Orthomyxoviruses

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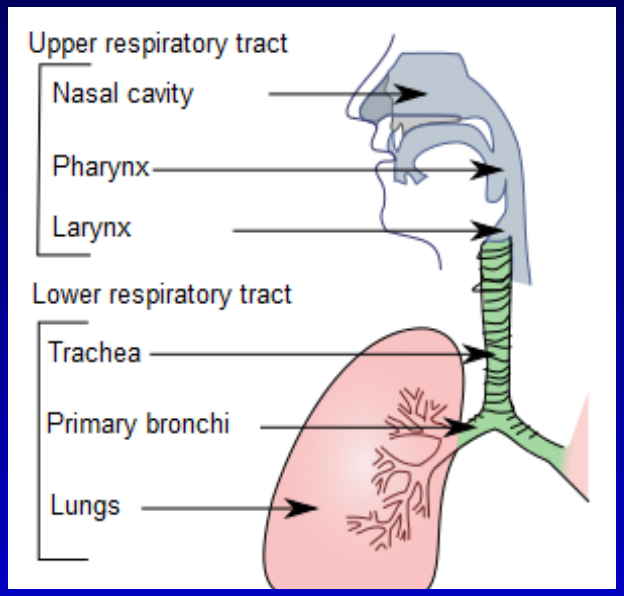
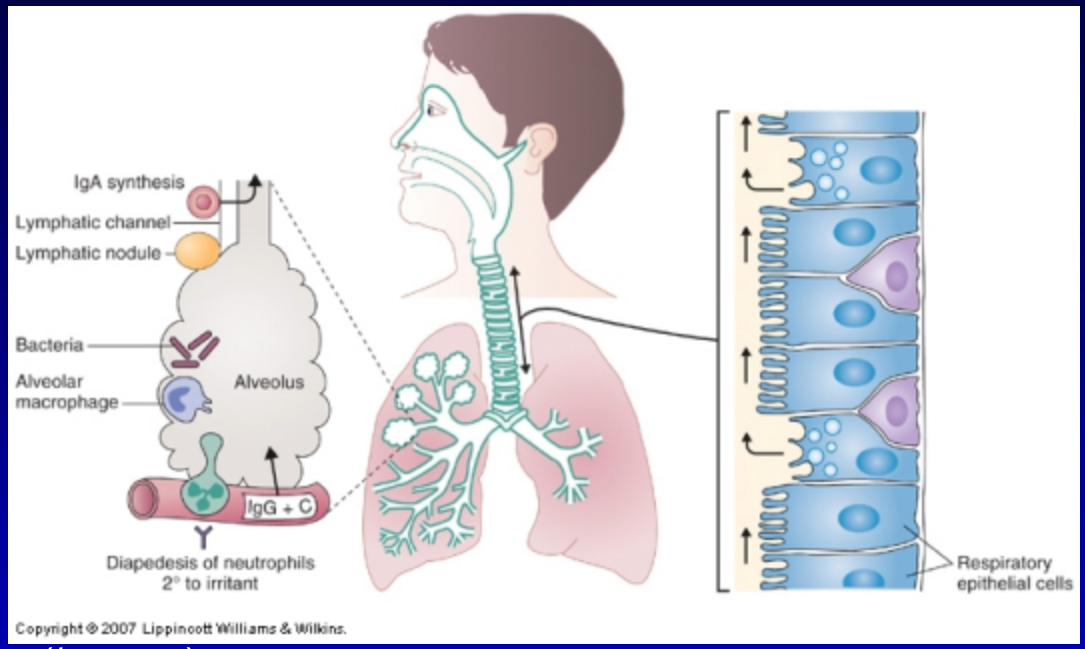
Respiratory Bacteria: Basic Pathogenesis

- Upper respiratory tract (URT)
  - Sinuses
  - Middle ear
  - Oropharynx
- Lower respiratory tract (LRT)
  - Trachea
  - Bronchi
  - Bronchioles
  - Alveoli and bronchoalveoli
  - alveolar macrophages and lungs



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)



classification

- Site: Upper *vs* . lower resp. tract infection

- Causative infectious organism:

✔ Viral
✔ Bacterial
✔ Fungal…

- Community acquired vs. hospital acquired

Viral respiratory tracy infections

Also observed -

- fatigue
- Diarrhoea
- Vomiting
- Chills
- Pneumonia
- Respiratory failure
- Conjunctivitis (rare)

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.

