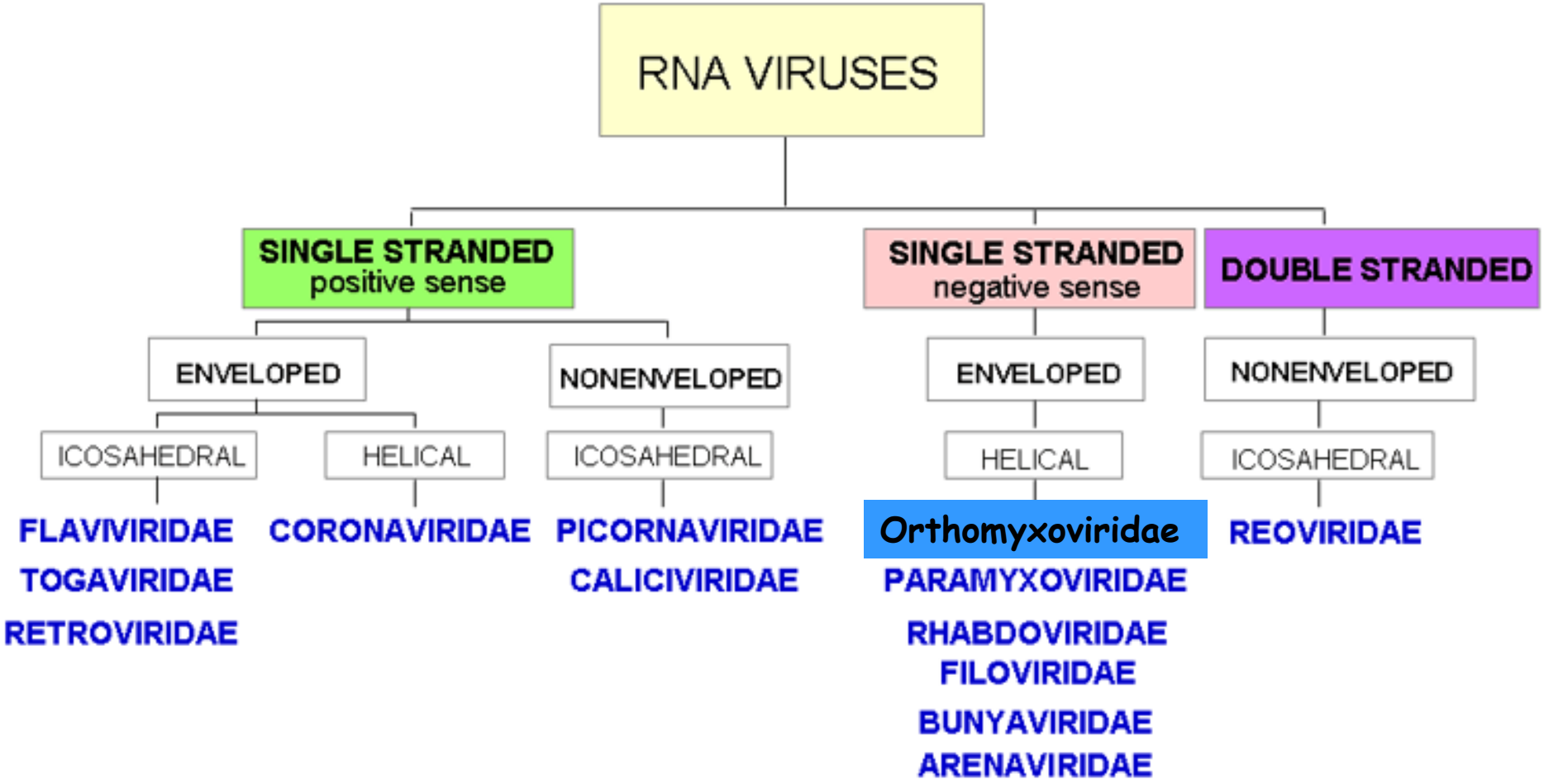
ORTHOMYXOVIRUSES

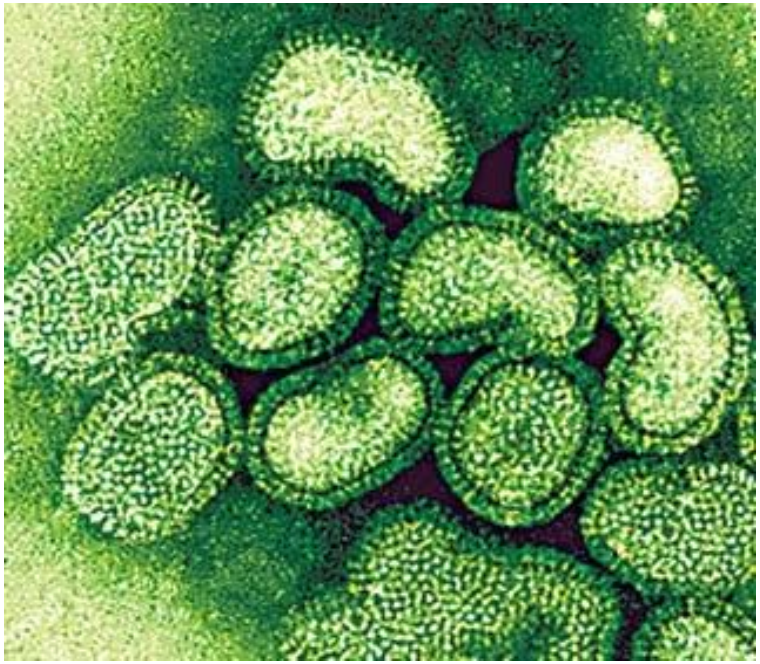
INFLUENZA VIRUSES

(A,B and C)



Modified from Volk et al., Essentials of Medical Microbiology, 4th Ed. 1991

Influenza Viruses



Epidemiology:

- Influenza “A” virus is so subjected to major antigenic changes that cause occasional world wide pandemics when a new subtype of influenza A appears. Between the pandemics, smaller epidemics are scattered in different locations at intervals of 2-3 years.
- Antigenic shifts happened in :
- **1918 (H1N1) Spanish flu > 20,000,000 died**
- **1957 (H2N2) Asian flu 100,000 died**
- **1968 (H3N2) Hong Kong flu 700,000 died**
- 1977 (H1N1) Russian flu (reemerged without epidemic)
- Since 1977 influenza A (H1N1) and (H3N2) viruses and influenza B viruses have been in global circulation.

Epidemiology of Influenza viruses

- **Influenza is an acute respiratory tract infection that usually occurs in epidemics.**

- **These viruses received their name from their special affinity to mucous.**

Epidemiology of Influenza viruses

- **Three immunologic types of influenza viruses are known designated:**
  - **A, B and C**
  - **based on different ribonucleoprotein antigens.**

Epidemiology of Influenza viruses

- **Antigenic changes continually occur within:**
  - **Type A**
  - **to a lesser degree in the type B,**

