Viral Respiratory Tract Infections (A)

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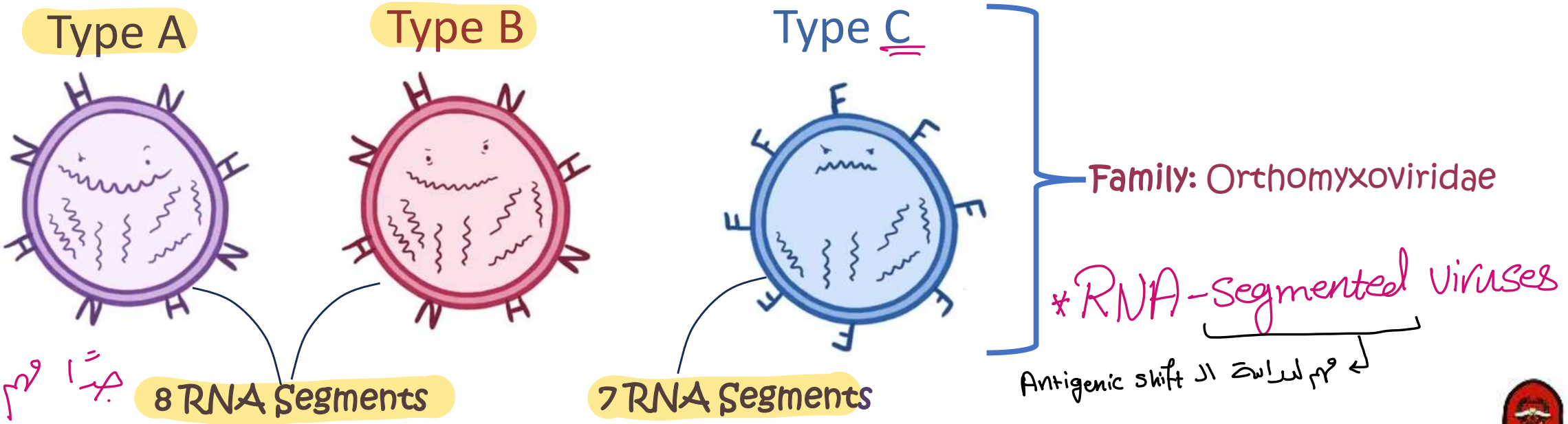
Influenza virus (Introduction)

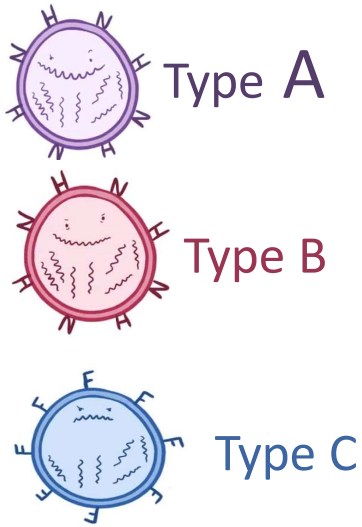
Common Cold	influenza
- low grad fever - runny nose - stable health	- high grad fever - sever illness - sever myalgia - Can't even get out of the bed

- **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

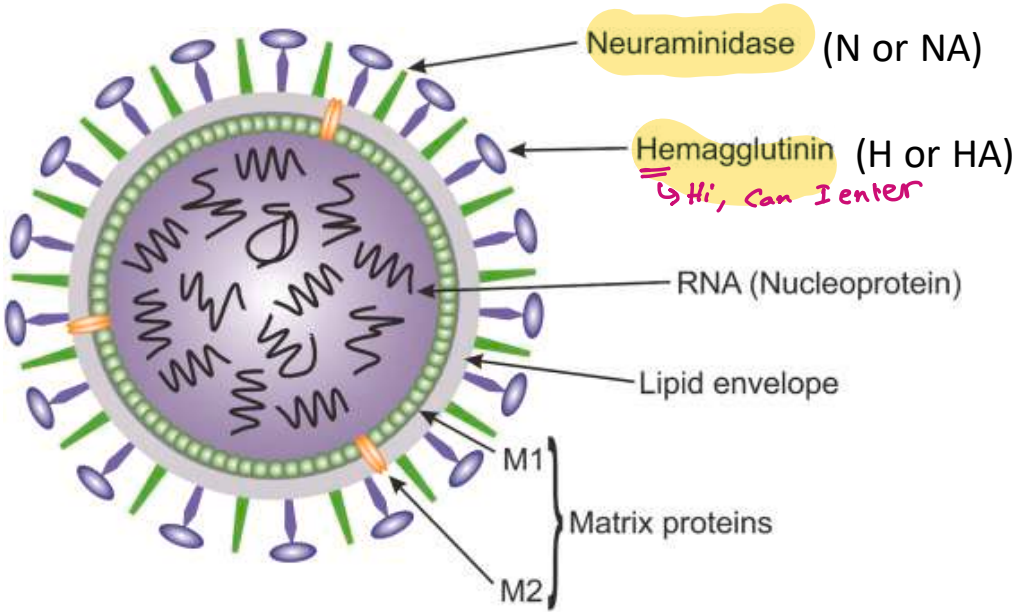
- Capsid: large (~ 80-120 nm in diameter), enveloped, helical
- Genome:
  - Single stranded RNA (ssRNA)
    - Linear
    - Negative sense
    - Segmented: 8 segments (types A and B), 7 segments in type C.
- Has RNA-dependent RNA polymerase (RDRP) → (important for infectivity/has transcription errors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