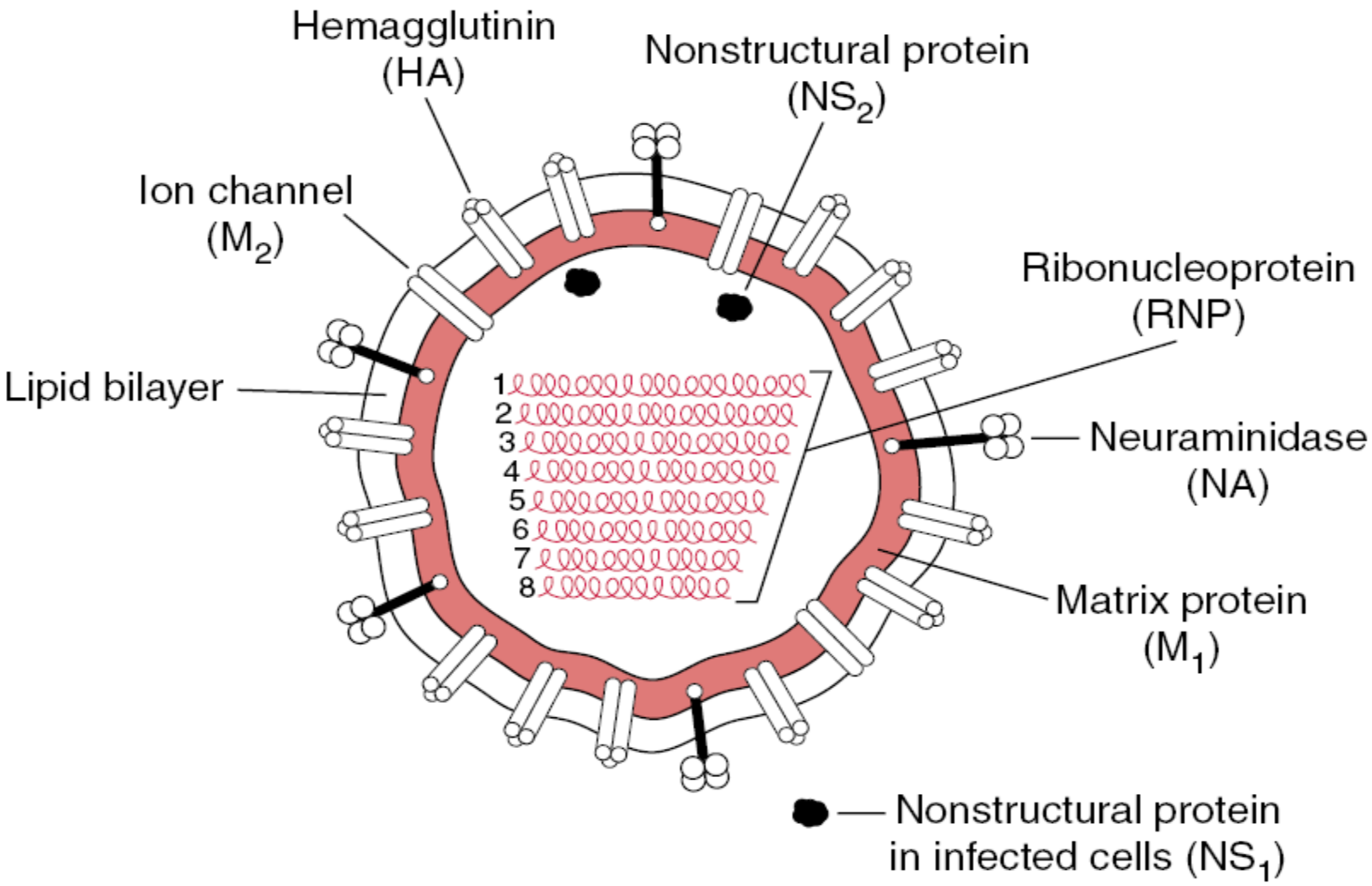
Orthomyxoviruses

- Includes the following main genera:
- 1. Influenza A 2. Influenza B 3. Influenza C.
- Structure:

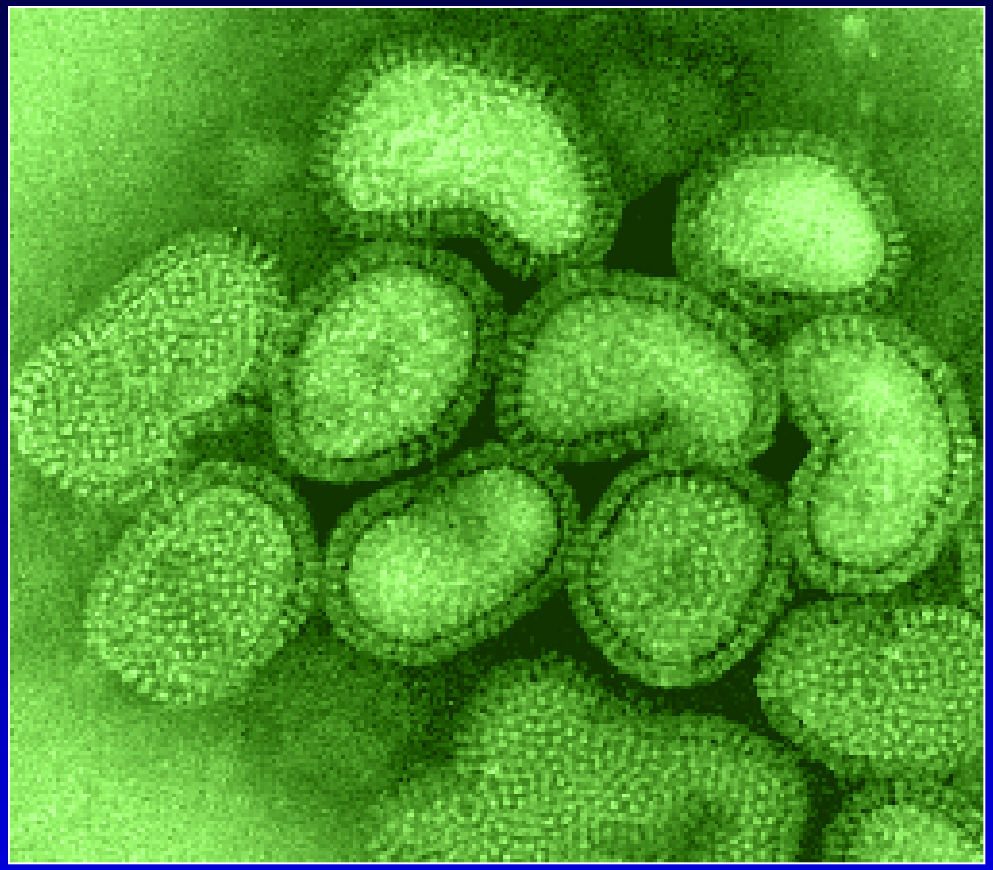
1. RNA enveloped viruses, ~ 80-120 nm in diameter.
2. Has RNA dependent RNA polymerase (important for infectivity/has transcription errors ~ 1: 10kb of the genome).
3. RNA:

A. Single stranded B. negative sense. C. approximately 8 segments (types A and B), 7 segments in type C.

Orthomyxoviruses / structure



Orthomyxoviruses (under E.M)



Orthomyxoviruses

4. Haemagglutinin (17 subtypes):
   - H or HA.
   - allows 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 erythrocytes.

