Respiratory Infections

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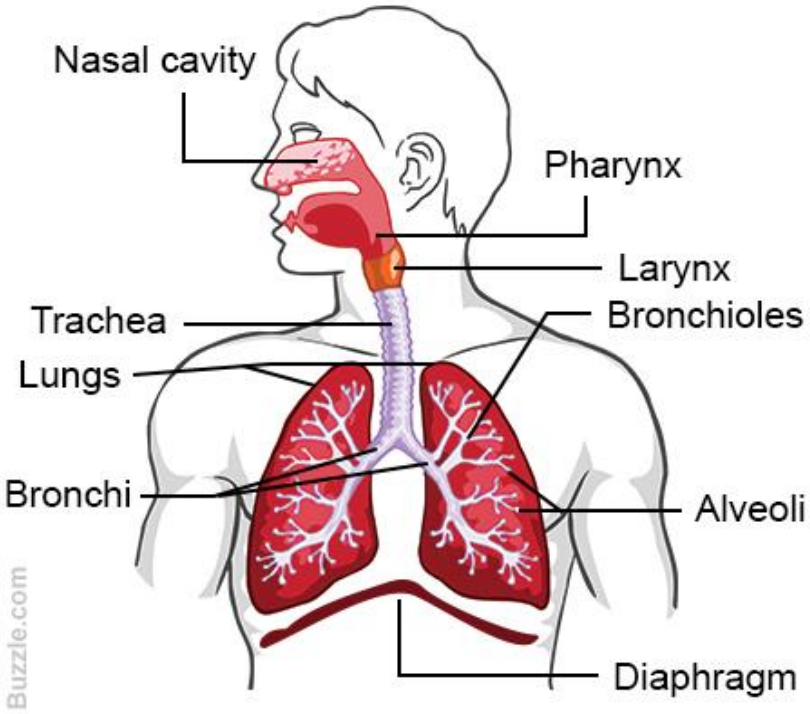
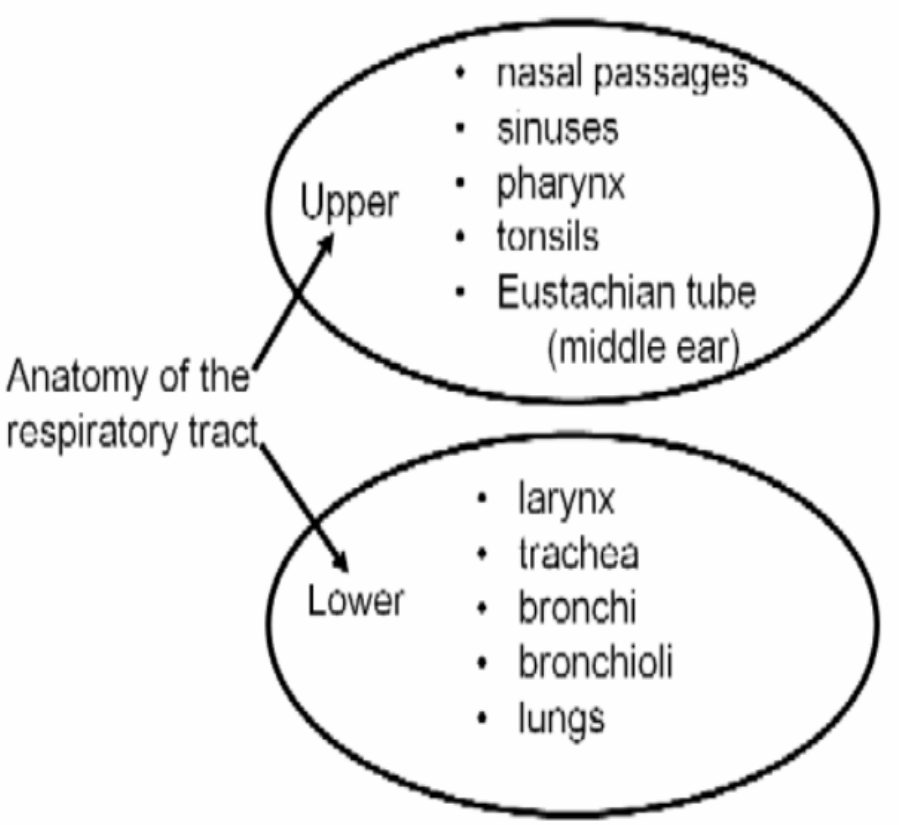
Contents of Teaching in Medical Virology Lecture:

1. Introduction to virology
2. Laboratory diagnosis
3. Childhood illnesses
4. Human herpesviruses
5. **Respiratory infections**
6. Gastroenteritis
7. Acute neurological syndromes
8. Hepatitis
9. Human retroviruses
10. Human papillomaviruses

Human Respiratory System





Clinical-anatomical definitions

Upper Respiratory Tract

1. Colds
2. Pharyngitis ("sore throat")
3. Tonsilitis
4. Sinusitis & Otitis Media

Lower Respiratory Tract

1. Laryngo-Tracheo Bronchitis (Croup)
2. Acute Bronchitis
3. Acute Bronchiolitis
4. Pneumonia & Bronchopneumonia

Infections of the respiratory tract are very common in both adults and children.