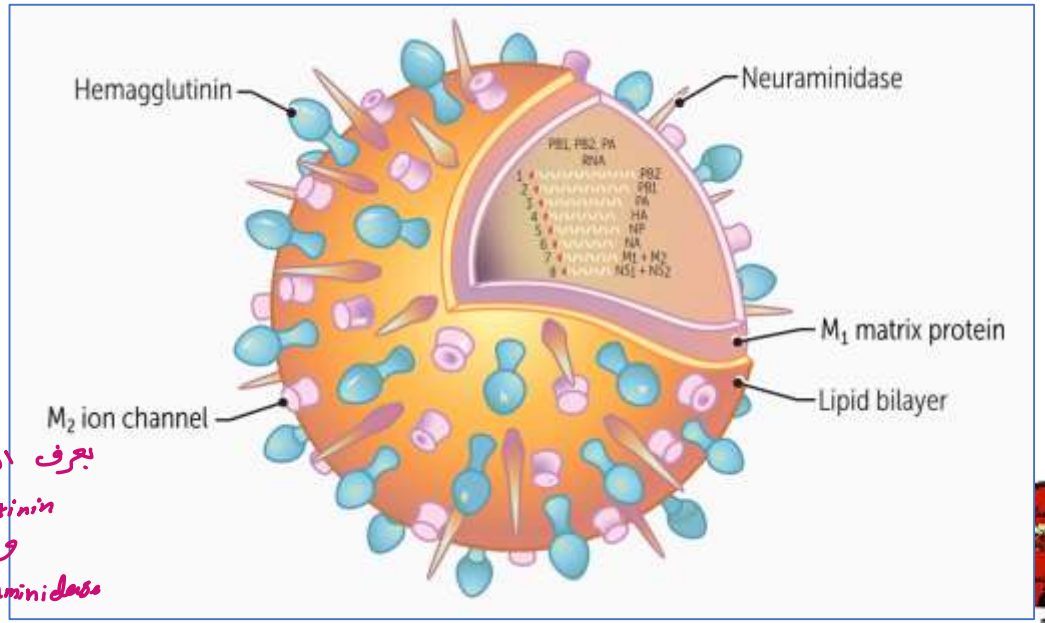
Orthomyxoviruses - Structure and basic features (continue)

- 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 ⇒ only in (type A)





Viral proteins

- **Hemagglutinin (HA) (18 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 (11 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.

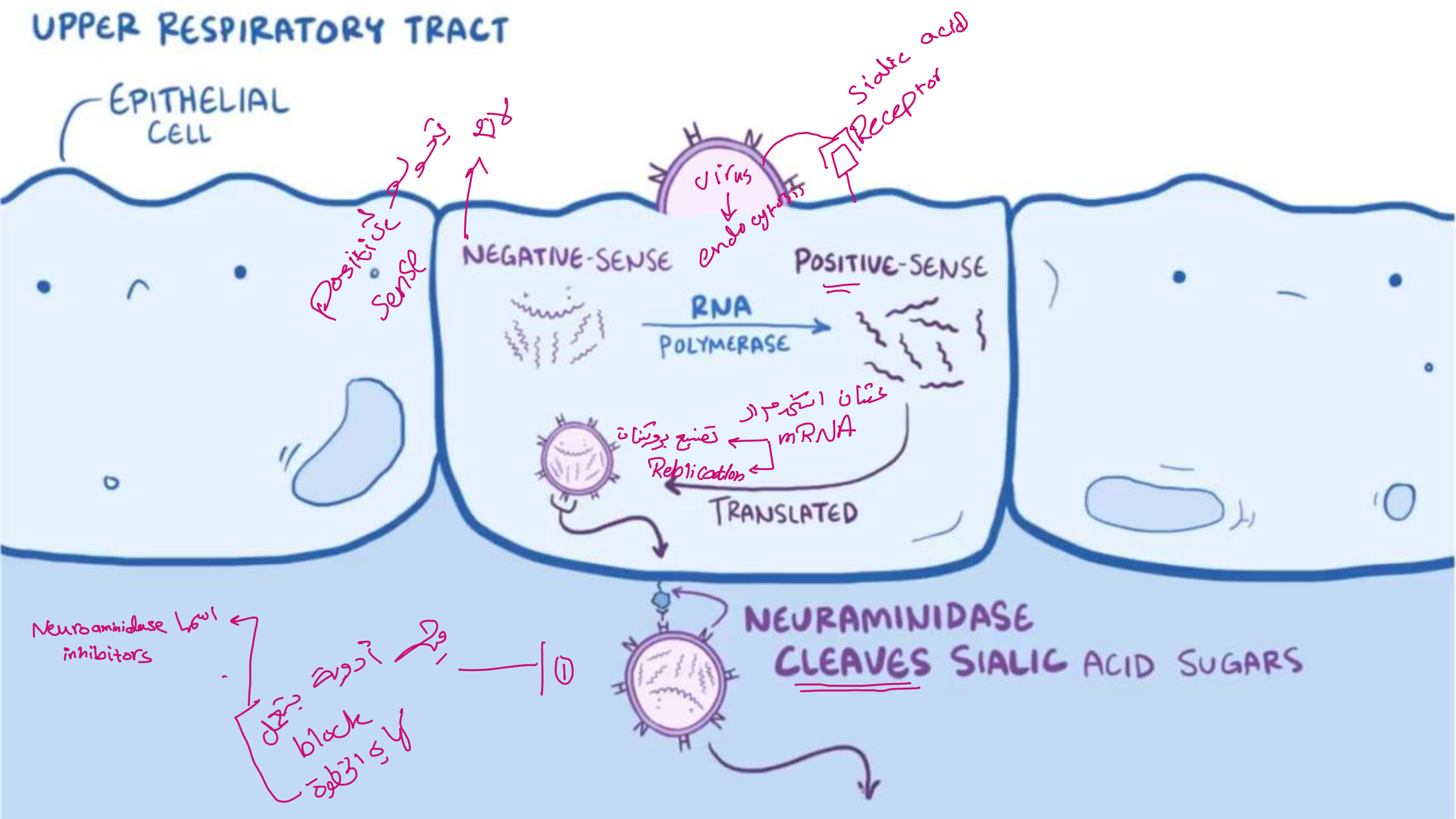
Determine the subtype:
E.g H1N1, H3N2, H5N1….

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

لأنه كلما صار release لل Viruses من Cell
كما راح ل Cells ثانية وصارت ال severity أعلى

Viral proteins (cont.)

- **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


UPPER RESPIRATORY TRACT
EPITHELIAL CELL
Positive sense
DNA
virus
endocytosis
Sialic acid
Receptor
NEGATIVE-SENSE
POSITIVE-SENSE
RNA
POLYMERASE
TRANSLATED
Replication
mRNA
NEURAMINIDASE
CLEAVES SIALIC ACID SUGARS
Neuraminidase
inhibitors
block