5. Neuraminidase (9 serotypes) (Not in type C):
   - N or NA.
   - allows release of newly formed viruses within host.
   - determinant of disease severity.
   - E.g H1N1, H3N2, H5N1….

Orthomyxoviruses

6. 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).

7. Ribonucleoproteins.

Orthomyxoviruses / Antigenicity

There are two types of antigens in influenza viruses:

1. Group specific antigens:

A. Determined by Ribonucleoproteins.

B. Distinguish types A, B and C.

2. Type specific antigens:

A. The HA and NA.

B. For serotyping.

N.B: HA antibodies are neutralising (protect) while NA antibodies are not.

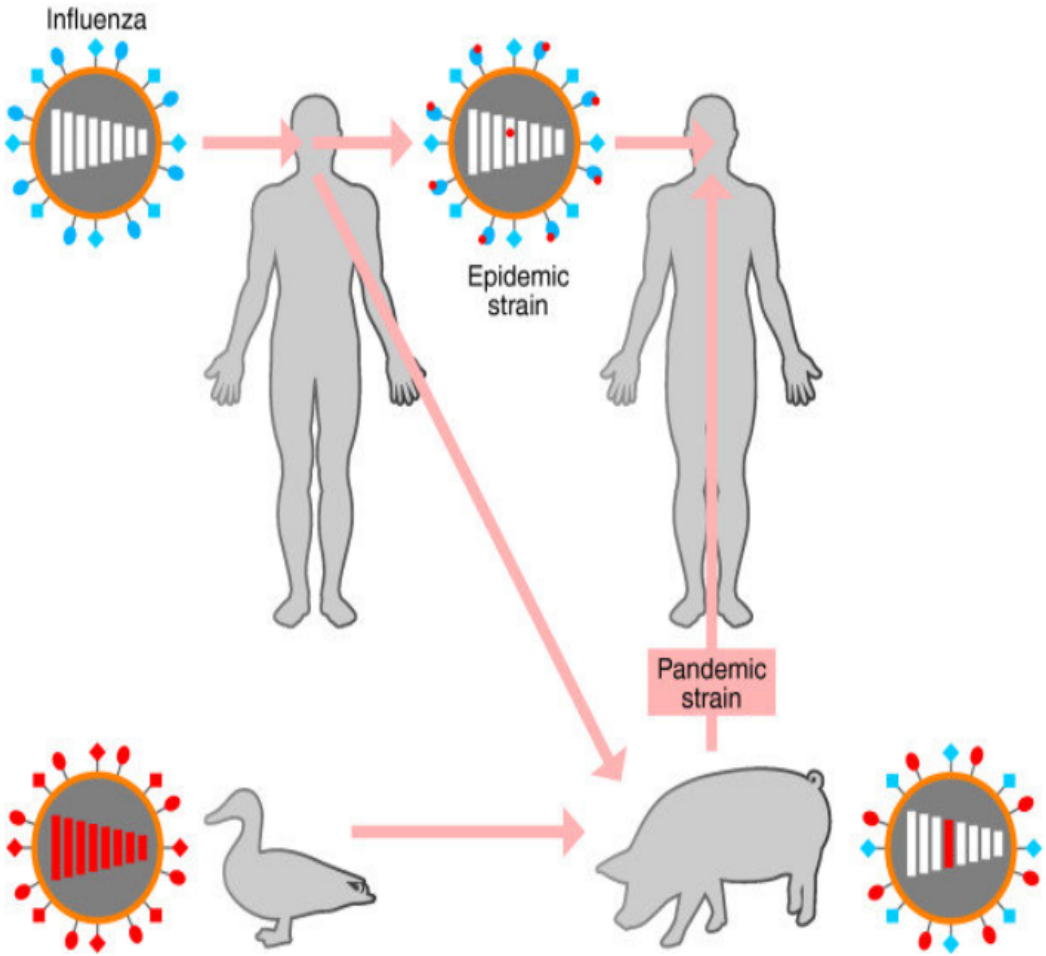
Antigenic changes (common in type A)

1. Antigenic shift (type A) > pandemics:

- Reassortment/swapping in the genomic RNA i.e a major change that may lead to the appearance of new HA and NA.
- pre-existing antibodies do not protect.
- Occurs when more than one variety of Influenza virus infect the same cell.