Type C is antigenically stable

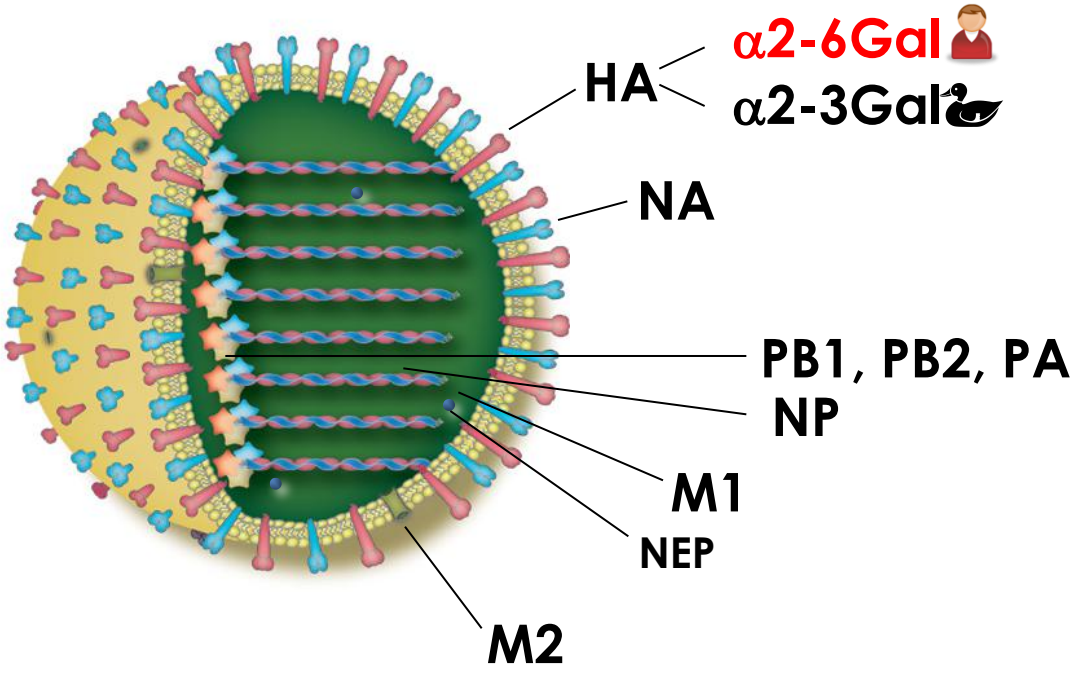
Epidemiology of Influenza viruses

- **Influenza A strains are also known for:**
  - **aquatic birds (e.g.ducks, turkeys, chickens, geese),**
  - **pigs**
  - **& horses.**

INFLUENZA TYPES B AND C
ARE
RESTRICTED TO HUMANS

Morphology:

- **Spherical virus, (filamentous forms occur).**
- **Helical nucleocapsid**
- **Segmented single stranded RNA(eight segments), to which protein capsomeres are attached.**
- **Enveloped**
- **Two virus encoded glycoproteins are inserted into the envelope, and are exposed as spikes: HA & NA**



Haemagglutinin spikes (HA)

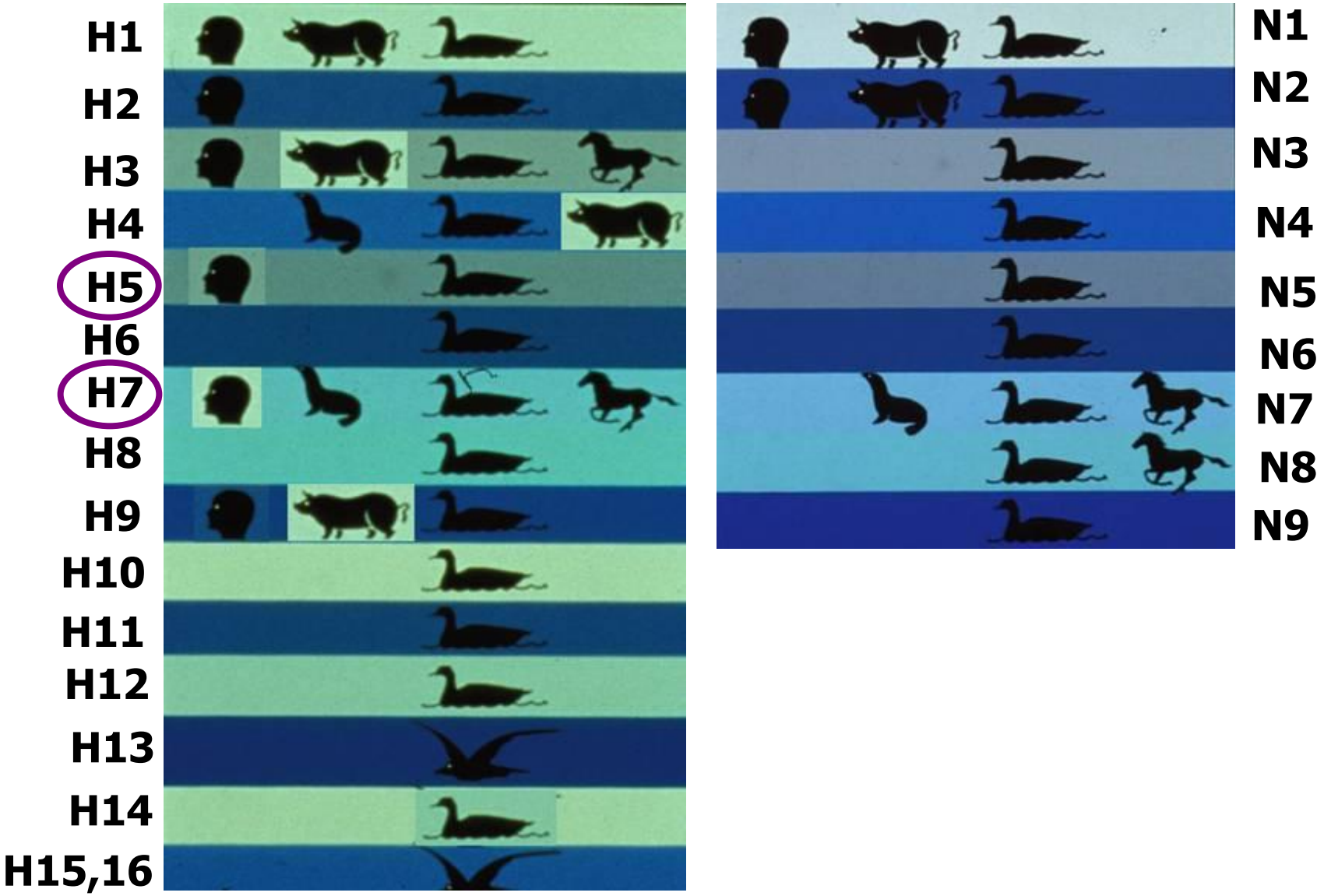
- **So far 15 antigenically different haemagglutinin subtypes exist (H1- H15), and they are strain specific.**

- **HA protein binds viral particles to susceptible cells, and is the major antigen against which neutralizing (protecting) antibodies are directed.**
- **It derives its name from its ability to agglutinate erythrocytes.**

Neuraminidase spikes (NA):

- They are mushroom shaped protrusions, antigenically distinct from haemagglutinins
- At least nine antigenic types exist (N1 –N9). NA function at the end of the viral life cycle
- Inactivate a free mucoprotein receptor in respiratory secretions
- Fusion of viral envelope with the host cell membrane
- They facilitate the release of viral particles from infected cell surfaces during budding, and prevent self aggregation of virions

Species Infected by Influenza A, HA and NA Subtypes



Influenza virus strain designation

- It has become necessary to design a system of nomenclature to compare the nature of the virus strains as they mutate year by year.