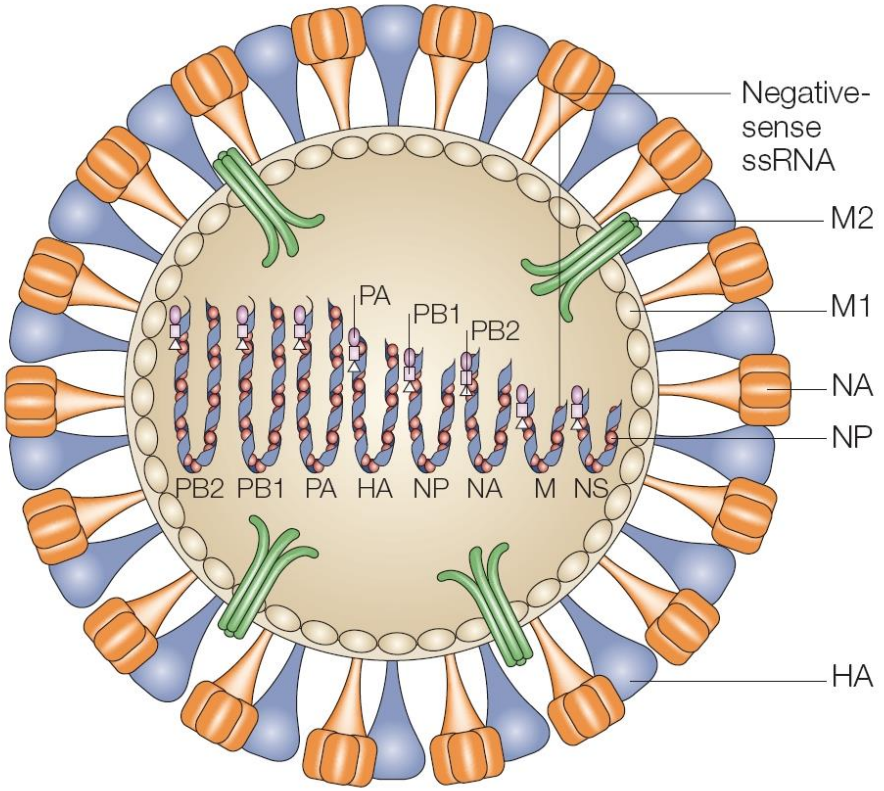
The Viruses

- Influenza
- Para-influenza 1, 2, 3 and 4
- Respiratory syncitial virus
- Human metapneumovirus
- Adenovirus
- Cytomegalovirus (in immuno-compromised patients)
- Rhinovirus
- Coronavirus

