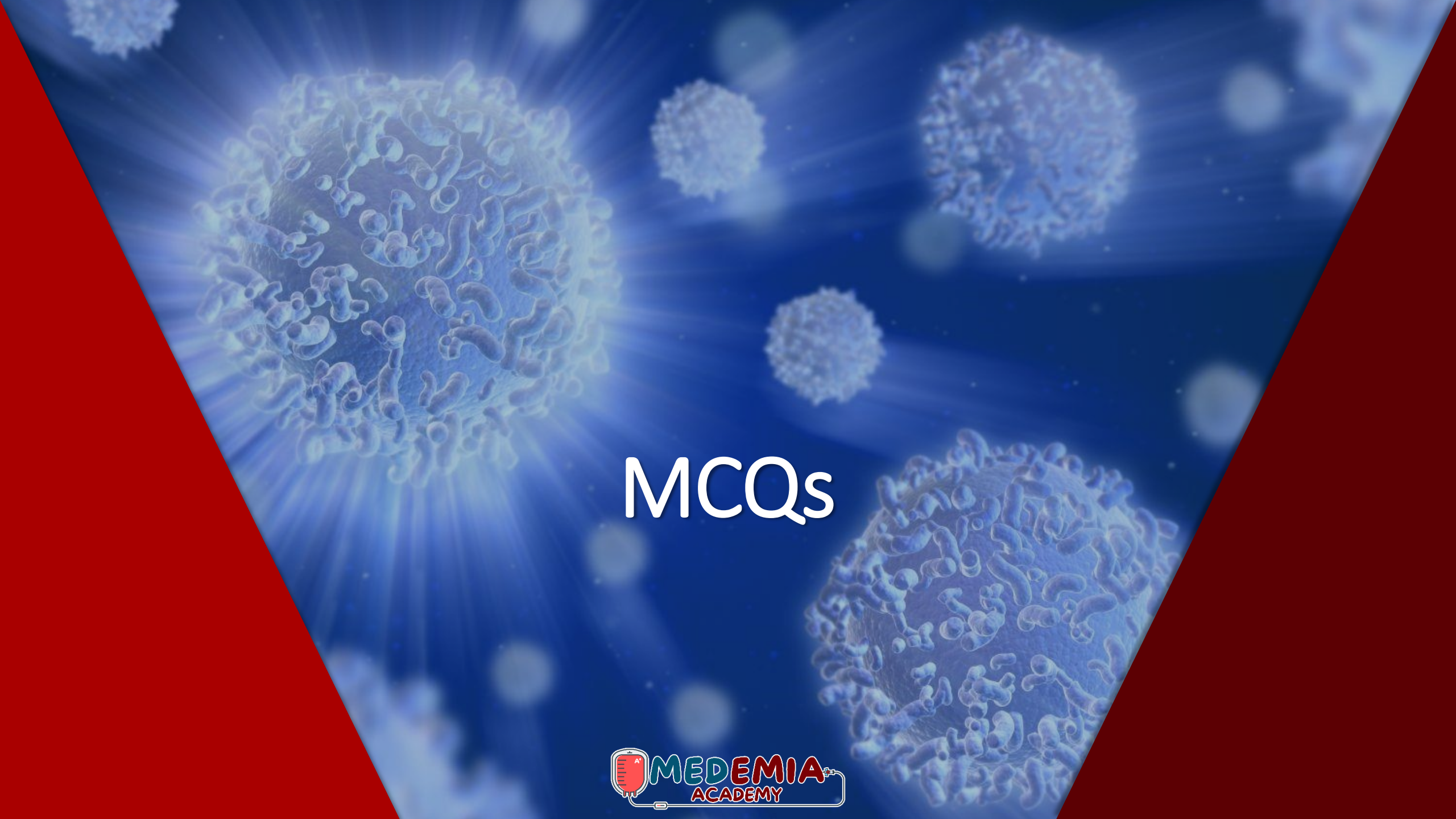
Orthomyxoviruses – Prevention & vaccine

- 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**:
  1. Inactivated (formaldehyde), egg grown – I.M
  2. Life attenuated - Nasally
  3. sub-unit vaccine for children.
- **Currently**: type A - H1N1, type A - H3N2 and 1-2 types of B