1. **Description of the "S" antigen (A, B or C).**
2. **Host origin:** if isolated from man is not indicated, but stated in the strains of non human hosts (avian, equine, swine, etc).
3. **Geographical origin.**
4. **Strain number and year of isolation**.
5. **Antigenic designation of the haemagglutinin and neuraminidase i.e subtype.(for type A)**

Influenza virus strain designation

Description of the "S" antigen	Host origin	Geographical origin	Strain number	year of isolation	Antigenic designation of the haemagglutinin and neuraminidase
A	----*	Hong Kong	1	68	H3, N2
A	Swine	New Jersey	8	76	H1, N1
A	Turkey	Wisconsin	1	66	H5N2
A	Poultry	Hong Kong	1	97	H5N1

* Human origin

Influenza virus strain designation

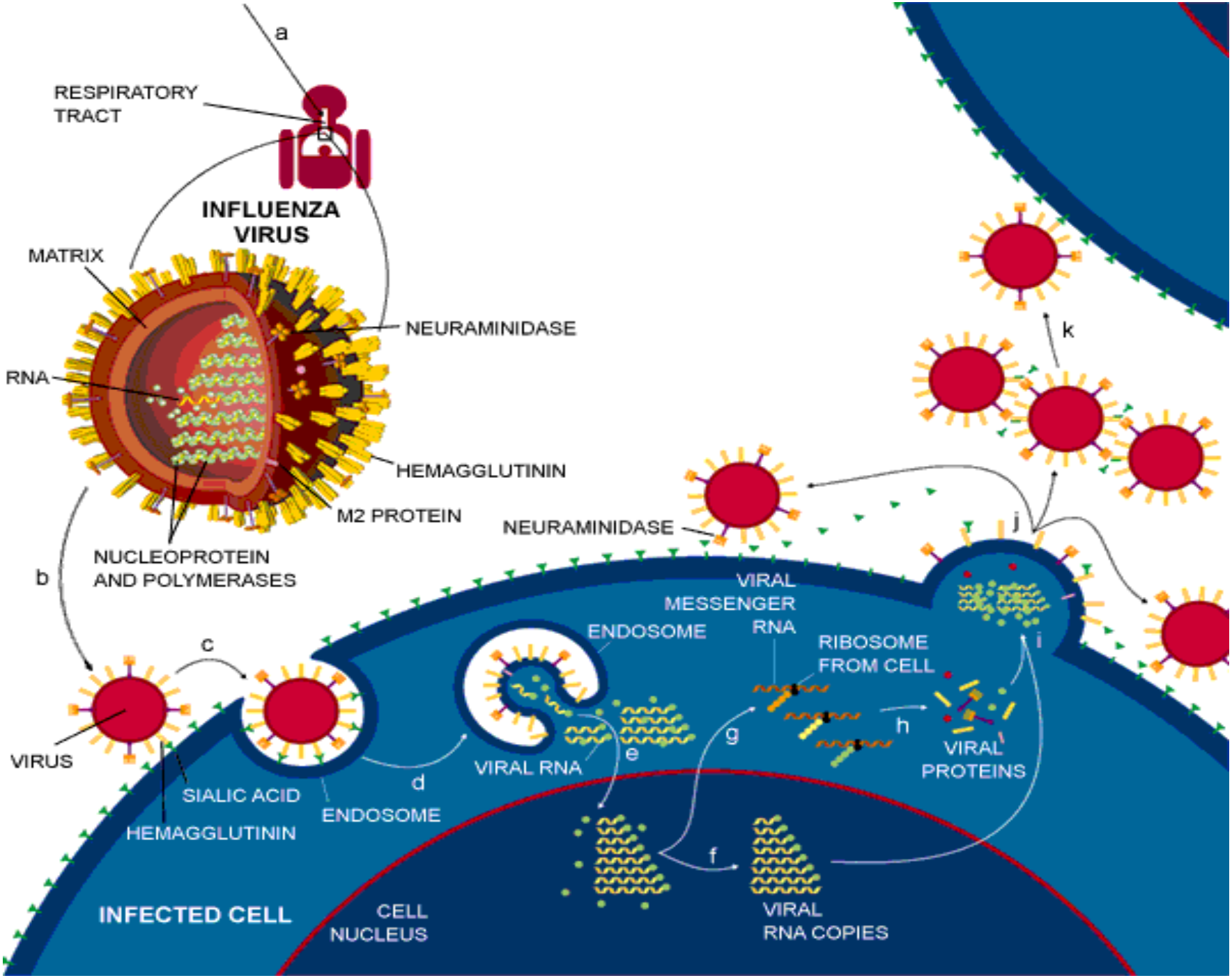
- ***Examples:***

  A/ Hong Kong/ 1/68 (H3, N2).

  A/Swine/New Jersey /8/76 (H1, N1).

  A/Turkey/Wisconsin/1/66 (H5, N2).

  A/Poultry/Hong Kong/1/97 (H5,N1).


a
RESPIRATORY TRACT
INFLUENZA VIRUS
MATRIX
NEURAMINIDASE
RNA
HEMAGGLUTININ
M2 PROTEIN
NUCLEOPROTEIN AND POLYMERASES
b
c
VIRUS
SIALIC ACID
HEMAGGLUTININ
ENDOSOME
d
VIRAL RNA
e
ENDOSOME
VIRAL MESSENGER RNA
RIBOSOME FROM CELL
g
h
VIRAL PROTEINS
i
j
k
NEURAMINIDASE
f
INFECTED CELL
CELL NUCLEUS
VIRAL RNA COPIES

Influenza virus Genome

- **Each of the RNA eight segments encode a certain viral protein.**
  - **Segment 4 encodes the haemagglutinin**
  - **Segment 6 encodes the neuraminidase, representing the two envelope spikes.**
- **The two surface antigens of influenza undergo antigenic variation independent of each other.**
- **Four HA (HA1-2-3-5)**

and

- **Two NA (NA1 &2) subtypes have been recovered from humans.**

Properties of Orthomyxoviruses:

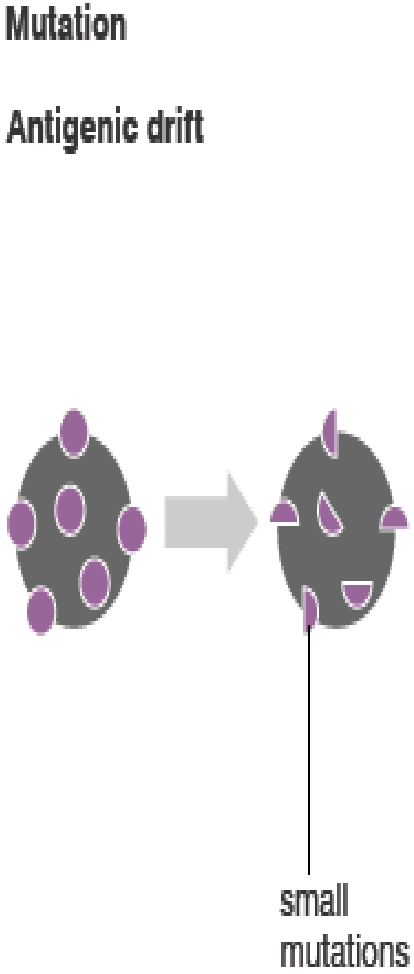
- **Mutability and high frequency of genetic reassortment are characteristics of orthomyxoviruses:**
  - **Antigenic Drift**
  - **Antigenic Shift**

"*Antigenic Drift*"

- **Antigenic changes within major subtypes can involve both the "H" and "N" antigens**

- **They result from as little as A SINGLE MUTATION IN THE VIRAL RNA, which leads to gradual changes of antigenic properties of the strain.**