2. Antigenic drift (all types) > outbreaks / epidemics:

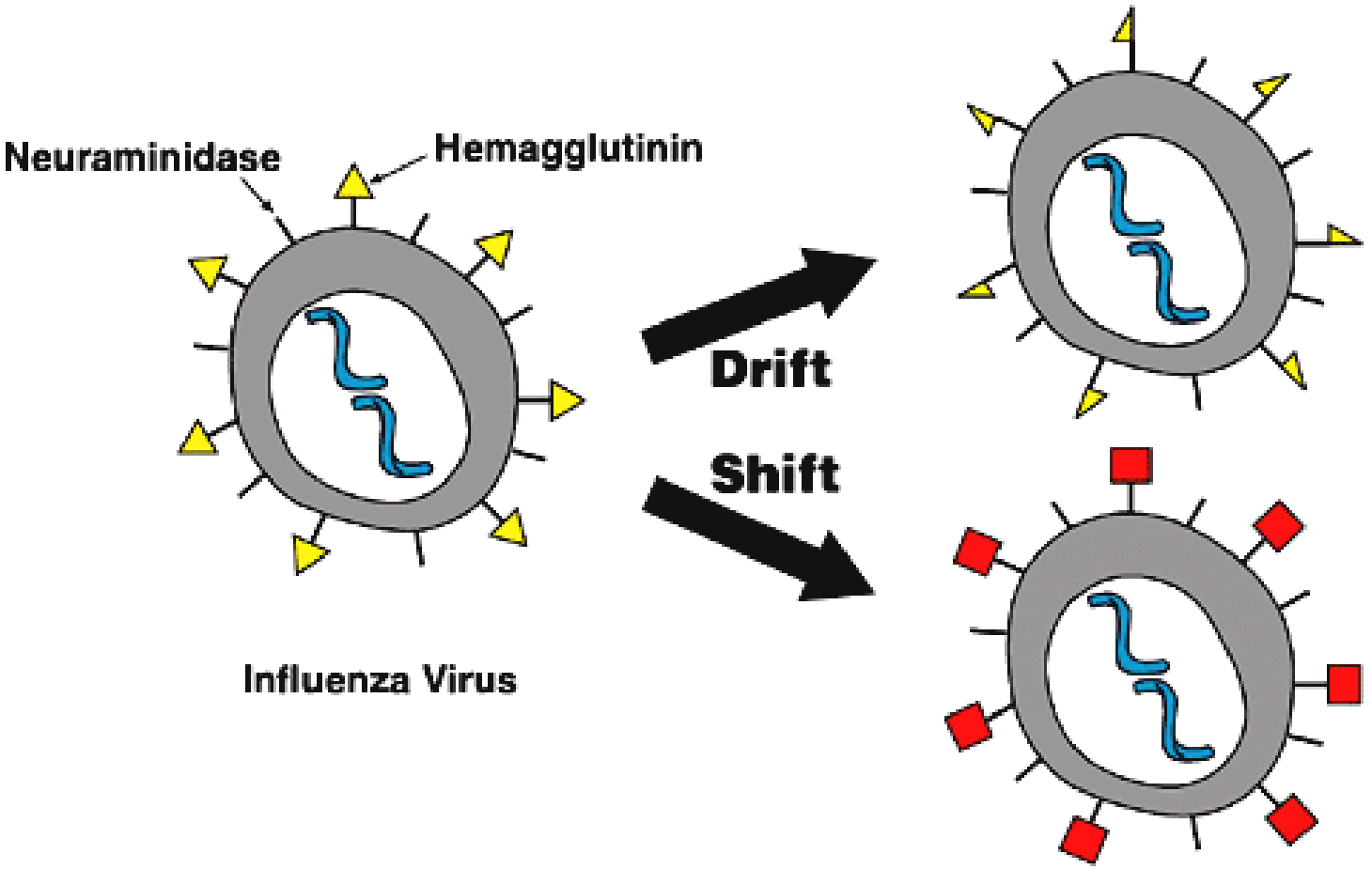
- HA and NA accumulate mutations.
- immune response no longer protects FULLY.