Life cycle summary

لساعدك على الفهم بس مش مطلوب

Orthomyxoviruses / Antigenicity

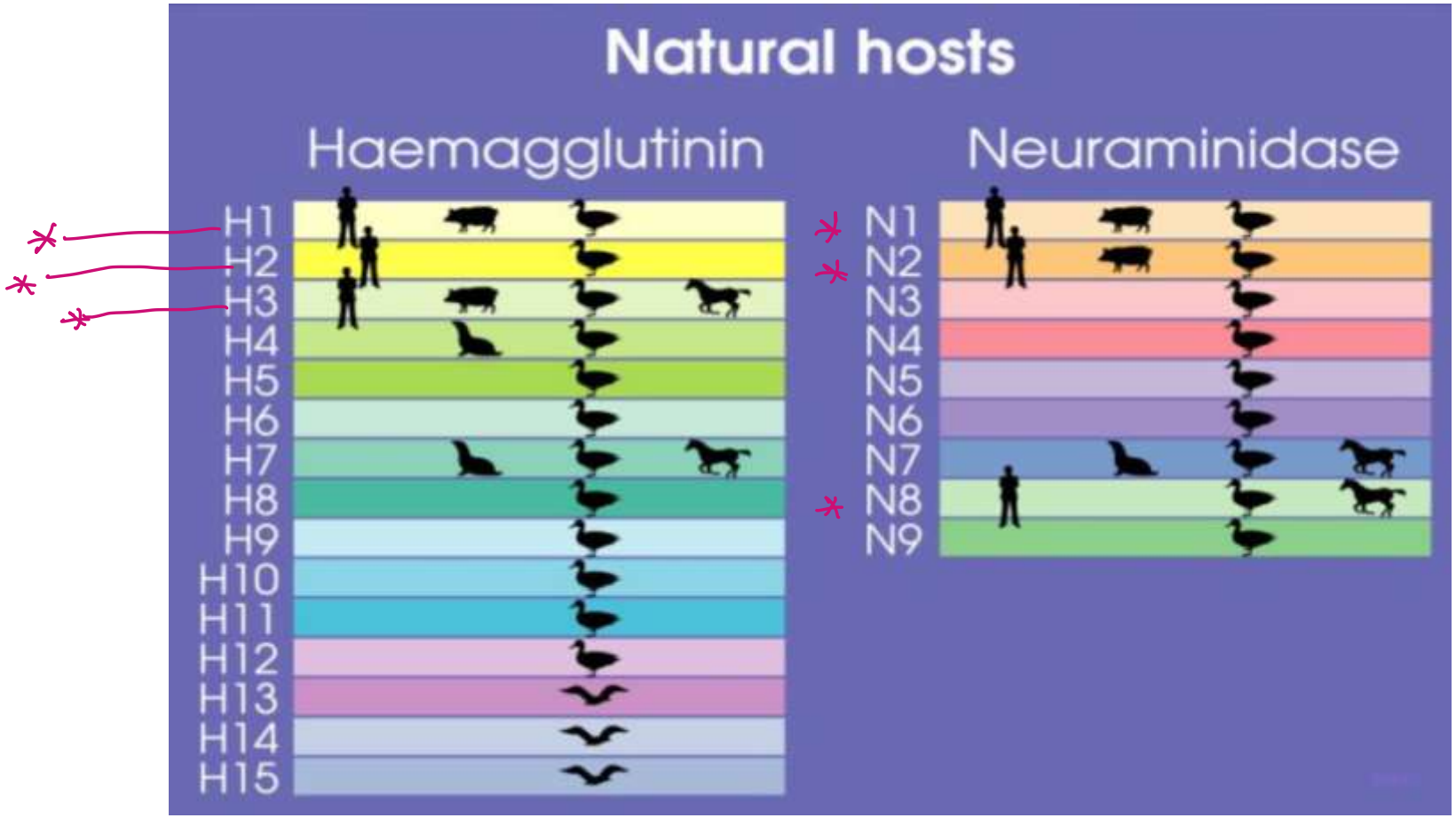
- Influenza viruses have two types of antigens: group-specific antigens and type-specific antigens.

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.

Natural hosts



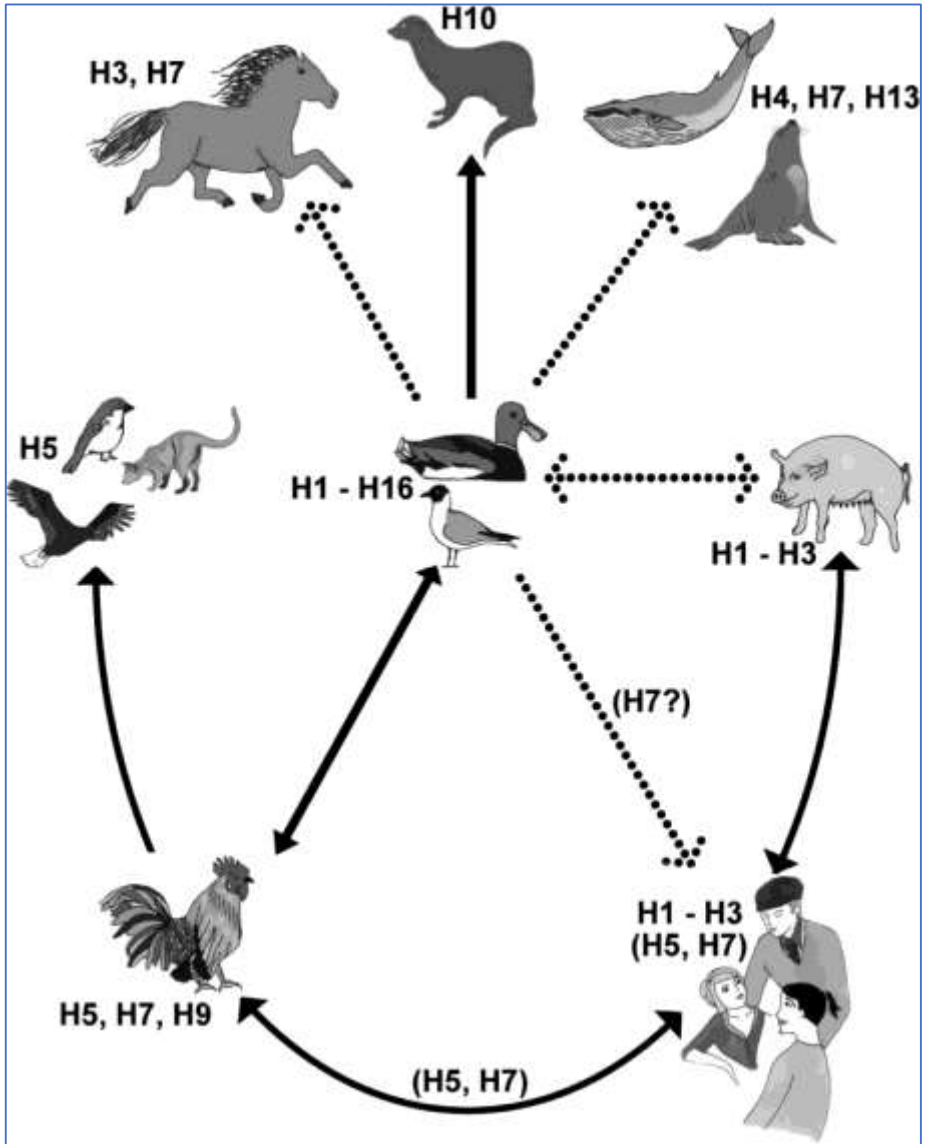
Note: Only memorize which proteins are found in humans.