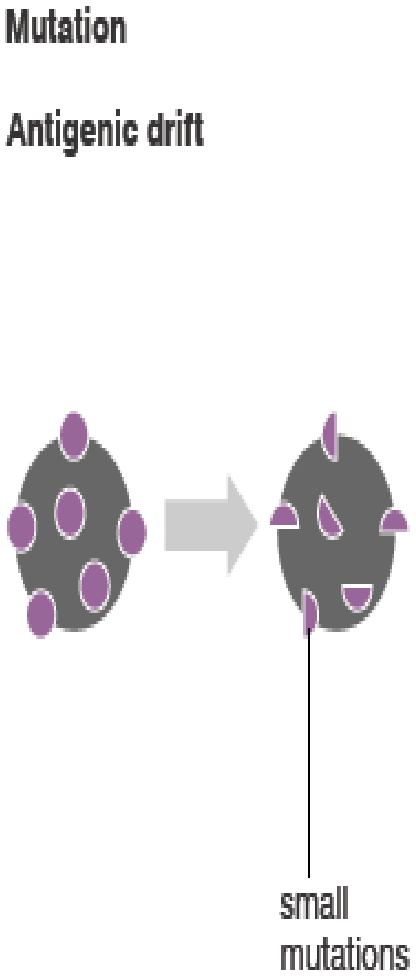
- **NEW STRAINS showing minor differences from the structure of previous years emerge,**



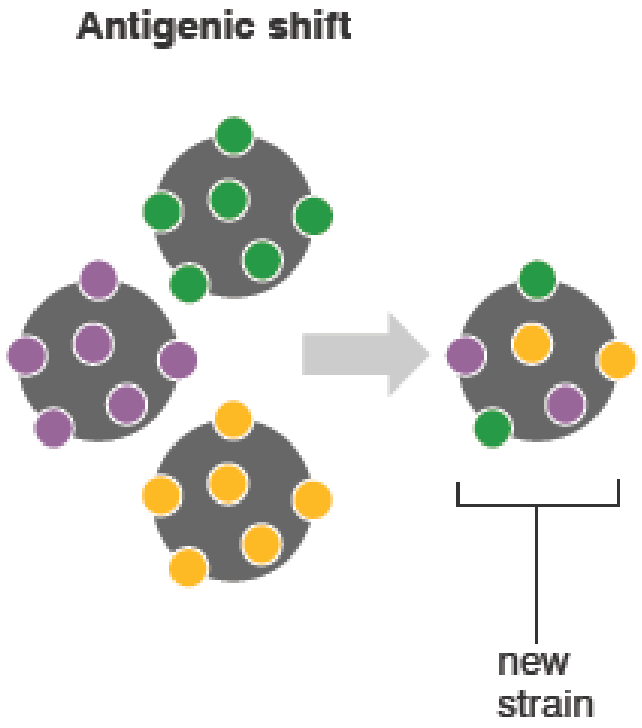
Result of continuous "*Antigenic Drift*"s

- **These drifts from season to season, allow some degree of infection to continue.**

- **Thus infectivity persists because TYPE-SPECIFIC IMMUNITY is not entirely protective against drifting strains.**

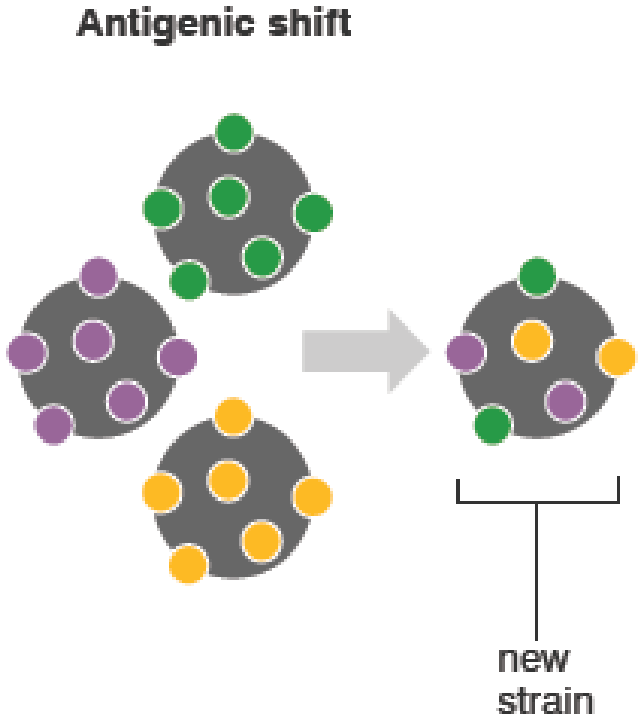


"*Antigenic Shift*".



- **However, in type "A" strains, a major interruption of these progressive changes can occur at long intervals varying from 10-40 years,**
- **A sudden and unpredictable appearance of an entirely new subtype may occur.**
- **This process is drastic and abrupt and is described as "*antigenic shift*".**

“*Antigenic Shift*”.



- **VIRUSES REASSORT READILY IN DOUBLY INFECTED CELLS.**

- **So, the mechanism for shift is genetic reassortment between human,avian, or swine influenza viruses.**

"Antigenic Shift".

- **Sequence analysis of influenza A viruses isolated from many hosts in different regions of the world support the theory that**

ALL MAMMALIAN INFLUENZA VIRUSES DERIVE FROM THE AVIAN INFLUENZA RESERVOIRS.

Avian influenza A virus (H5N1)

- **The first documented infection of humans by avian influenza A virus (H5N1) occurred in:**

  1997 in Hong Kong .

- **The source was domestic poultry.**

- **The virus did not appear till now to be transmissible from human to human.**

- **Isolates from human cases contained all eight RNA gene segments from avian viruses indicating that the avian virus had jumped directly from birds to humans.**

Avian influenza viruses & Human Pandemics

- With the exception of the Hong Kong outbreak 1968

- All human pandemic strains have been re-assortants between avian and human influenza viruses.

Pigs Serve As Mixing Vessels for reassortants

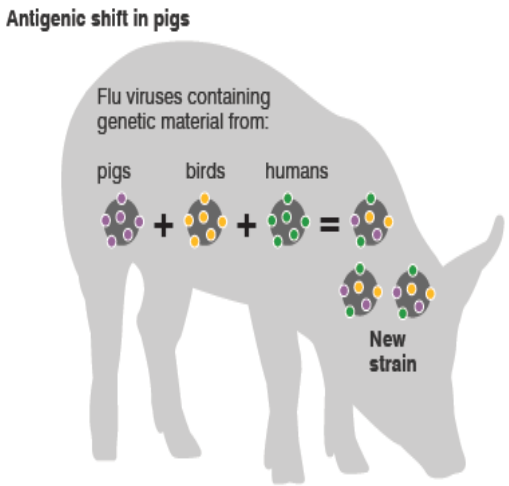
- **Pig cells contain receptors for both human and avian viruses.**

Aquatic birds and domestic Poultry (Avian virus)

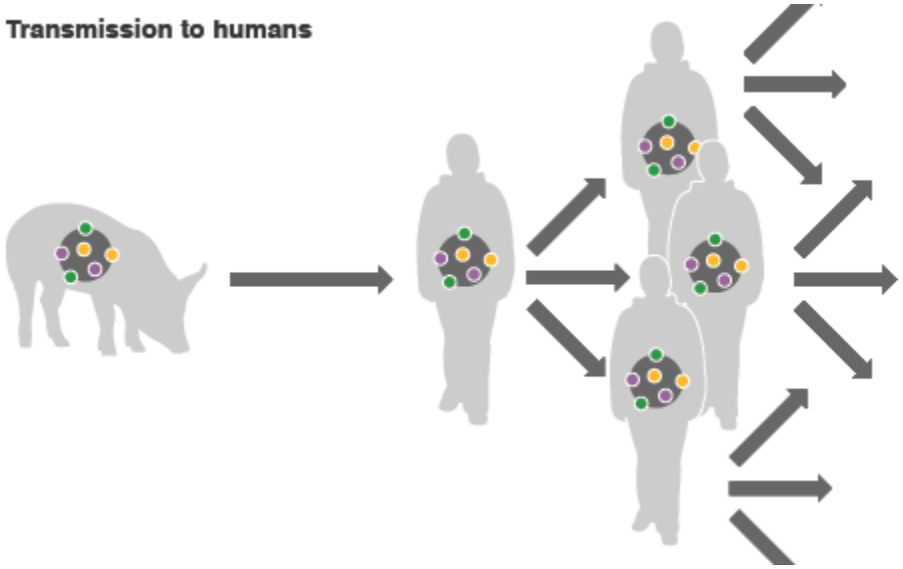
Pigs

Human (Human virus)