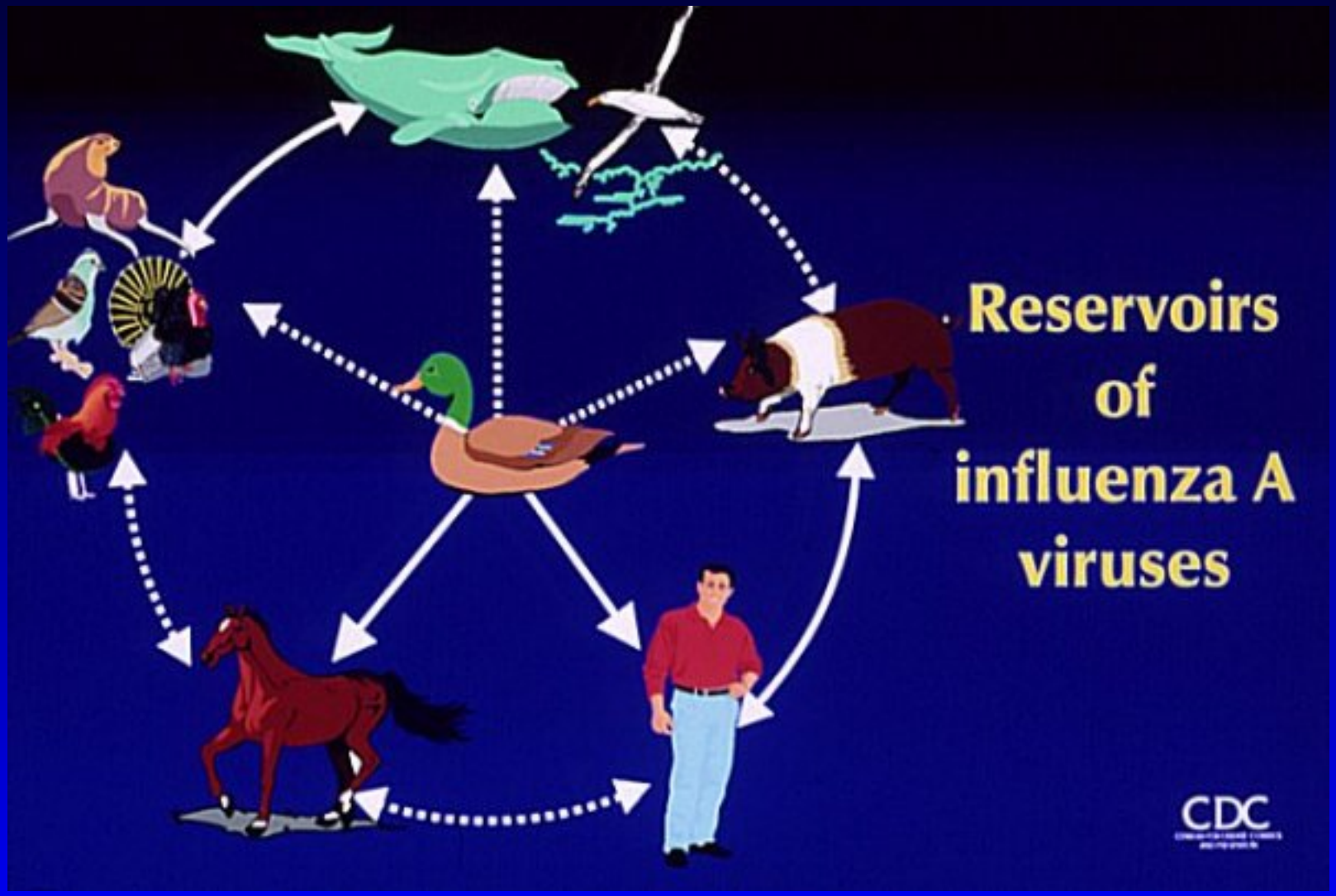
Figure

Caption

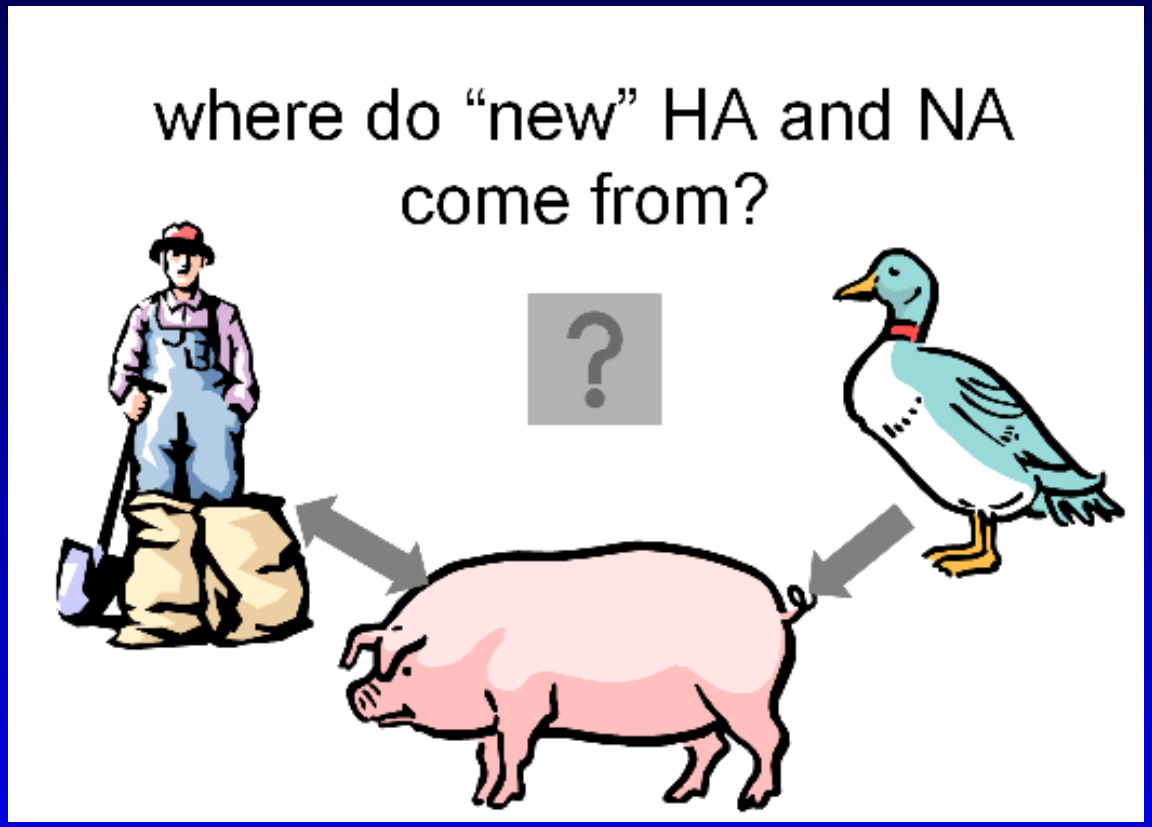
Figure 1: Antigenic drift and antigenic shift in different hosts of influenza virus. The surface hemagglutinin and neuraminidase molecules (blue) of influenza viruses undergo frequent mutation (antigenic drift) in their human hosts, giving rise to new variants (red dots) that can elude antibodies made in many individuals against the parent virus. Less frequently, entire segments of the eight-segment genome of an avian influenza virus and a human virus become reassorted into the same virion, usually through infection of swine by both viruses, and this can result in a virus that is still adapted to infect humans but expresses an avian hemagglutinin or neuraminidase (antigenic shift) to which there is no prior immunity in human populations. Figure reproduced with permission from –17 of: DeFranco AD, et al. Immunity Oxford University Press; 2007.