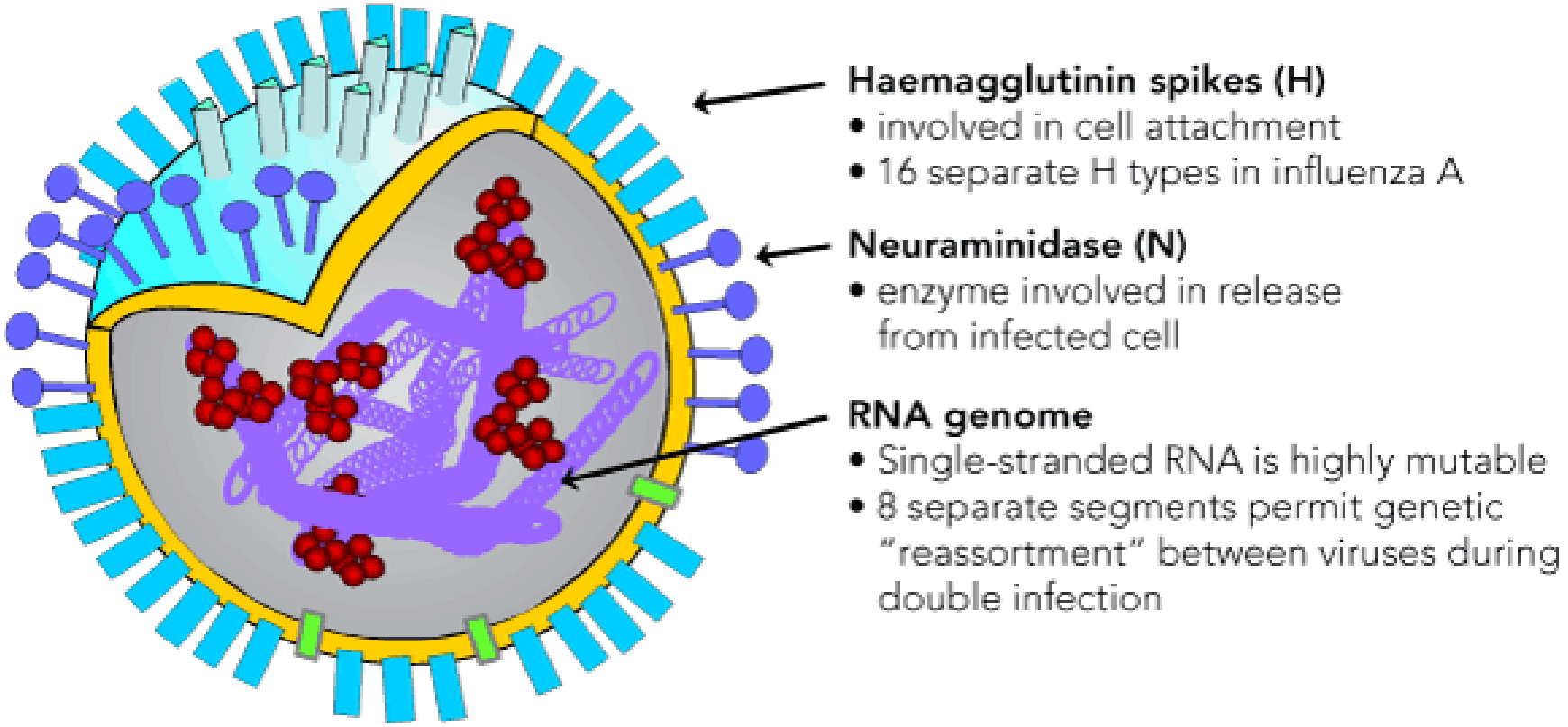
Influenza viruses

Virology

- Family: Orthomyxovirus
- Genera: influenzavirus A,B,C
- Single strand RNA virus with segmented genome
- Enveloped with two surface glycoprotein: H - Haemagglutinin - responsible for viral attachment N - Neuraminidase - responsible for viral exit from infected cell



There are 16 Haemagglutinin (H) types and 9 Neuraminidase (N) types of influenza A that exist in nature, mainly found in the natural reservoir wild aquatic birds.



Influenza A is the type that is responsible for pandemics. It can be further subtyped according to its H and N group. Only H1, 2 and 3 and N1 and 2 subtypes circulate widely in human.
Both Haemagglutinin and Neuraminidase are important antigens that confer subtype specific immunity and are therefore used in the vaccine formulations

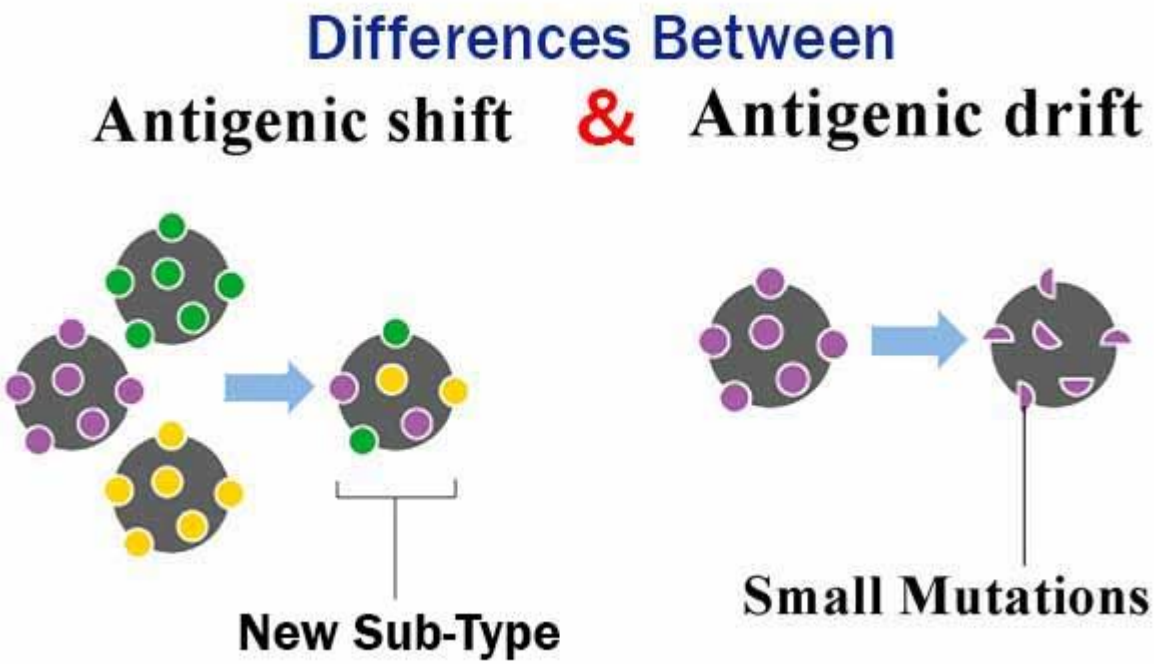
	Influenza A	Influenza B	Influenza C
Most dangerous	●		
Least dangerous			●
Most common		●	
Least common			●
Causes most pandemics	●		
Least likely to cause pandemics			●
More common in children than adults			●
Strong ability to mutate and evolve into more dangerous strains	●		

Drift (minor antigenic change)

The envelope glycoproteins (HA and NA) of influenza virus change their antigenic character gradually over time. This is due to random point mutations introduced during replication of the viral genome. The viral RNA polymerase has no proof-reading function and is therefore highly error prone. Drift results in annual epidemics of influenza A and B in humans.