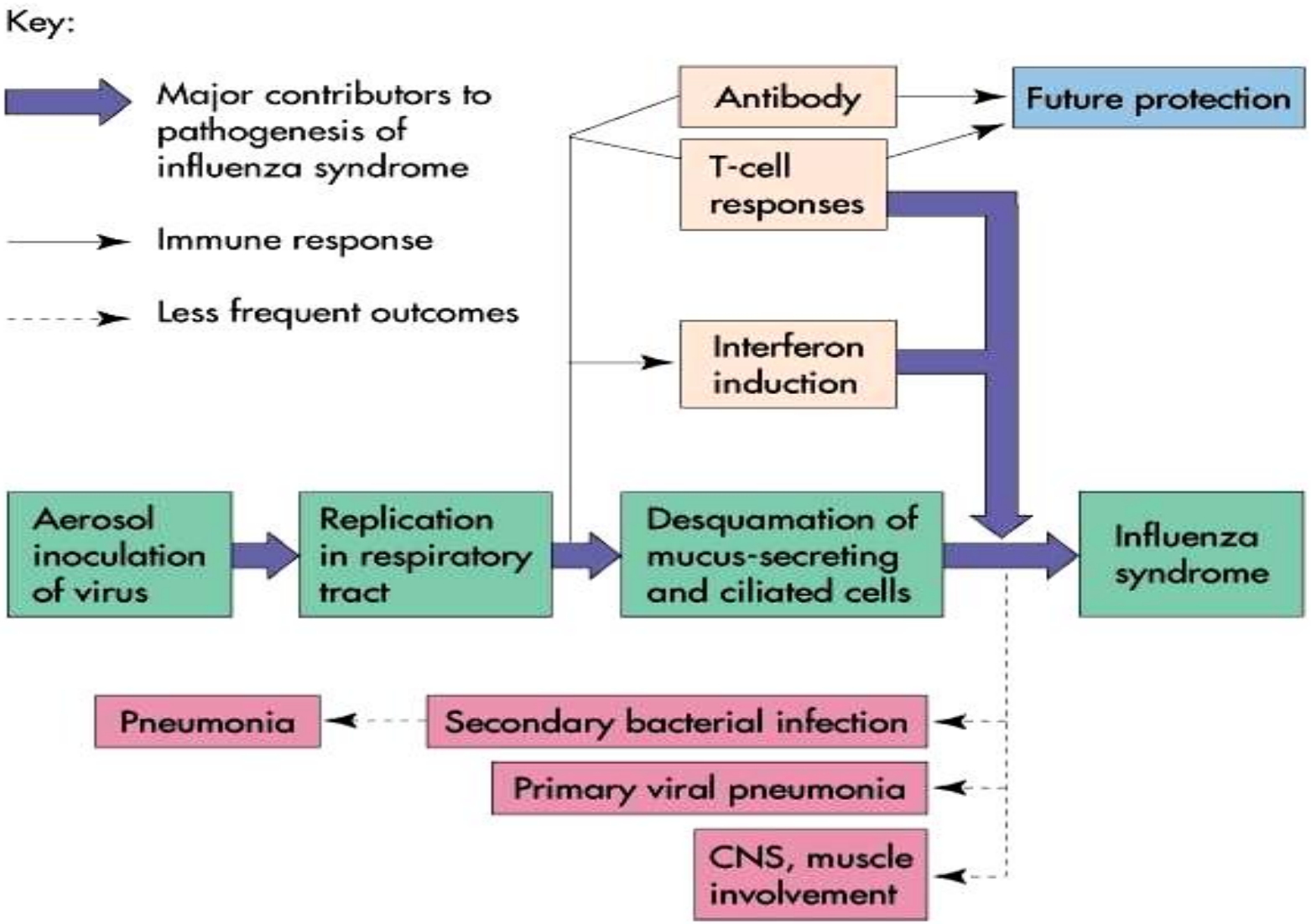
Human (reassortant virus)