Neuraminidase
Hemagglutinin
Drift
Shift
Influenza Virus

Influenza A / Many reservoirs



Antigenic shift?



Antigenic shift?

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.

Nomenclature / WHO

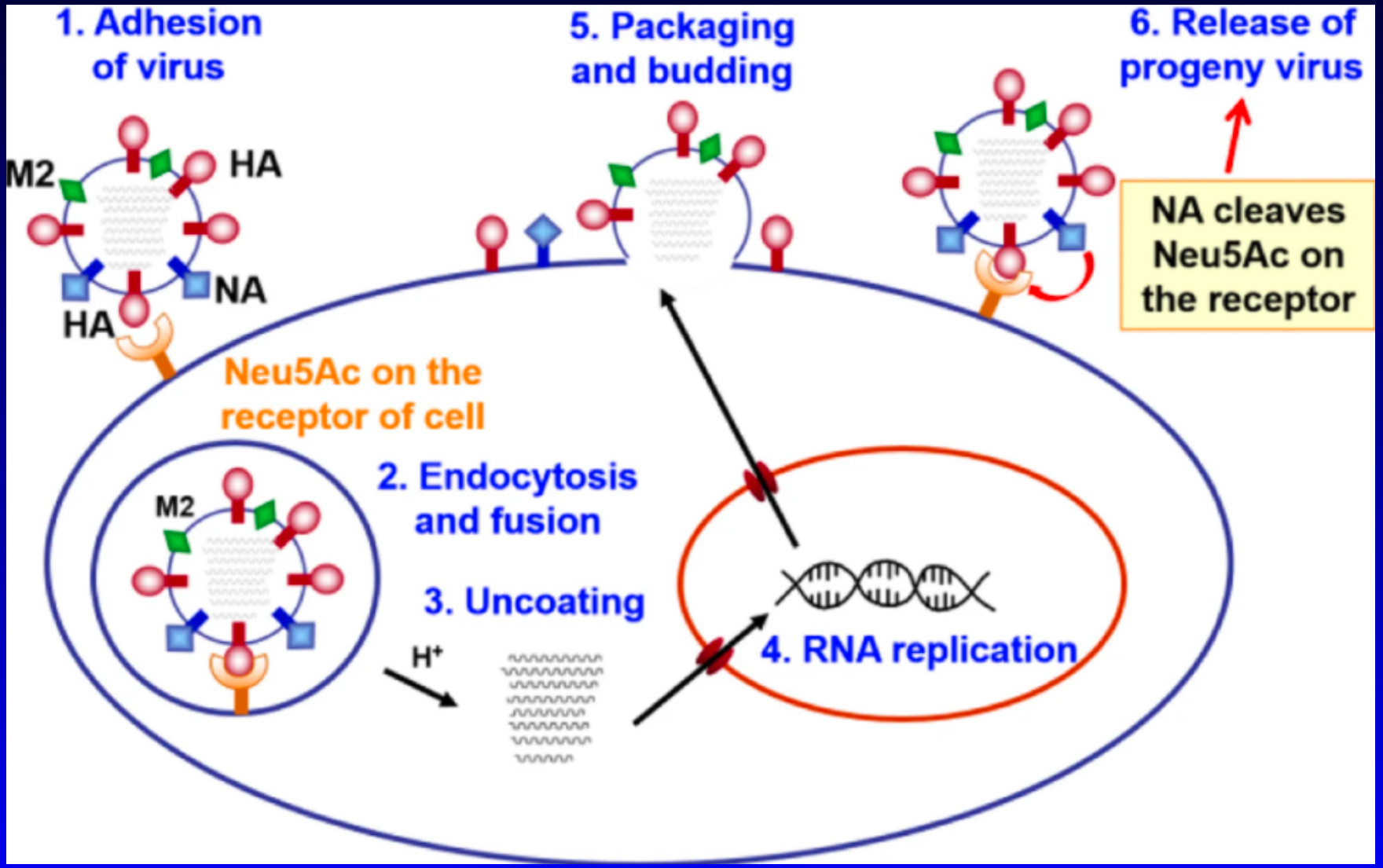
1. If isolated from human:

- Type > place where strain isolated> strain number> year of first isolation > subtype:
  - For example: **A / Beijing / 32 / 92 (H3N2)**

2. If not isolated from a human, we mention the source:

e.g: A/swine/Ioaw/3/70 (H1N1)