H_1, H_2, H_3

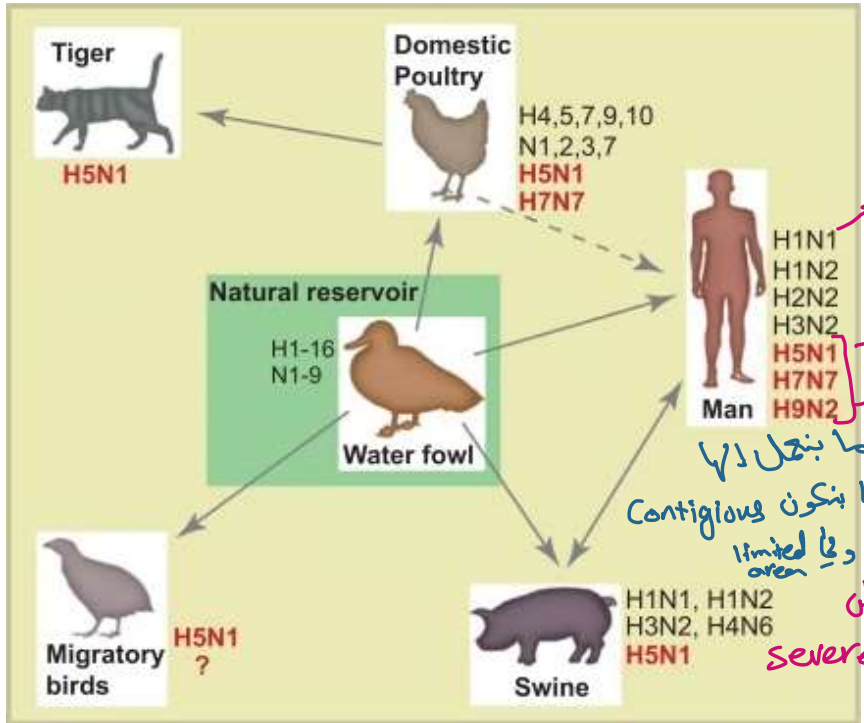
N_1, N_2, N_8

موجودين Human

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.



Nomenclature

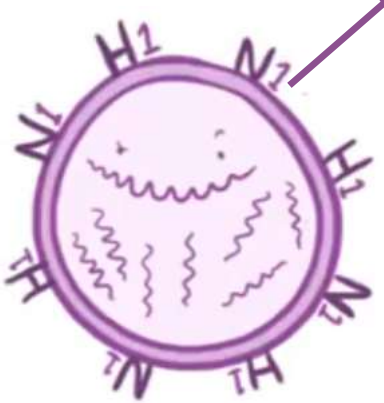
- Influenza A has 18 distinct H subtypes and 11 distinct N subtypes, of which only H1, H2, H3, N1, and N2 have been associated with epidemics of disease in humans.

- 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 vs Antigenic Shift

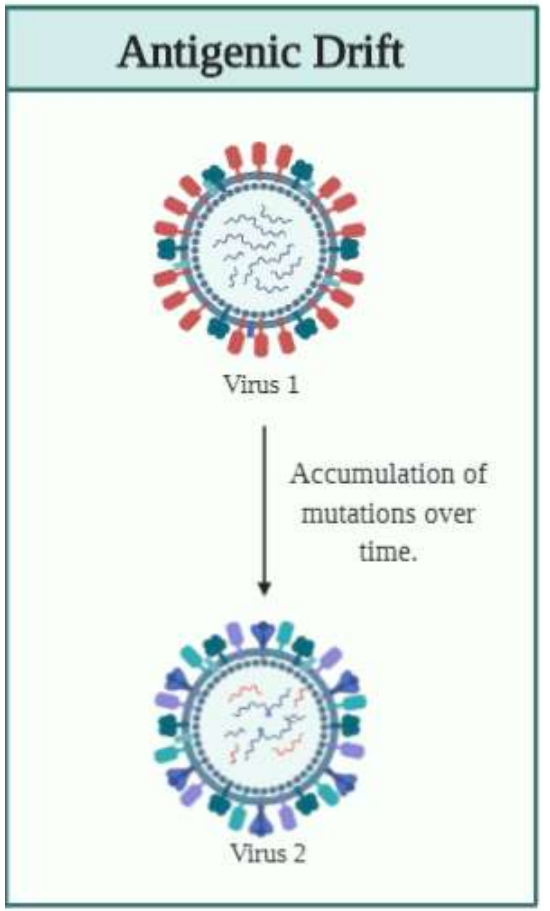
Antigenic Drift ←

* بسبب الـ Mutations اللي كان يحدث

1/10k ← (RDRP)

Antigenic Drift

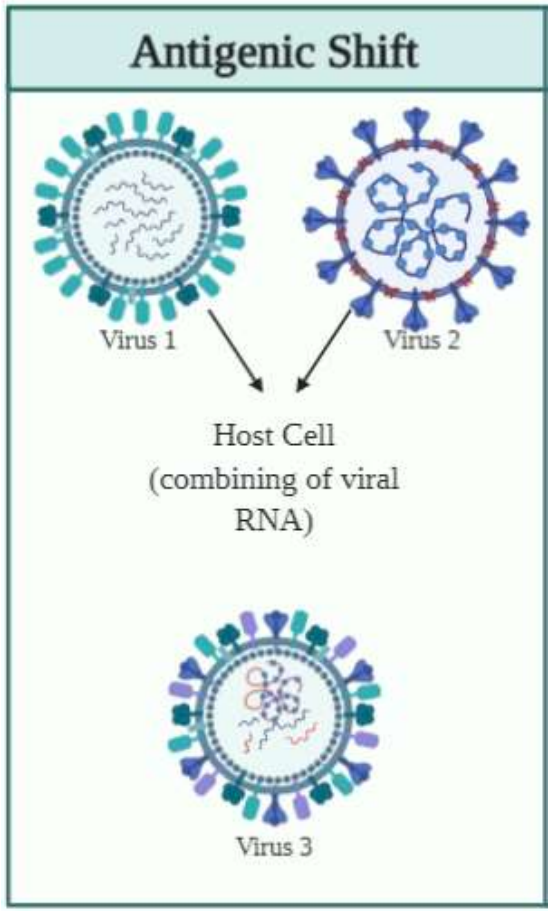
- **What is it?**
  - Gradual Changes Over Time
  - Antigenic drift refers to small, gradual changes that occur in the genetic material of the influenza virus over time, particularly in the genes that code for its surface proteins like **hemagglutinin (H)** and **neuraminidase (N)**. These changes lead 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