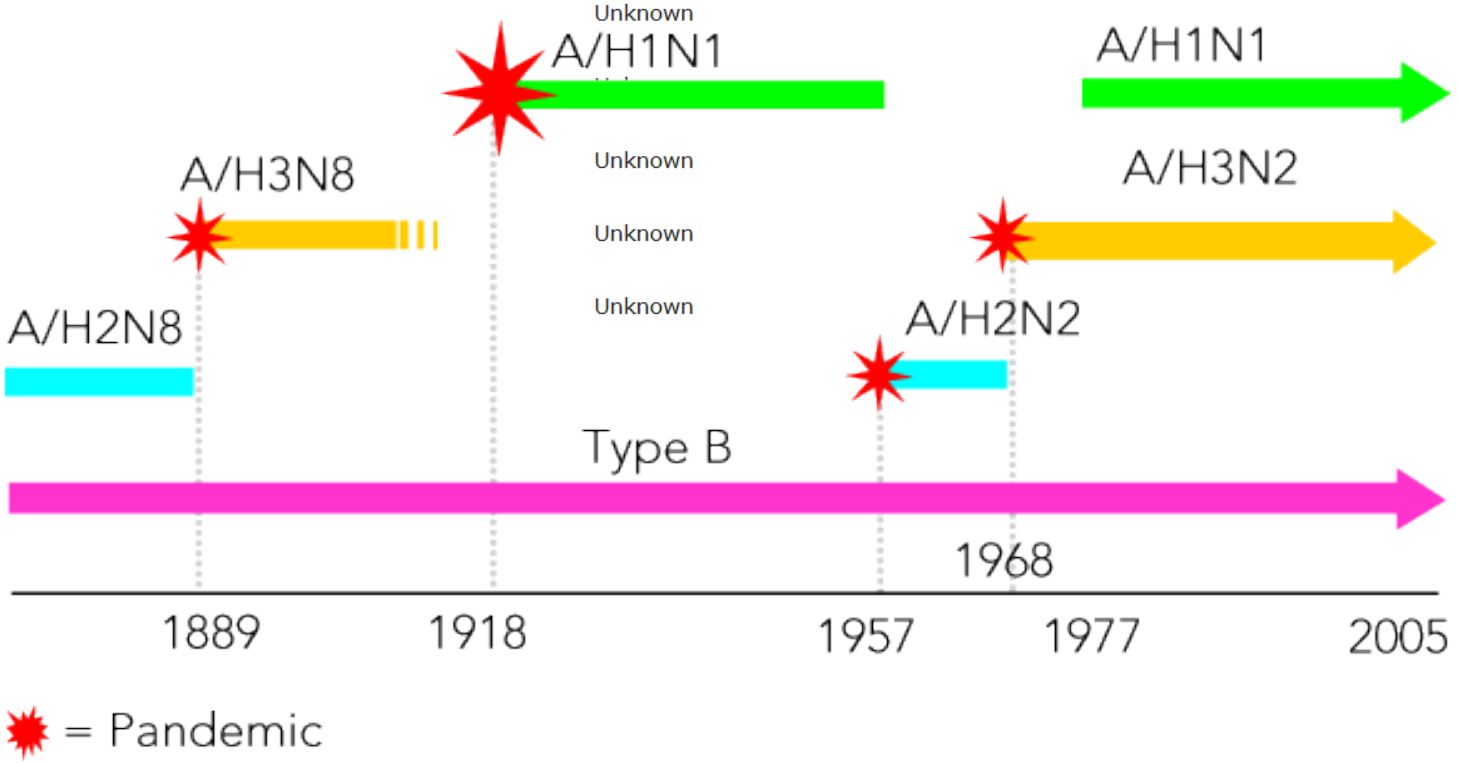
Shift (major antigenic change)

Influenza viruses have segmented genomes (each gene is on a separate gene segment). If a single cell is simultaneously infected with 2 different influenza viruses, gene swapping can occur during the formation of new virus particles. This genetic change process is called reassortment. Global herd immunity to the new virus is usually very low and this can result in a new flu pandemic. This phenomenon only occurs with influenza A.