The virus life cycle

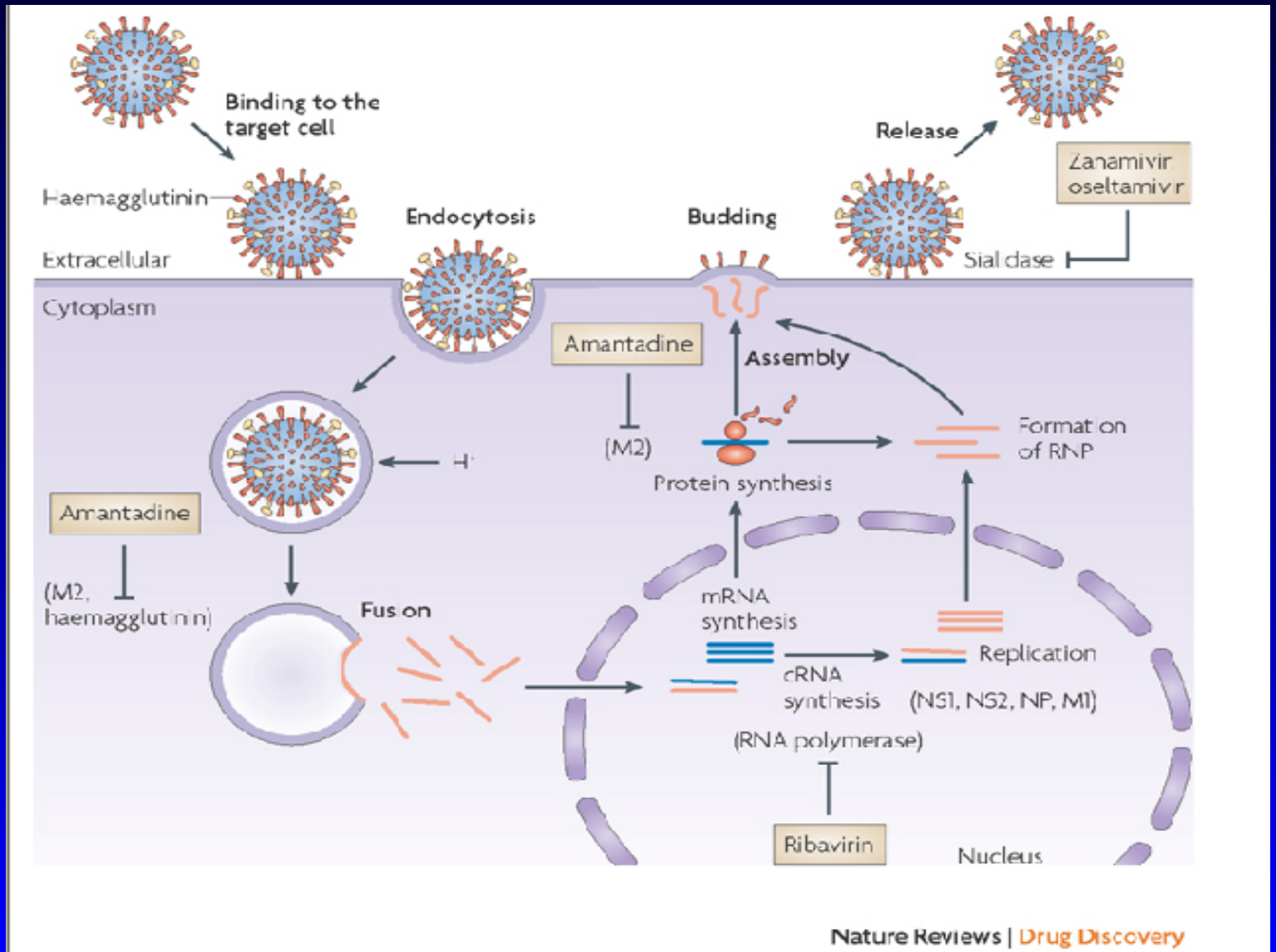


Orthomyxoviruses / life cycle (summary)

HA attachment to the cell receptors (sialic acid receptors)

- Then, penetration of the cell into endosomes.
- the acidic changes (M2 protein) /lysozymes in the endosome lead to virus uncoating
- the RNA polymerase will then transcribes the genomic -ssRNA into mRNA which is translated in the cytoplasm into viral proteins.
- Progensy –ssRNA genome also synthesized in the nucleus.
- Assembly in the cytoplasm.
- Release by budding? (facilitated by NA).
- Spread and infection of new cells.

Life cycle


Binding to the target cell
Haemagglutinin
Extracellular
Endocytosis
Budding
Release
Zanamivir
oseltamivir
Sialidase
Cytoplasm
Amantadine
(M2)
Assembly
Protein synthesis
Formation of RNP
Amantadine
(M2, haemagglutinin)
Fusion
mRNA synthesis
Replication
cRNA synthesis
(NS1, NS2, NP, M1)
(RNA polymerase)
Ribavirin
Nucleus
Nature Reviews | Drug Discovery

Orthomyxoviruses / pathogenesis

- Usually no viremia.
- Multifactorial:

1. Host factors e.g immunity, congenital abnormalities
2. Viral factors:

- Infectious dose/droplet size
- Viral-respiratory cells tropism.

3. environmental:

crowdedness, season...

Orthomyxoviruses / Pathogenesis

- Mechanism:

1. Structural and functional damage of resp. Cells > desquamation > affects resp. clearance mechanism & stimulates inflammatory response.
2. Direct tissue toxicity.
3. increased susceptibility to bacterial infections (superinfection).

Host response/Recovery

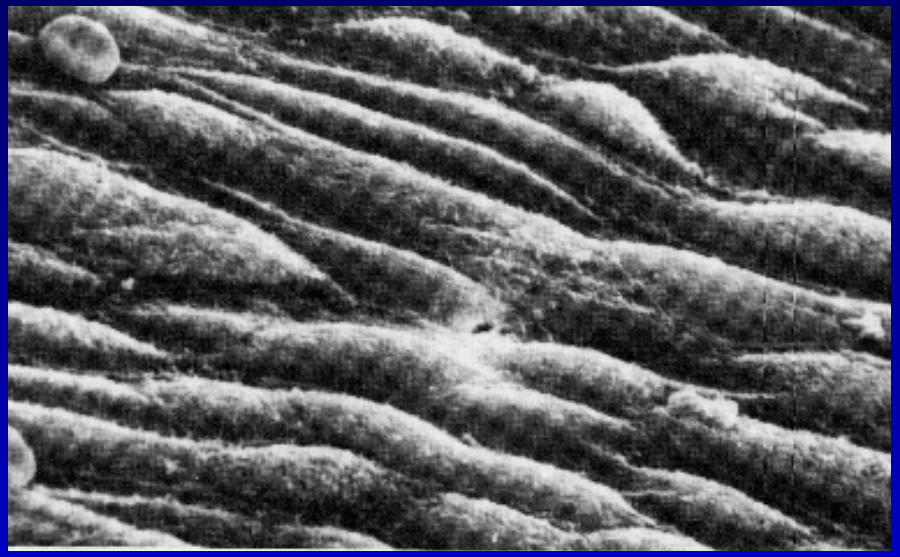
1. Initial control:
   - Interferon production:
     limits further virus replication.
     flu – like symptoms
   - Rapid generation of natural killer cells.
   - class I major histocompatibility complex (MHC)–restricted cytotoxic T cells appear in large numbers to participate in the lysis of virus-infected cells.