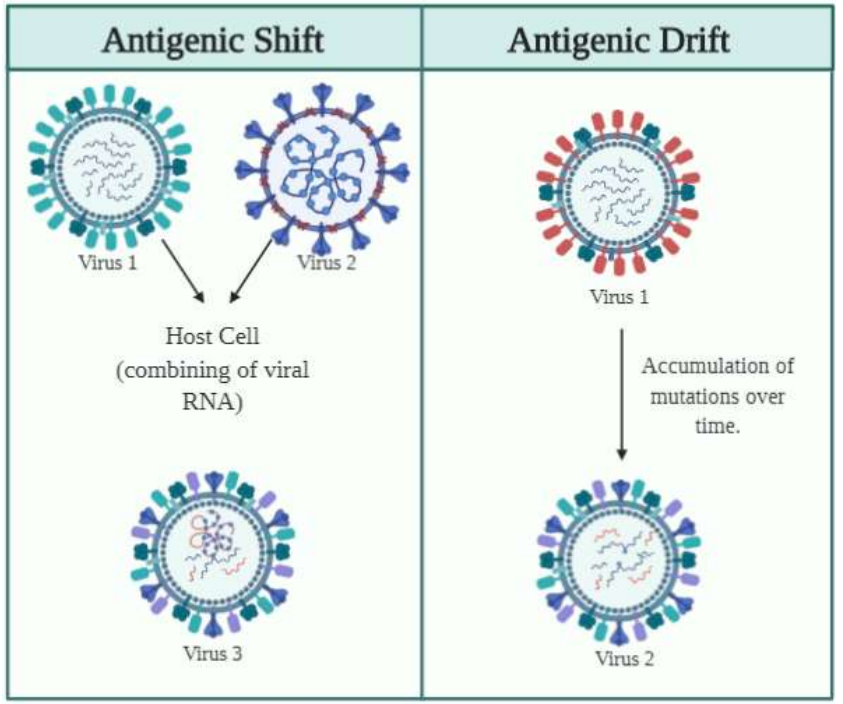
بحصل انفلاروس كامل ؟ Major changes

- **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.



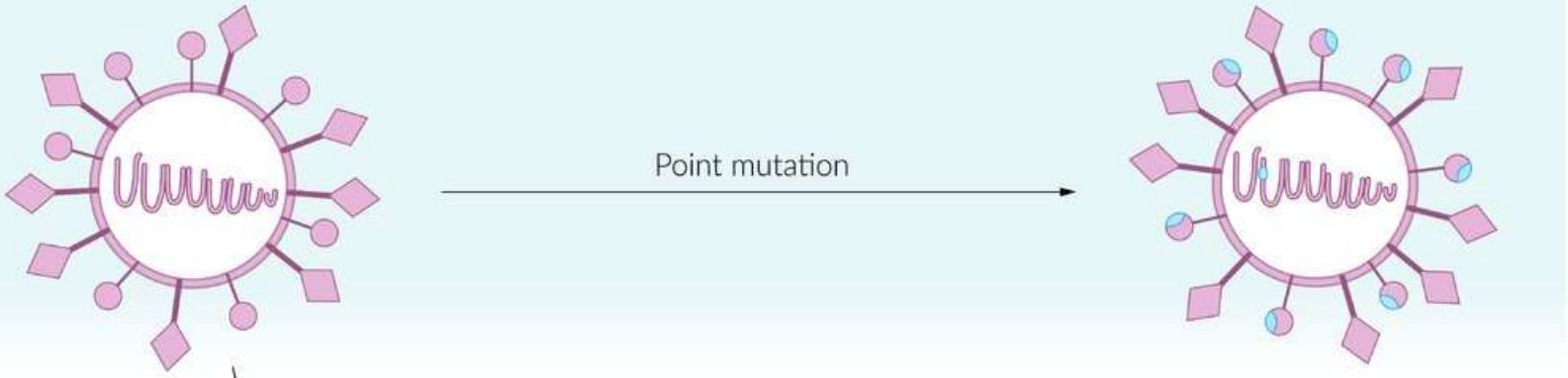
Shift vs Drift

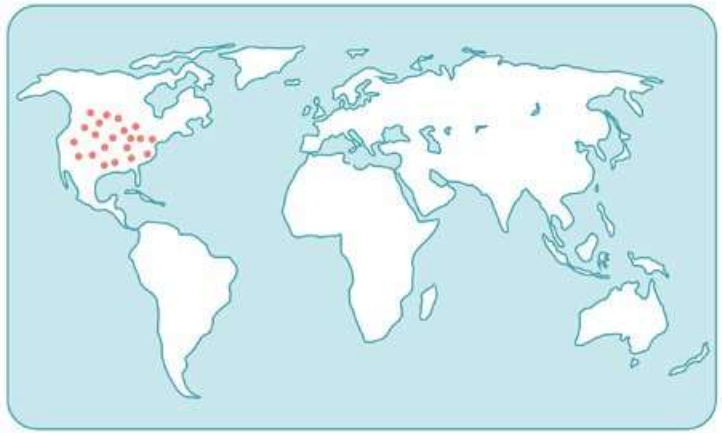
- **Why Does It Matter?**
  - **Antigenic Drift**: Causes gradual mutations, leading to seasonal flu outbreaks/epidemics and necessitating annual vaccine updates. The lack of proofreading by the virus's **RdRp** enzyme makes antigenic drift more frequent.
  - **Antigenic Shift**: Can cause major pandemics 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?
  - Why Does Antigenic Drift Occur in Influenza A, B, and C?
  - What is the epidemiological outcome for each case?