Influenza pandemics and probable pandemics during the past three centuries

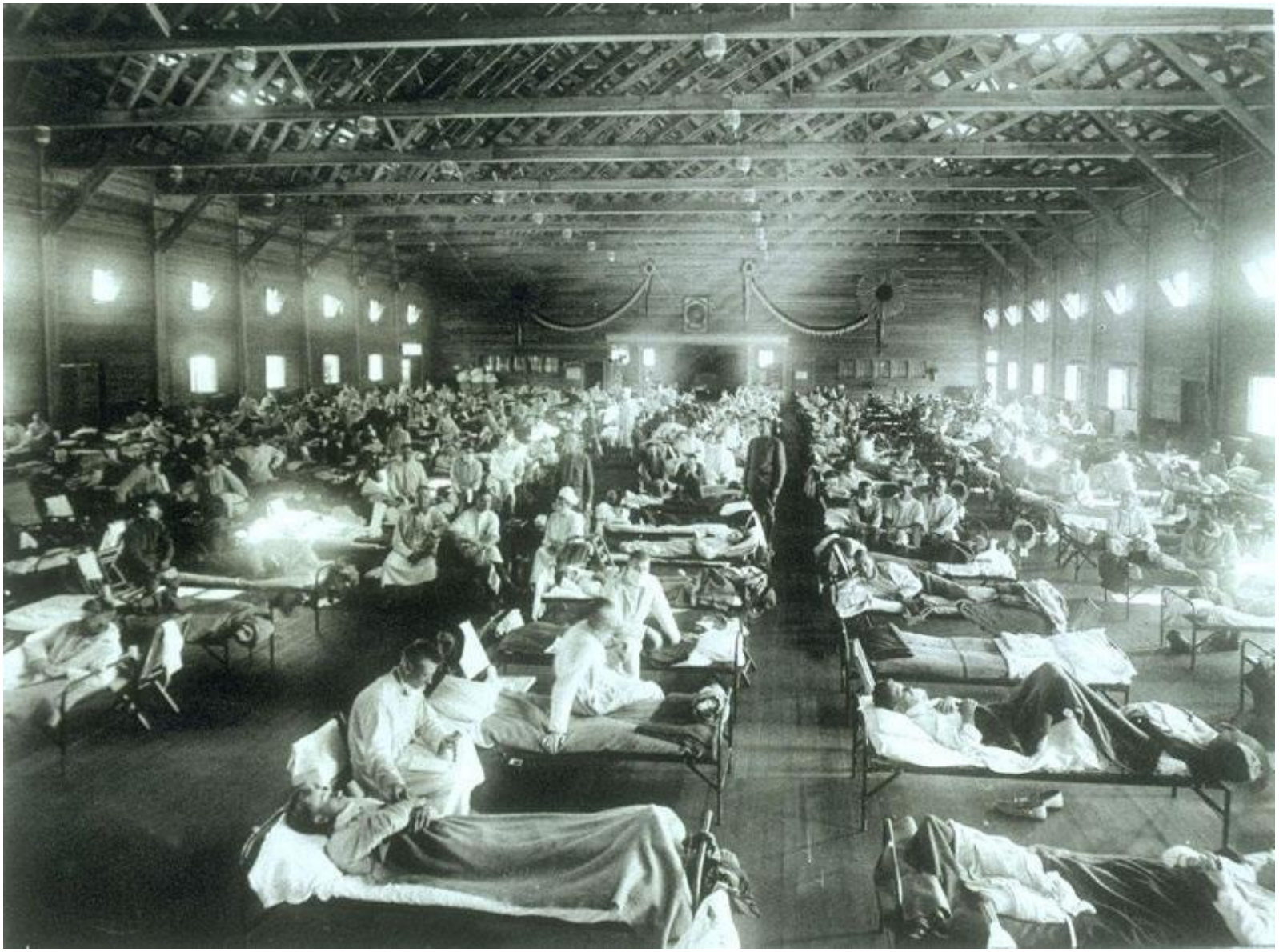
Years	Probable origin	Virus subtype
1968–1969	China	H3N2
1957	China	H2N2
1918–1919	Uncertain: possibly United States	H1N1
1898–1900	Unknown	H3(N8)
1889–1890	Russia	H2N?
1833	Russia	Unknown
1830–1831	Asia	
1781–1782	China	Unknown
1732–1733	Russia	Unknown
1729–1730	Russia	Unknown



The influenza viruses
Alan W Hampson and John S Mackenzie
Med J Aust 2006; 185 (10): 39

Fig. Eras of human influenza viruses

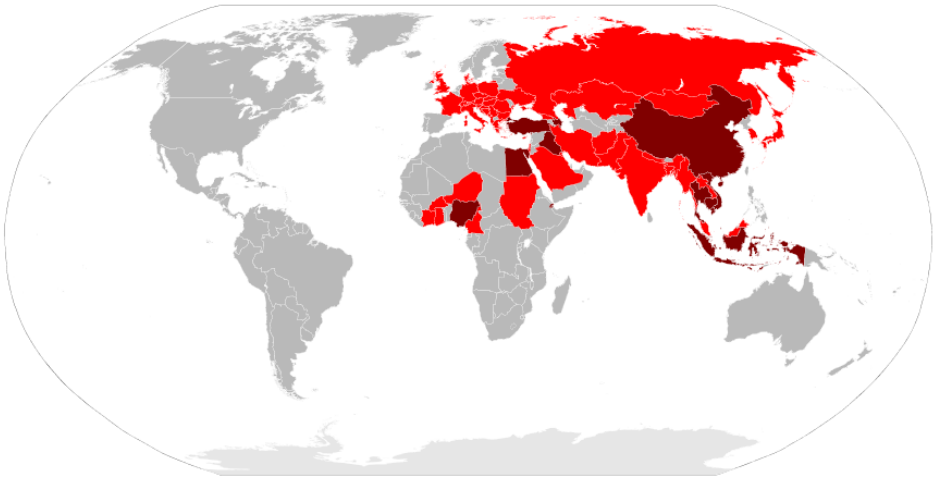
The 1918 flu pandemic (January 1918 – December 1920)