Orthomyxoviruses – Prevention & vaccine

- Should be updated and given annually.
- **Side effects**: flu-like symptoms, localized injection site pain, GBS?
- Who should get it? Many, including
  - Extreme ages
  - Immunocompromised
  - Patient with chronic illnesses, lung and heart problems.
  - Pregnant women at any stage
- In general, avoid in:
  - Severe egg allergy (Not a valid contraindication any more) or previous vaccine allergy
  - Acute fever
  - In pregnant and people with immunosuppressant conditions; avoid life-attenuated


MCQs
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MCQs

❖ **Each of the following statements concerning diagnosis, prevention and treatment of influenza is correct EXCEPT?**

a.The influenza vaccine is a trivalent vaccine
b.The main antigen in the vaccine that induces protective antibody is the hemagglutinin
c.QUICKVUE Influenza Test is a rapid test based on detection of viral neuraminidase
d.Amantadine block the M2 ion channel, thereby inhibiting uncoating
e.Zanamivir is a member of a class of drugs called neuraminidase inhibitors

Answer : C

❖ **Each of the following statements concerning influenza viruses is correct EXCEPT?**

a.Major epidemics of the disease are caused by influenza A virus
b.The virion contains an RNA genome with negative polarity
c.Likely sources of new antigens for influenza A viruses are the viruses that cause influenza in animals
d.The neuraminidase on the virion surface mediates the interaction of the virus with the receptors on the respiratory tract epithelium
e.H1N1 is a swine flu virus

Answer : D

MCQs

- **Antigenic shift, one is wrong?**
  - a. It is seen in influenza A virus
  - b. Caused by minor point mutation
  - c. Pre-existing antibodies do not protect fully against the shifted virus

  - Answer : B

- **What causes shift mutation in its genome?**
  - a. Adenovirus
  - b. Influenza A
  - c. Paramyxovirus
  - d. Rhinovirus

  - Answer : B

MCQs

- **Antigens that are group specific:**
  - a. Ribonucleoprotein
  - b. NA
  - c. HA
  - Answer : A
- **Neutralizing antibodies for influenza are for?**
  - a. Hemagglutinin
- **Zanamivir and oseltamivir?**
  - a. Neuraminidase inhibitors

MCQs

❖**Type-specific antigen of influenza virus is:**

a. Ribonucleoprotein

b. HA only

c. HA and NA

d. M protein

Answer : C

MCQs

- **Each year there are discussions about new formulations of the vaccine for influenza A virus. Why?**
  a. Because the vaccine is comprised of several drugs that are active against the virus for one season
  b. Because of the changes that occur in the neuraminidase protein together with the nucleocapsid antigen
  c. Because mutations occur mainly in the envelope proteins, hemagglutinin, and neuraminidase
  d. Mutations predominantly take place in the matrix protein that interacts with the host cell receptor
  e. The half-life of the vaccine is a few months and degrades quickly in host cells

Answer : C

MCQs

❖ **Regarding influenza virus and the disease influenza, which one of the following statements is MOST ACCURATE?**

a. Antigenic shift involves major changes in antigenicity that result from reassortment of the segments of its RNA genome

b.The genome of influenza A virus has eight segments, but the genome of influenza B virus is in one piece

c.The killed vaccine induces lifelong immunity

d.The classification of influenza viruses into A, B, and C viruses is based on antigenic differences in their hemagglutinin

e.Chronic carriers (i e, patients from whom influenza virus is isolated at least 6 months after the acute disease) are an important source of human infection

Answer : A

Thank you

Dr. Reef Alqaissi

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