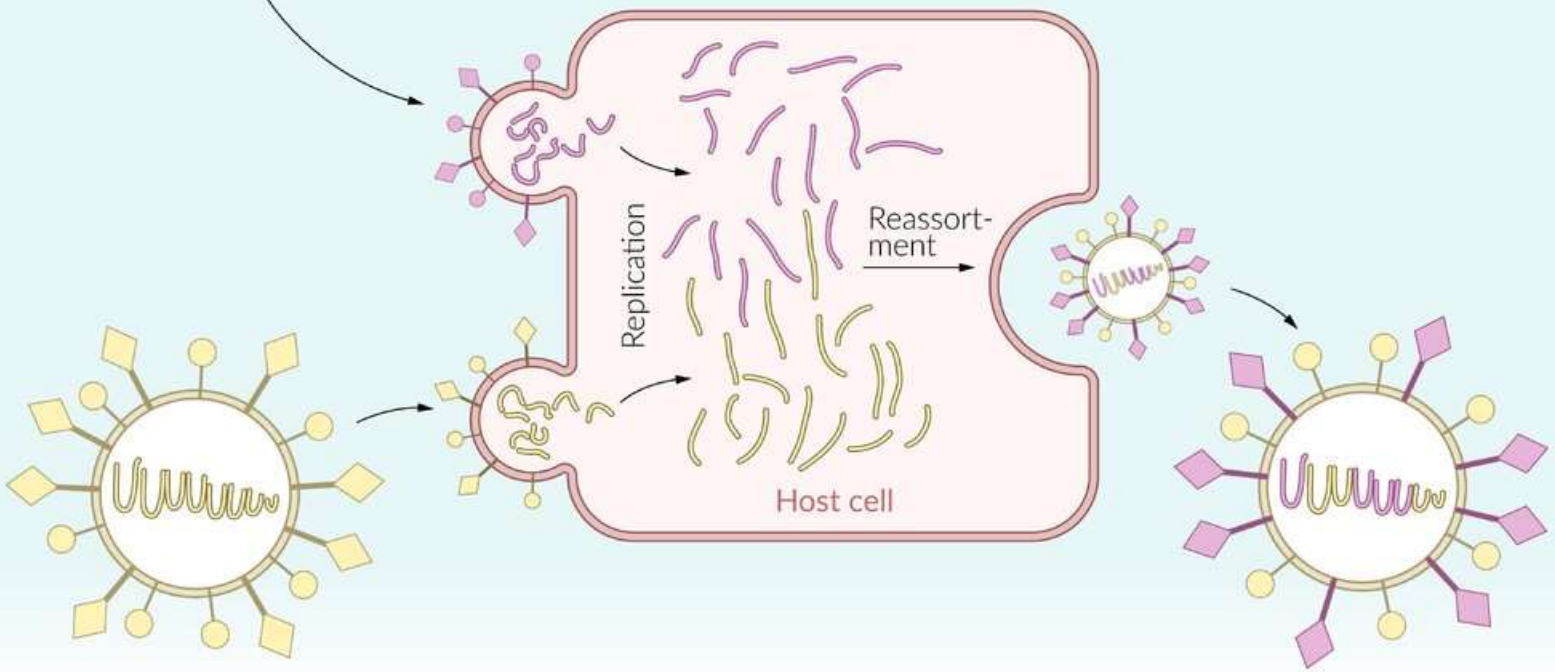
Antigenic drift





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.

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

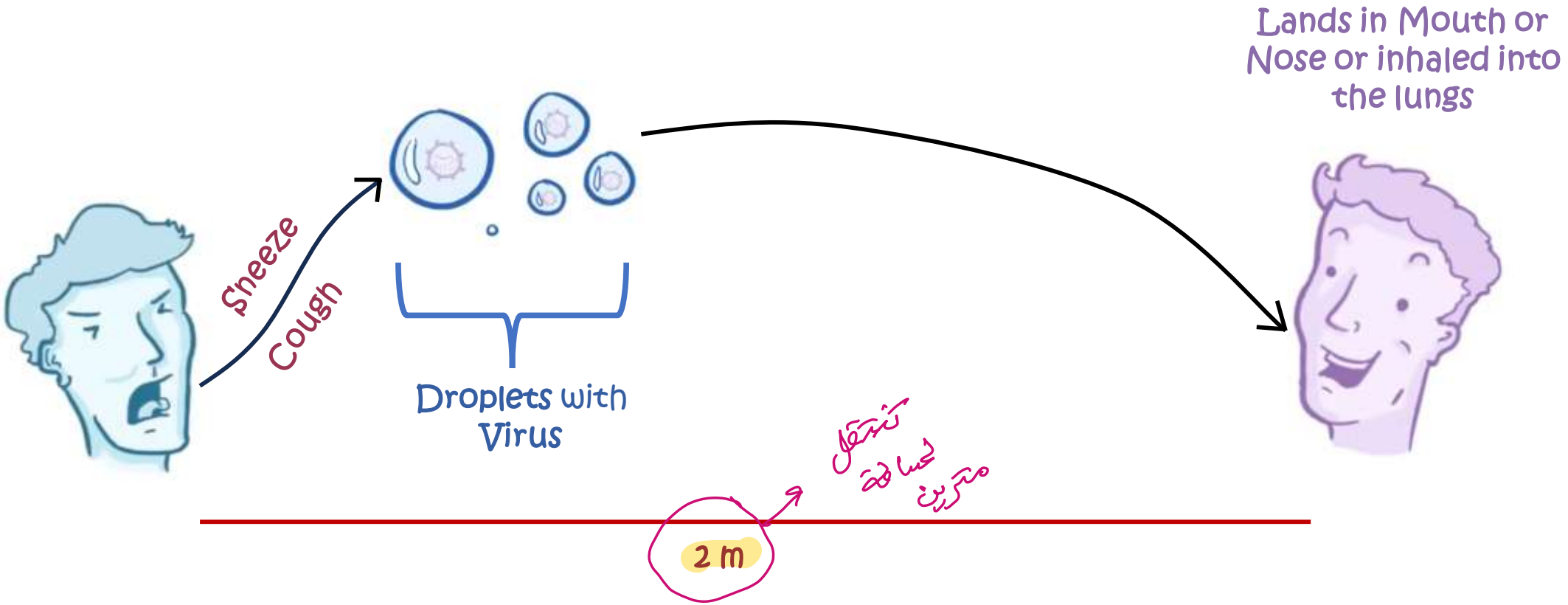
Orthomyxoviruses - Physical & biological characteristics

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.