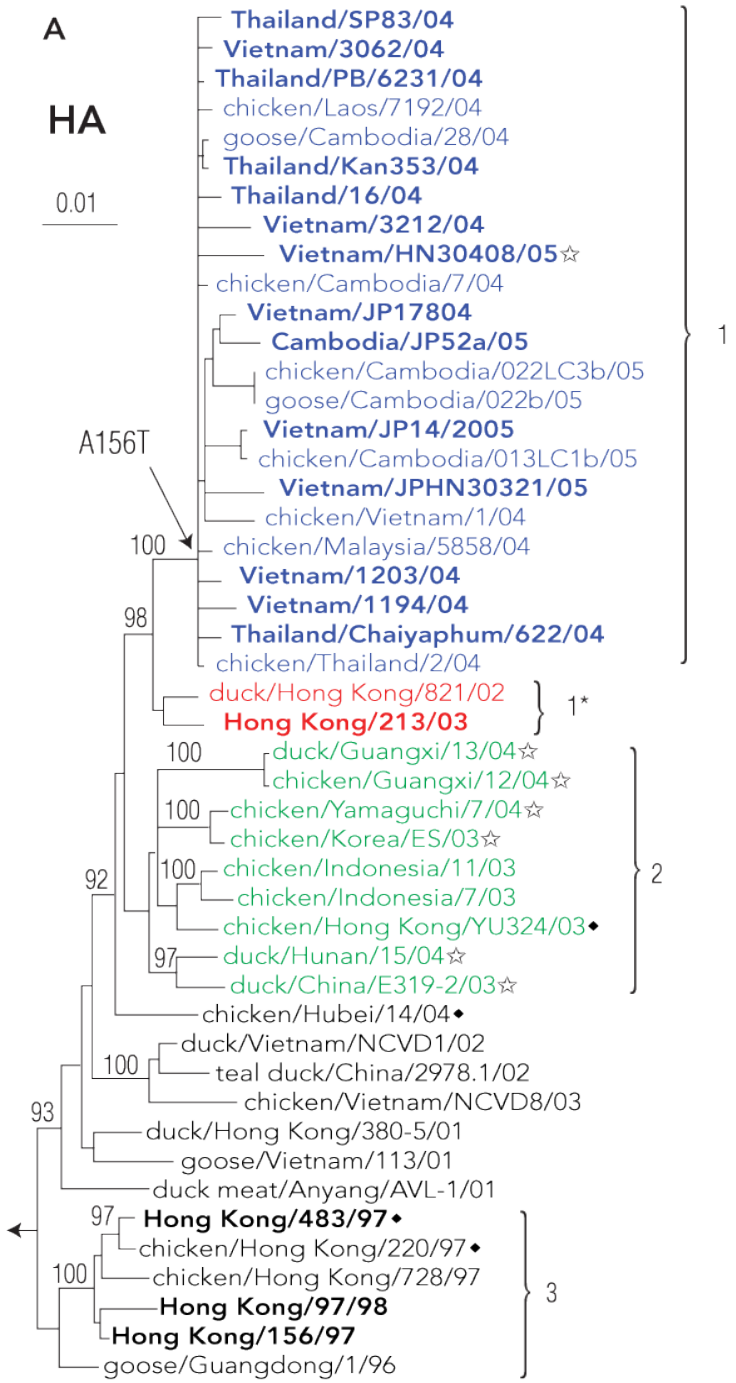


Soldiers from Fort Riley, Kansas, ill with Spanish influenza at a hospital ward at Camp Funston.

WHO Pandemic Influenza Phases (2009)[92][*dead link*][93]	
Phase	**Description**
Phase 1	No animal influenza virus circulating among animals have been reported to cause infection in humans.
Phase 2	An animal influenza virus circulating in domesticated or wild animals is known to have caused infection in humans and is therefore considered a specific potential pandemic threat.
Phase 3	An animal or human-animal influenza reassortant virus has caused sporadic cases or small clusters of disease in people, but has not resulted in human-to-human transmission sufficient to sustain community-level outbreaks.
Phase 4	Human to human transmission of an animal or human-animal influenza reassortant virus able to sustain community-level outbreaks has been verified.
Phase 5	Human-to-human spread of the virus in two or more countries in one WHO region.
Phase 6	In addition to the criteria defined in Phase 5, the same virus spreads from human-to-human in at least one other country in another WHO region.
Post peak period	Levels of pandemic influenza in most countries with adequate surveillance have dropped below peak levels.
Post pandemic period	Levels of influenza activity have returned to the levels seen for seasonal influenza in most countries with adequate surveillance.