2. Then, in few days (3-5 days)
   - This is followed by the appearance of local and humoral antibody (inhibits spread) along with an evolving cellular immunity.

3. Finally, is the repair of tissue damage (2-10 w).

pathogenesis

NORMAL TRACHEAL MUCOSA



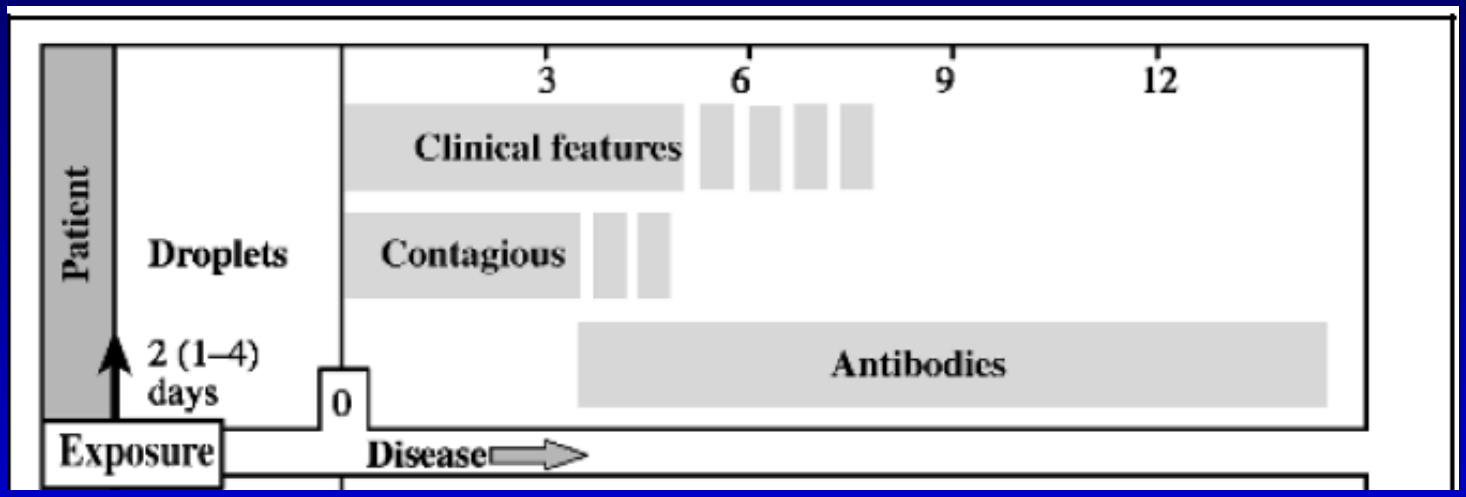
3 DAYS POST-INFECTION

Orthomyxoviruses / clinically

Mode of transmission: Respiratory droplets/ airborne - More in winter, crowded areas.

Clinically / cont'd

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



Clinically/cont'd

1. Main symptoms (mainly type A):

Sudden onset:

- FEVER, CHILLS (1-5 days) (s.t febrile convulsions in children).
- HEADACHE, MYALGIA, COUGH, ANOREXIA.
- RHINITIS, OCULAR SYMPTOMS.
- N.b: 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*

Clinically/cont'd

3. Non-pulmonary complications:

- Cardiac: myositis (rare, > in children, > with type B).

- liver and CNS.

  - Reye's syndrome

  1. (encephalopathy+liver degeneration).
  2. Precipitated by Aspirin.
  3. Reye's also caused by parainfluenza and chickenpox.

- peripheral nervous system
  - Guillian-Barré syndrome/Ascending paralysis. (autoimmune disease)

Pandemics

- 1918 Spanish Flu H1N1: 20-40million 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 / 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

A. Needs 2 serum samples (paired) during the acute illness and 10-14 days later.

B. 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)

Treatment / cont'd

B. Neuroaminidase inhibitors

Zanamavir (Relenza/inhalation) and Oseltamivir (Tamiflu/orally), Permivir (Rapivab I.V).

. Treatment of type A and B.

. MOA 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

Orthomyxoviruses / 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.
   Germs spread this way.

4. Avoid contact with sick people.
5. 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:

1. Inactivated (formaldehyde), egg grown – I.M
2. Life attenuated - Nasally

2. sub-unit vaccine for children.

- BEST GUESS' OF MAIN ANTIGENIC TYPES
  - CURRENTLY
    - type A - H1N1, type A - H3N2 and 1-2 type B

Vaccine

- Should be updated and given annually.
- Side effects: flu like symptoms, loclised 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
- Previous history of GBS

- In pregnant and people with immunosupressant conditions; avoid life attenuated

The End

WHO Pandemic Alert Phase