Transmission to Humans



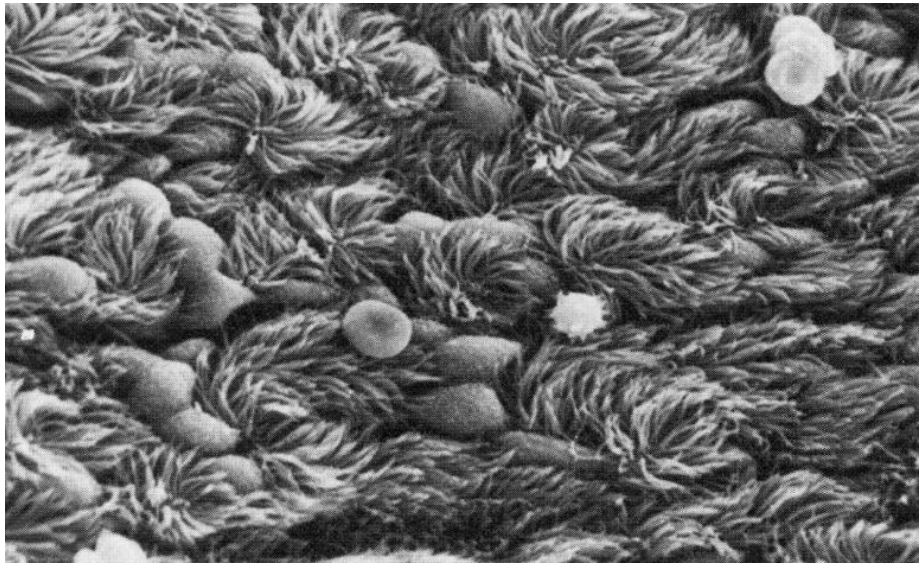
Influenza pathogenesis

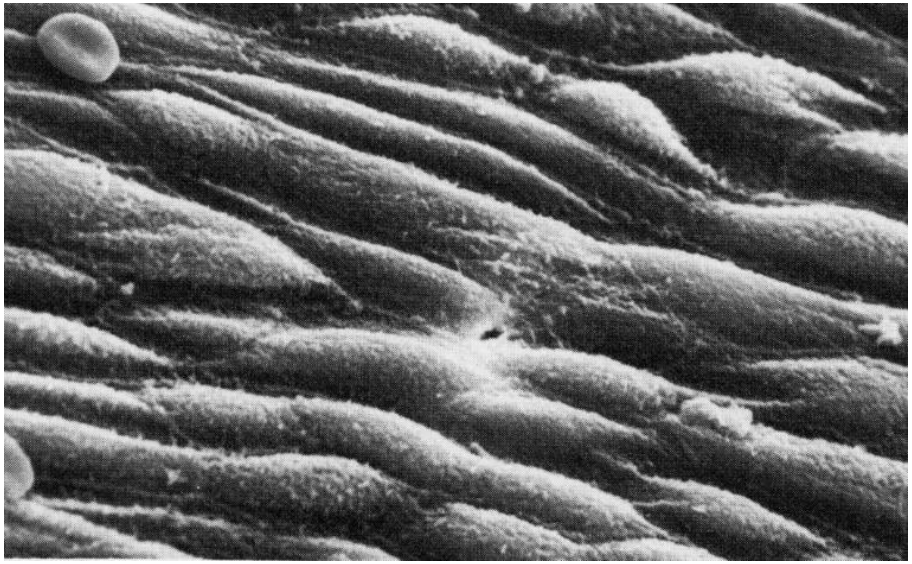


Virulence factors of Influenza

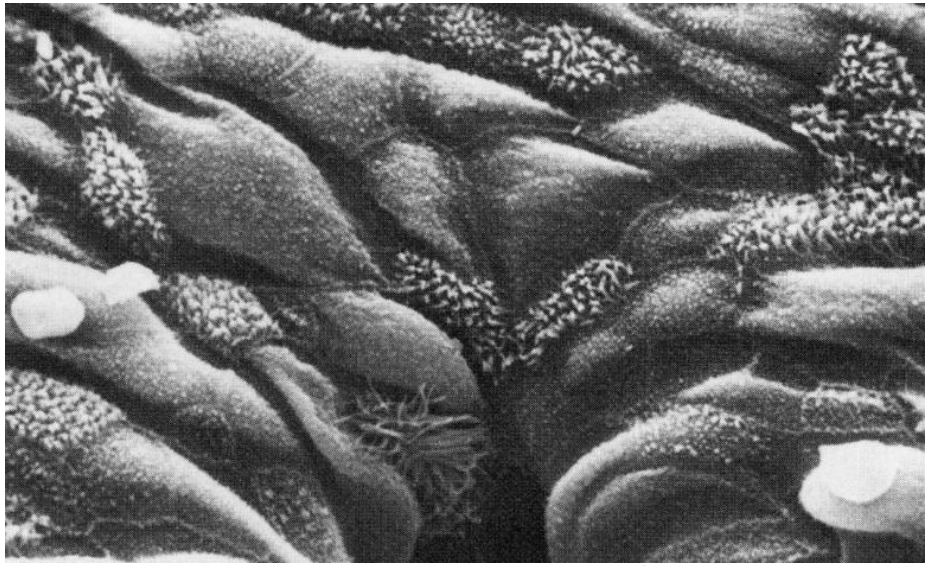
- Ability to infect lower respiratory tract
- A strong induction of pro-inflammatory cytokines and chemokines (cytokine storm)
- Apoptosis induction
- Systemic infection (spreading beyond the respiratory tract)
- Evasion of innate immune response (IFN)

NORMAL TRACHEAL MUCOSA





3 DAYS POST-INFECTION



7 DAYS POST-INFECTION

SYMPTOMS

- FEVER
- HEADACHE
- MYALGIA
- COUGH
- RHINITIS
- OCULAR SYMPTOMS

CLINICAL FINDINGS

- SEVERITY
  - VERY YOUNG
  - ELDERLY
  - IMMUNO-COMPROMISED
  - HEART OR LUNG DISEASE

PULMONARY COMPLICATIONS

- CROUP (YOUNG CHILDREN)
- PRIMARY INFLUENZA VIRUS PNEUMONIA
- SECONDARY BACTERIAL INFECTION
  - *Streptococcus pneumoniae*
  - *Staphlyococcus aureus*
  - *Hemophilus influenzae*

NON-PULMONARY COMPLICATIONS

- myositis (rare, > in children, > with type B)
- cardiac complications
- recent studies report encephalopathy
  - studies of patients <21 yrs in Michigan - 8 cases seen last season
- liver and CNS
  - Reye syndrome
- peripheral nervous system
  - Guillian-Barré syndrome

Reye’s syndrome

- liver - fatty deposits
- brain - edema
- vomiting, lethargy, coma
- risk factors
  - youth
  - certain viral infections (influenza, chicken pox)
  - aspirin

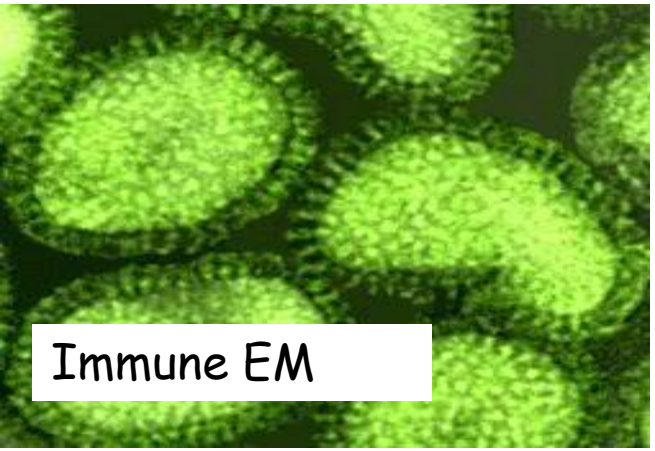
Laboratory Diagnosis of Influenza Virus infections

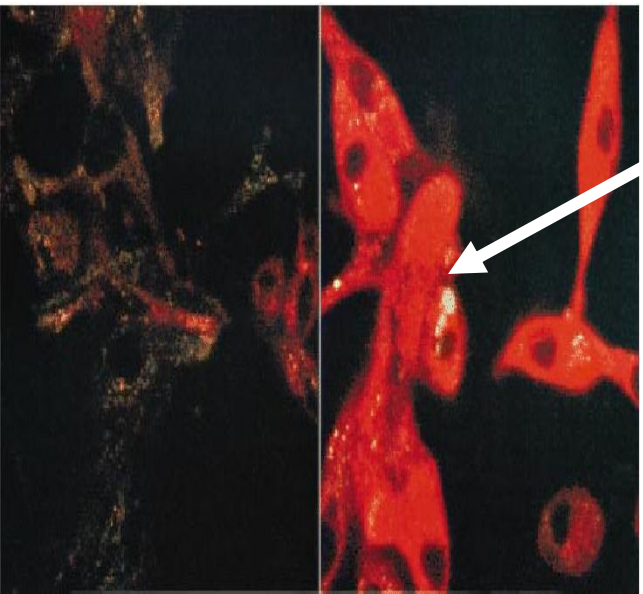
- **Direct detection of viral antigens in infected cells**
  Immuofluorescent staining

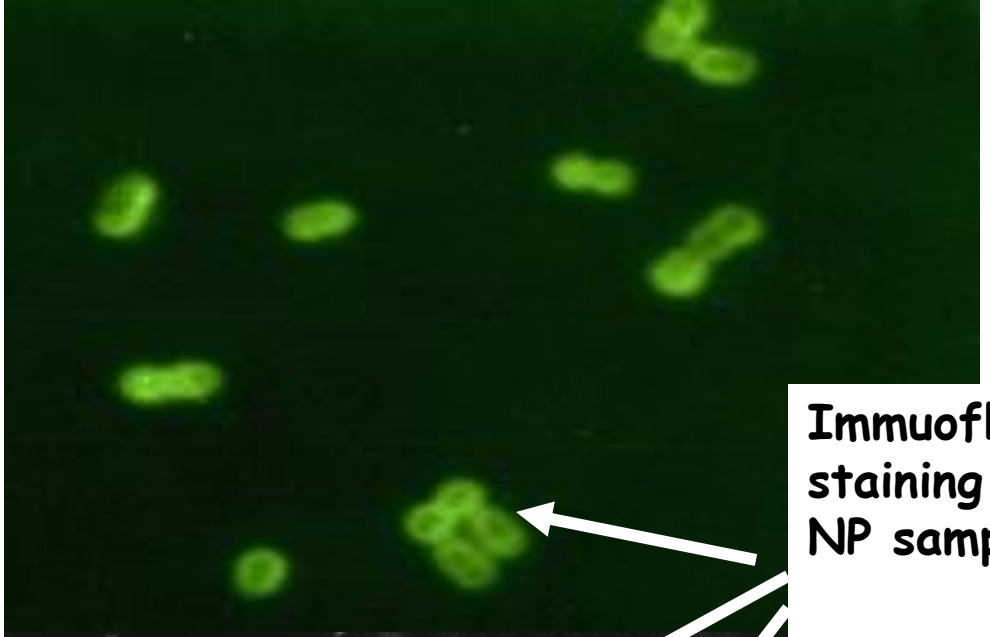
- **Isolation:**
  - **Inoculation into** the amniotic cavity of the chick embryo. detect HA then confirm & type by HAI
  - Primary Monkey Kidney cell lines
    - Detect HA & confirm and type by HAI of culture supernatant
    - Haemadsorption affinity of Tissue culture cells confirm and type by Haemadsorption Inhibition