2 & enveloped

rarely

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

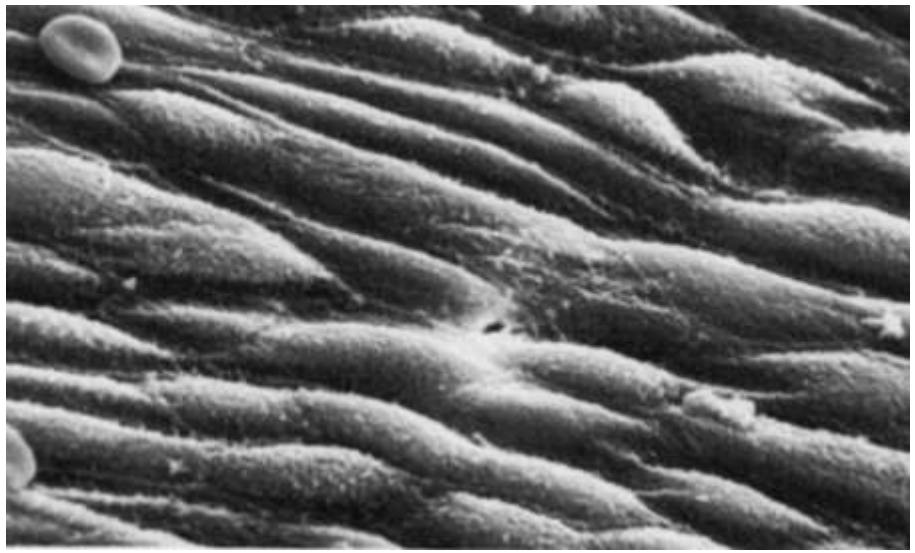
Orthomyxoviruses: Pathogenesis

- 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)

- 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***).

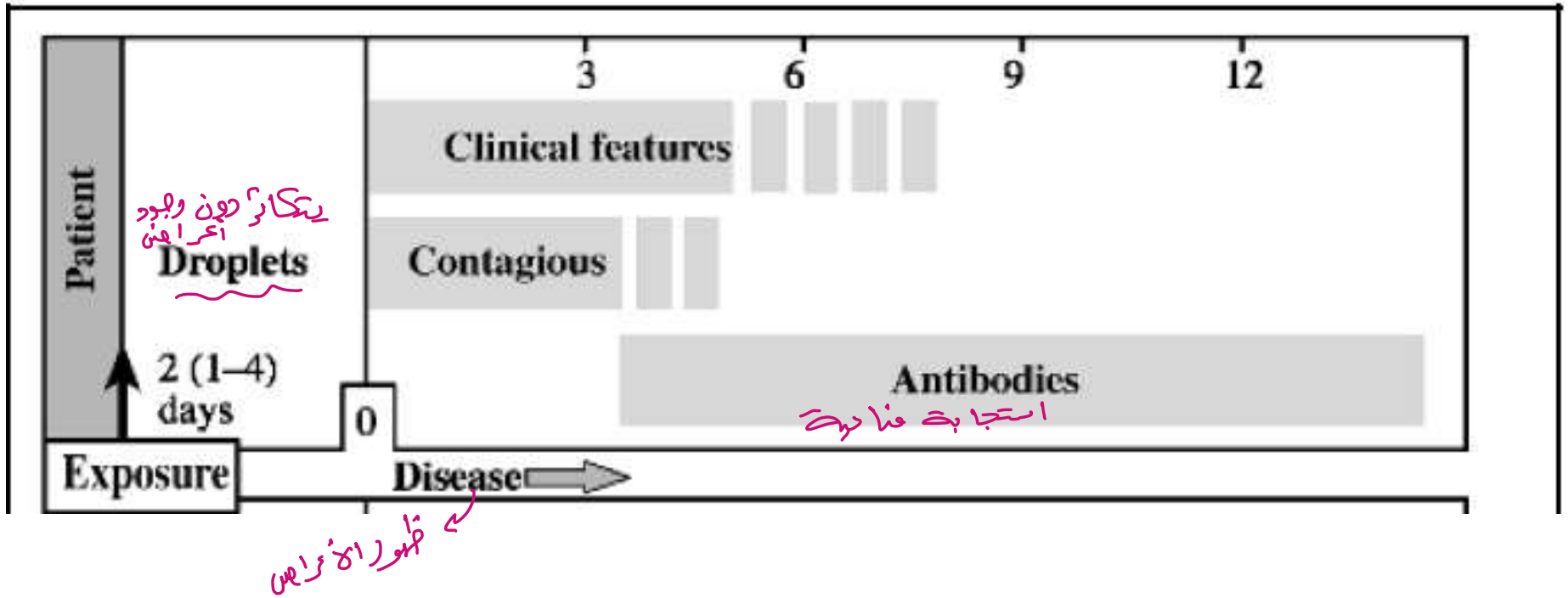
NORMAL TRACHEAL MUCOSA



3 DAYS POST-INFECTION after influenza A virus

Clinical Features

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



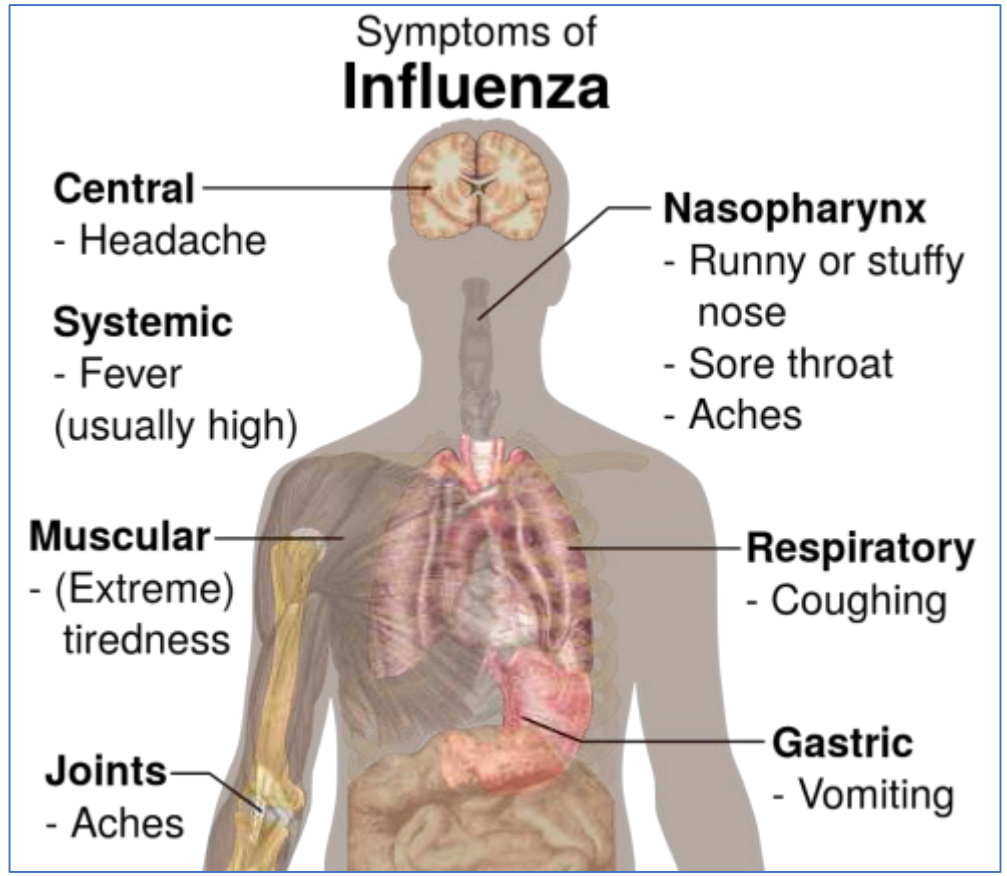
Clinically

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.