  - **Serology:**
    - haeagglutination-inhibition (HAI)
    - ELISA
    - Complement fixation

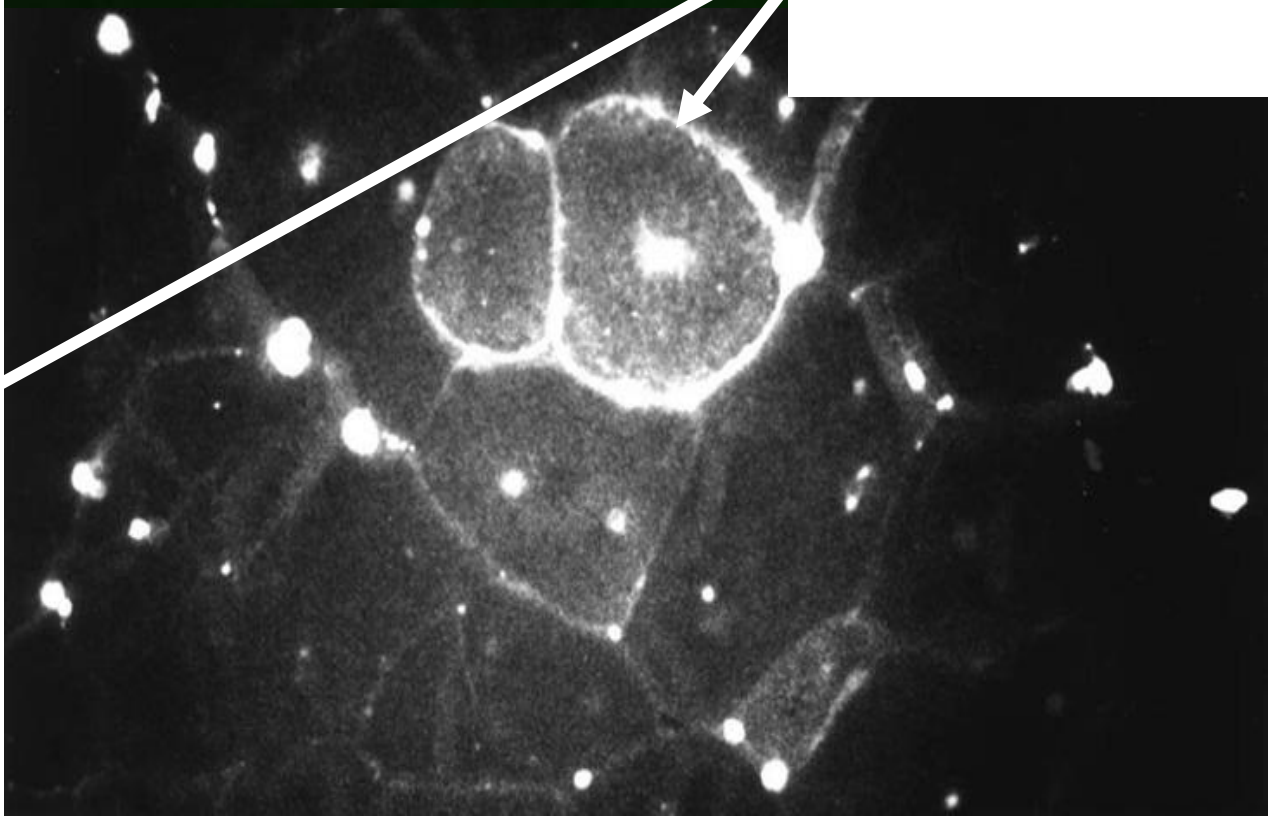
1. Direct detection



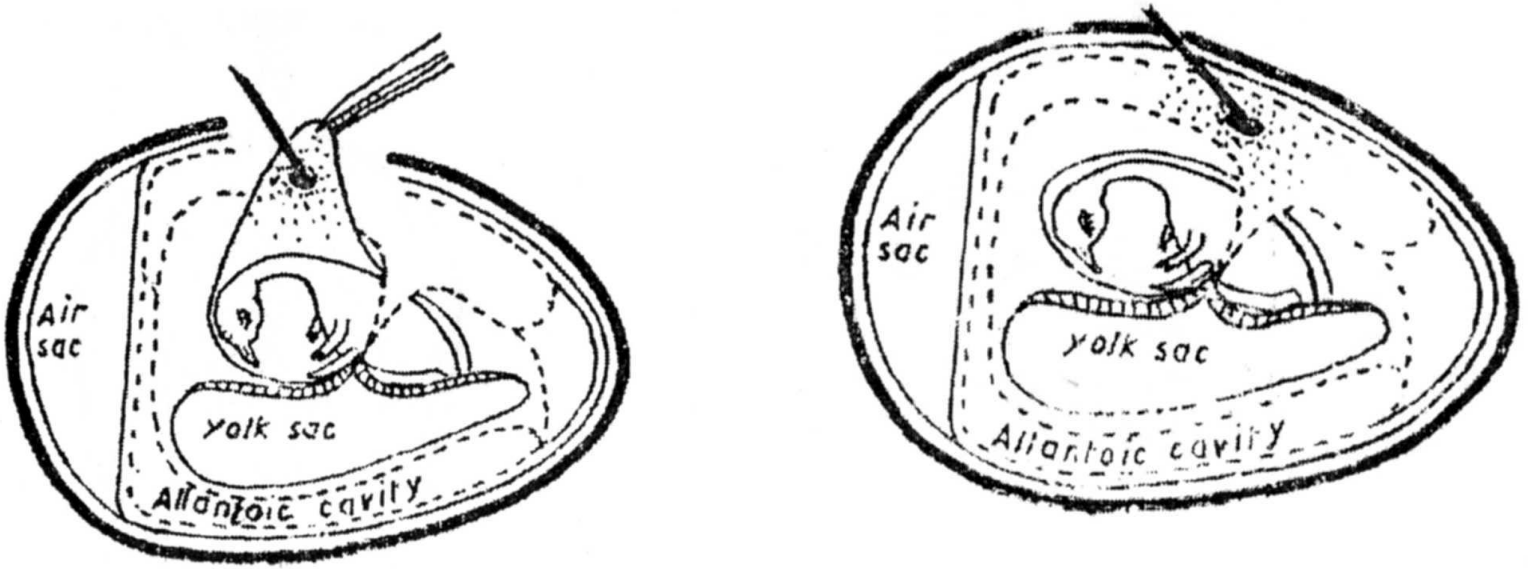




Immuofluorescent staining of OP or NP samples



Isolation:



Inoculation into the amniotic cavity of the chick embryo

Prevention and Treatment:

- Amantadine hydrochloride and one of its analogues, rimantadine, are antiviral drugs for systemic use in prevention of influenza “A”.

- They induce 70% protection against influenza “A” and should be considered in high risk groups.

- They also modify the severity of influenza “A” if administration is begun within 24-48 hours after onset of illness.

Prevention and Treatment:

- **The neuraminidase inhibitors zanamivir (given by inhalation) and oseltamivir (orally) were approved in 1999 for treatment of both influenza A and B.**

- **To be maximally effective the drugs must be administered very early in the disease.**

WHOM TO TREAT

- Antiviral treatment with oseltamivir or zanamivir is recommended for all patients with confirmed or suspected influenza virus infection
  - **WHO ARE HOSPITALIZED**

  or
  - **WHO ARE AT HIGHER RISK FOR INFLUENZA COMPLICATIONS**

Surveillance

- **Surveillance programs by government agencies and the WHO constantly monitor subtypes of influenza circulating around the world to promptly detect the appearance and spread of new strains.**

- **Surveillance also extends to:**
  - **animal populations especially birds, pigs, and horses, as pandemic strains usually arise from re-assortants of human and animal strains.**

Prophylaxis

Because of:

- **the short incubation period**

&

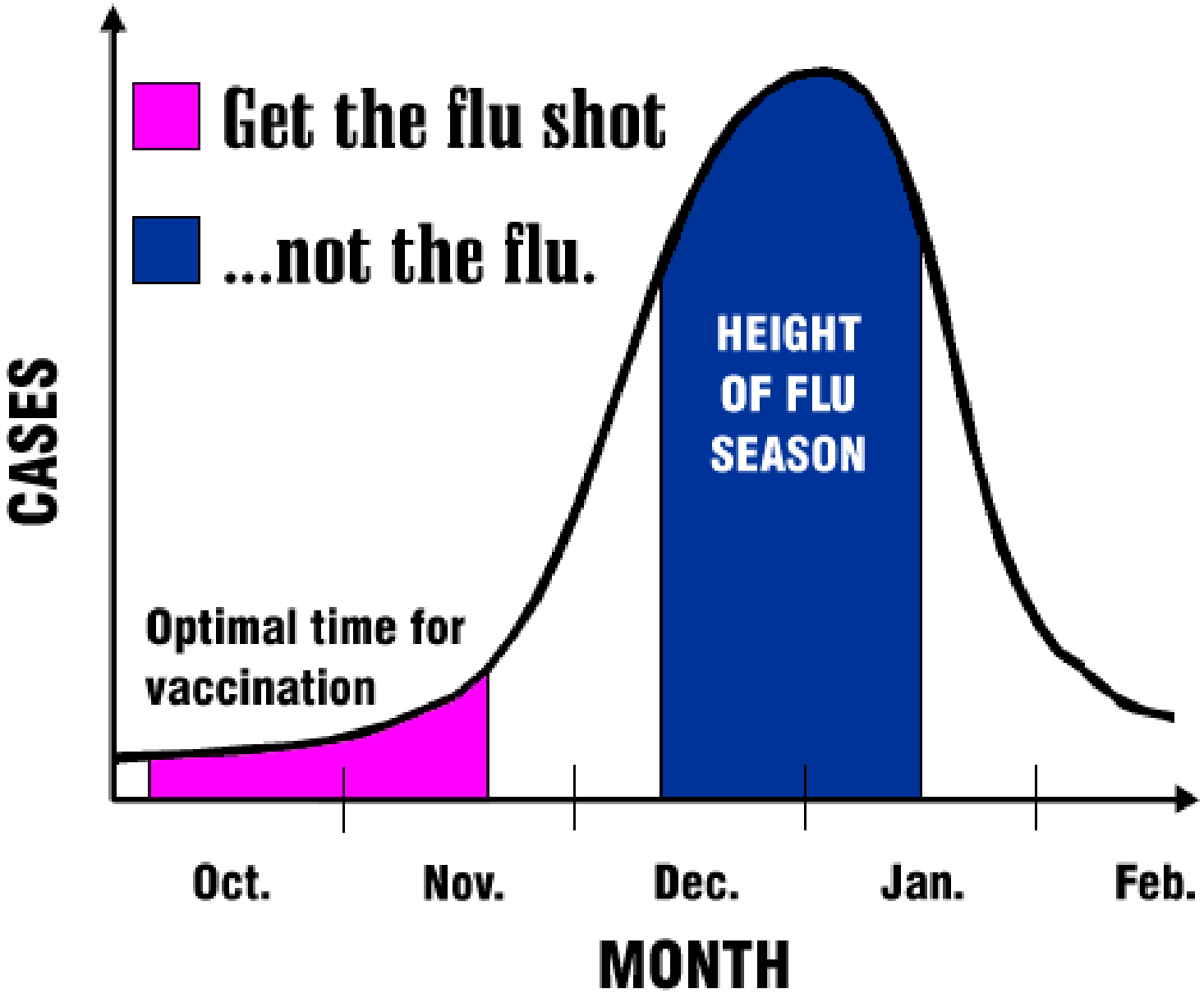
- **high attack rate**

The best to be done, is to use a suitable vaccine, and to immunize those at risk.

Influenza Vaccines

- Though existing vaccines are continually being rendered obsolete as viruses undergo antigenic drift and shift.

- Yet controlled trials of influenza vaccines indicate that a moderate degree of protection (50-80%) is attainable.


Get the flu shot
...not the flu.
HEIGHT OF FLU SEASON
Optimal time for vaccination
CASES
Oct.
Nov.
Dec.
Jan.
Feb.
MONTH

Inactivated influenza vaccines

- Is a cocktail containing **one or two type A viruses and a type B virus** of the strains isolated in the previous winter's outbreak.

- **Vaccines are either whole virus (WV) vaccine** which contains intact, inactivated virus

- **or subvirion (SV) vaccine:**
  - contains purified virus disrupted with detergents.

  - **Surface antigen vaccines (subvirion vaccine)** contain purified HA and NA glycoproteins.

ALL THE ABOVE ARE EFFICACIOUS.

Live influenza vaccines:

- **A cold-adapted donor virus (able to grow at 25°C but not at 37°C)** introduced intranasally should replicate in the nasopharynx but not in the lower respiratory tract, its multiplication stimulate the local production of IgA. (Flumist)

- Approved for healthy people between 2-49yrs

RECOMMENDATIONS

Persons at High Risk for Influenza-Related Complications

· ≥ 65 years

· residents of nursing homes and other chronic-care facilities

· adults/children who have chronic pulmonary or cardiovascular disorders, including asthma

· adults/children who have required regular medical follow-up or hospitalization during the last year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications)

RECOMMENDATIONS

Persons at High Risk for Influenza-Related Complications

· children and teenagers (6 mths to 18 yrs) receiving long-term aspirin therapy - might be at risk for developing Reye syndrome after influenza

· women who will be in the 2nd or 3rd trimester of pregnancy during the influenza season.

RECOMMENDATIONS

Persons aged 50-64 years

increased prevalence of high-risk conditions

from public health point of view, easier to target by age than by high-risk condition (which may not have been discovered)

RECOMMENDATIONS

· physicians, nurses, and other personnel in both hospital and outpatient-care settings

· employees of nursing homes and chronic-care facilities who have contact with patients or residents

· employees of assisted living and other residences for persons in high-risk groups

· persons who provide home care to persons in high-risk groups

· household members (including children) of persons in high-risk groups.

RECOMMENDATIONS

Children from 0-23 mths are at increased risk for hospitalization from influenza, vaccination is encouraged for their household contacts and out-of-home caretakers, particularly for contacts of children aged 0–5 months because influenza vaccines have not been approved for use among children aged <6 months.

	TYPE A	TYPE B	TYPE C
severity of illness	++++	++	+
animal reservoir	yes	no	no
human pandemics	yes	no	no
human epidemics	yes	yes	no (sporadic)
antigenic changes	shift, drift	drift	Drift, stable
segmented genome	yes	yes	yes
amantadine, rimantidine	sensitive	no effect	no effect
zanamivir	sensitive	sensitive	
surface glycoproteins	2	2	(1)