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

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

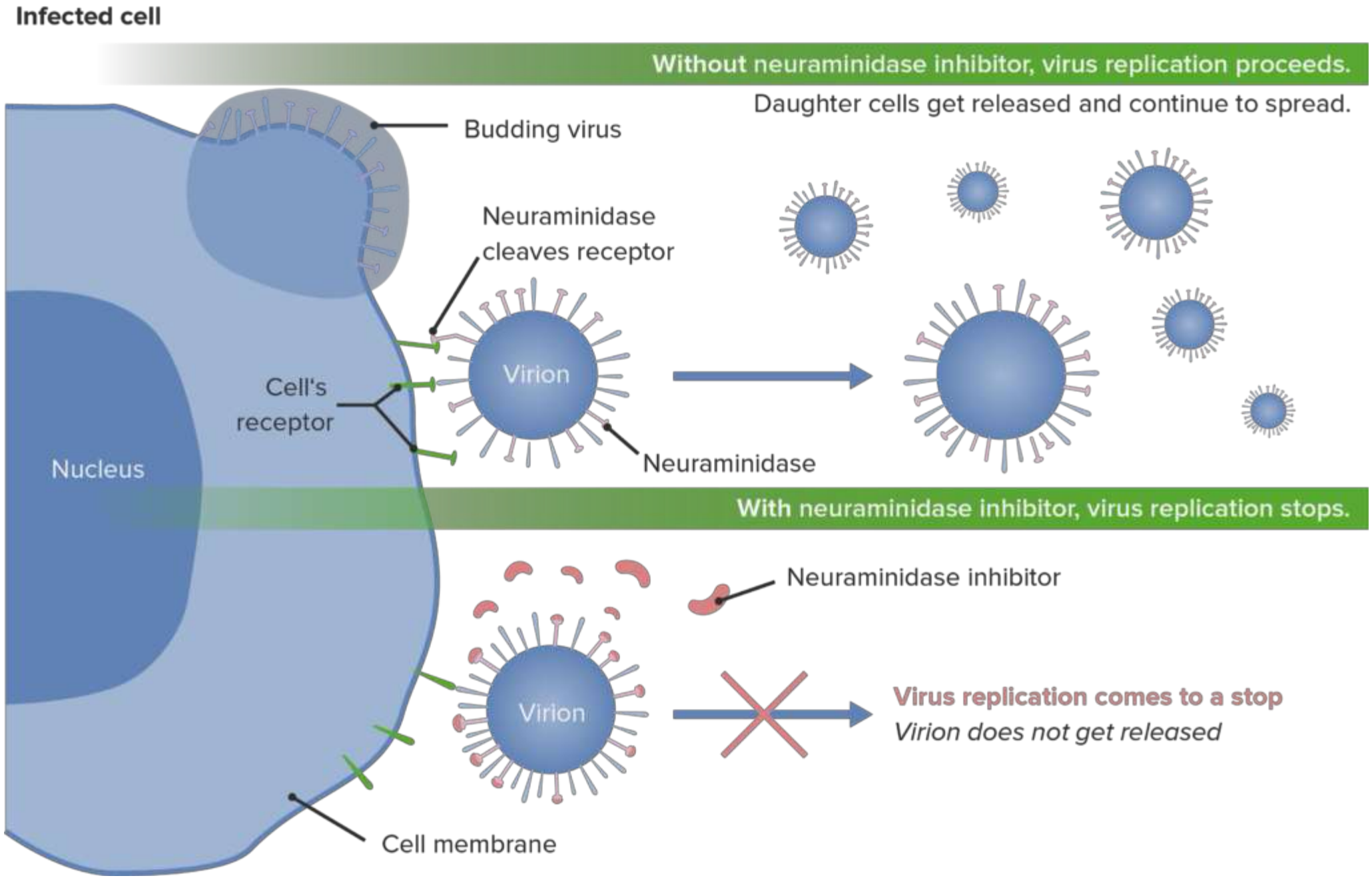
1. Symptomatic:
   - Fluids, analgesia BUT no ASPIRIN in children (<18).

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 (diagram next slide)
      - 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


Infected cell
Without neuraminidase inhibitor, virus replication proceeds.
Daughter cells get released and continue to spread.
Budding virus
Neuraminidase cleaves receptor
Virion
Cell's receptor
Nucleus
Neuraminidase
With neuraminidase inhibitor, virus replication stops.
Neuraminidase inhibitor
Virion
Virus replication comes to a stop
Virion does not get released
Cell membrane

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

Trivalent
Not Quadrivalent

- The aim is to produce HA antibody in the vaccines 2 weeks post vaccine.
- The 2025-2026 influenza vaccines are trivalent, containing influenza hemagglutinin proteins, which are surface glycoproteins, for two flu A[1,2] strains, and one flu B strain.[3]
  - B/Yamagata or B/Victoria
  - * New formulas trivalent
- Major vaccine types:
  - Inactivated (formaldehyde-killed, egg-grown) - I.M.
  - Live-attenuated influenza vaccine (egg-based)- Intranasal spray
  - Recombinant influenza vaccine (synthetically created without the use of any egg products)

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 كبار السن
  2. Immunocompromised
  3. Patient with chronic illnesses, lung and heart problems.
  4. Pregnant women at any stage

Vaccine C/I

- In general avoid in:
  - History of anaphylaxis after vaccination for influenza
  - History of severe allergic reaction to any influenza vaccine component (excluding egg protein allergy)
  - Acute fever
  - In pregnant and people with immunosuppressant conditions; avoid life attenuated

- Although egg protein allergy is listed on package inserts as a contraindication to egg-based influenza vaccines, the Advisory Committee on Immunization Practices (ACIP) (reference) states that egg allergy of any severity is not a contraindication for any influenza vaccine.