Highly pathogenic H5N1





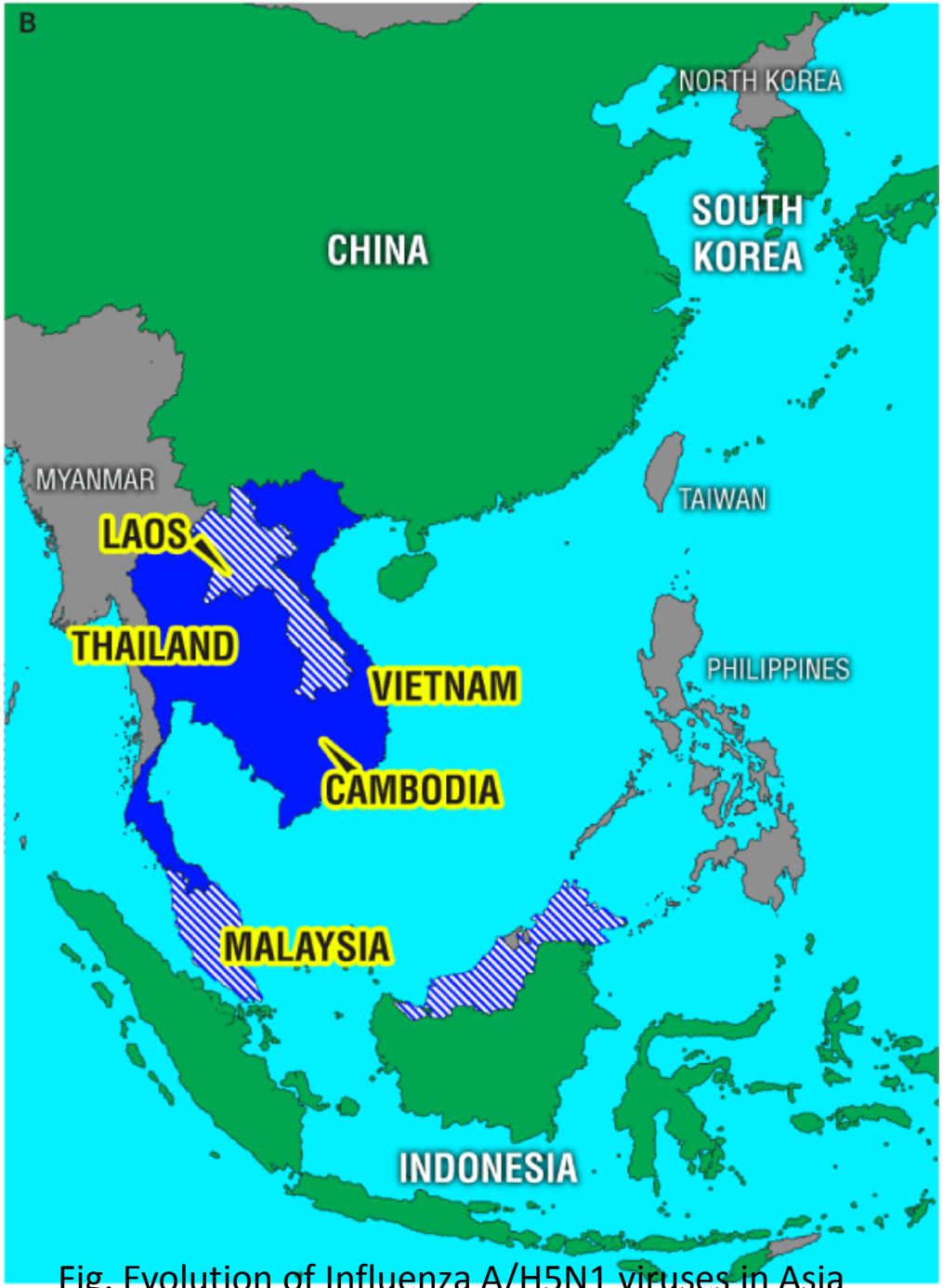


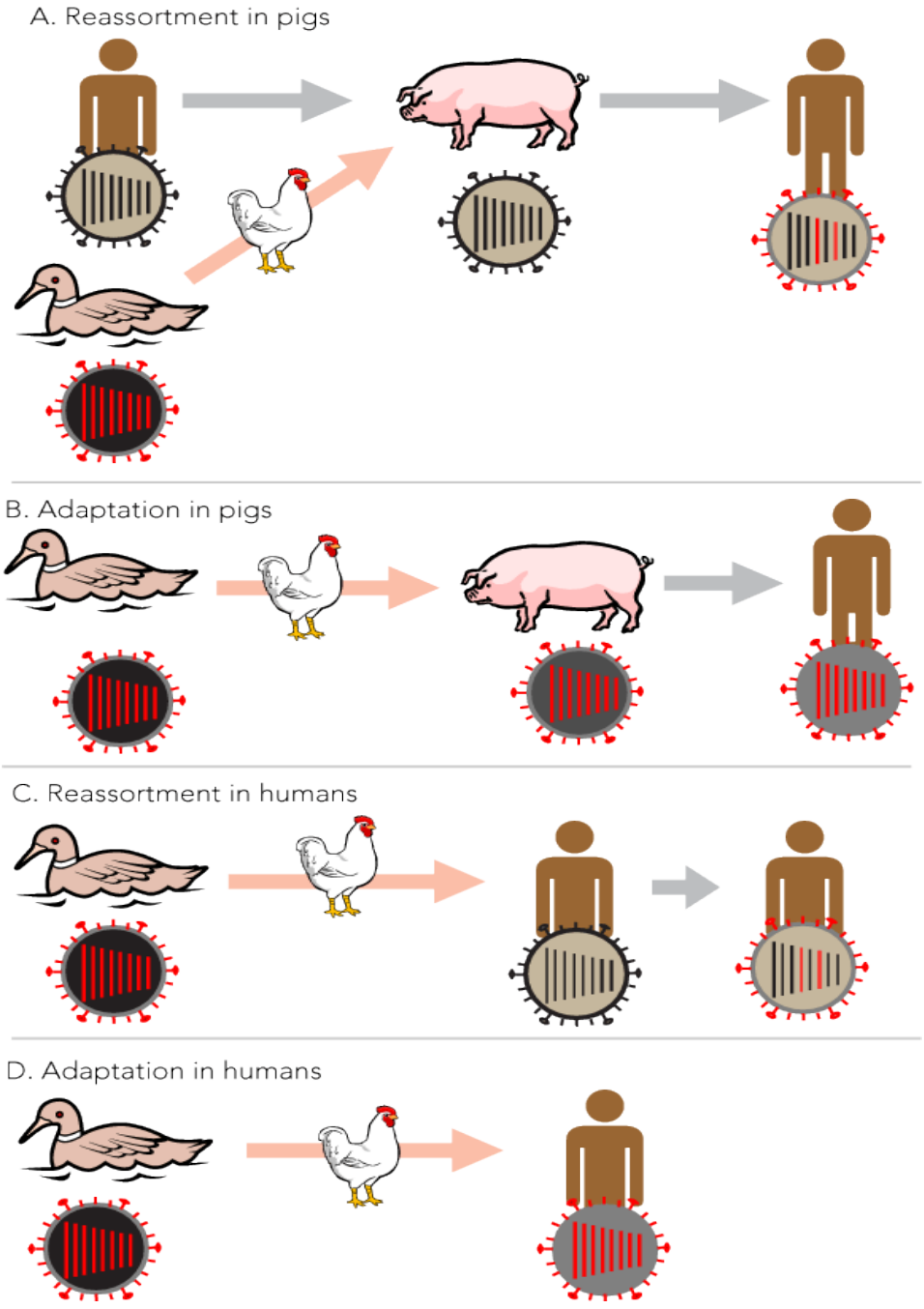
Fig. Evolution of Influenza A/H5N1 viruses in Asia

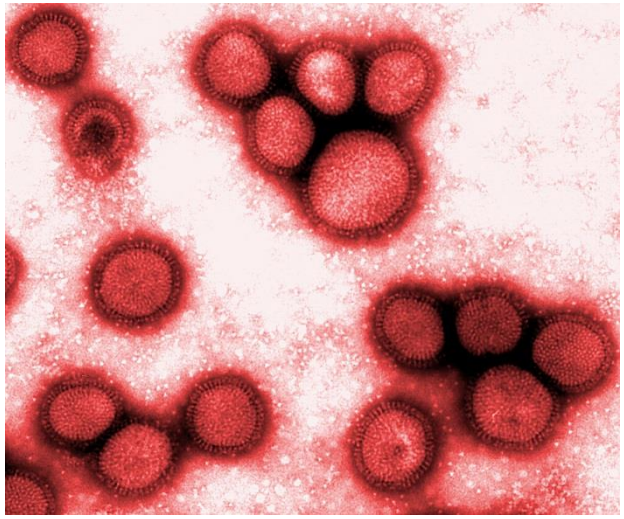
Phylogenetic relationships among H5 haemagglutinin genes from avian influenza A/H5N1 viruses, and their geographic distribution.

Viral isolates collected before and during the 2004–2005 outbreak in Asia and selected ancestors are included in the analysis.

A: The differing groups or “clades” of haemagglutinin are coloured blue, red, and green. Names in bold denote isolates from human infections.

B: Geographic distribution of H5N1 in East Asia: solid blue denotes countries reporting infections with clade 1 H5N1 in humans and birds, cross-hatched blue denotes countries reporting clade 1 H5N1 infections in birds only, and green denotes countries reporting bird infections with clade 2 H5N1.





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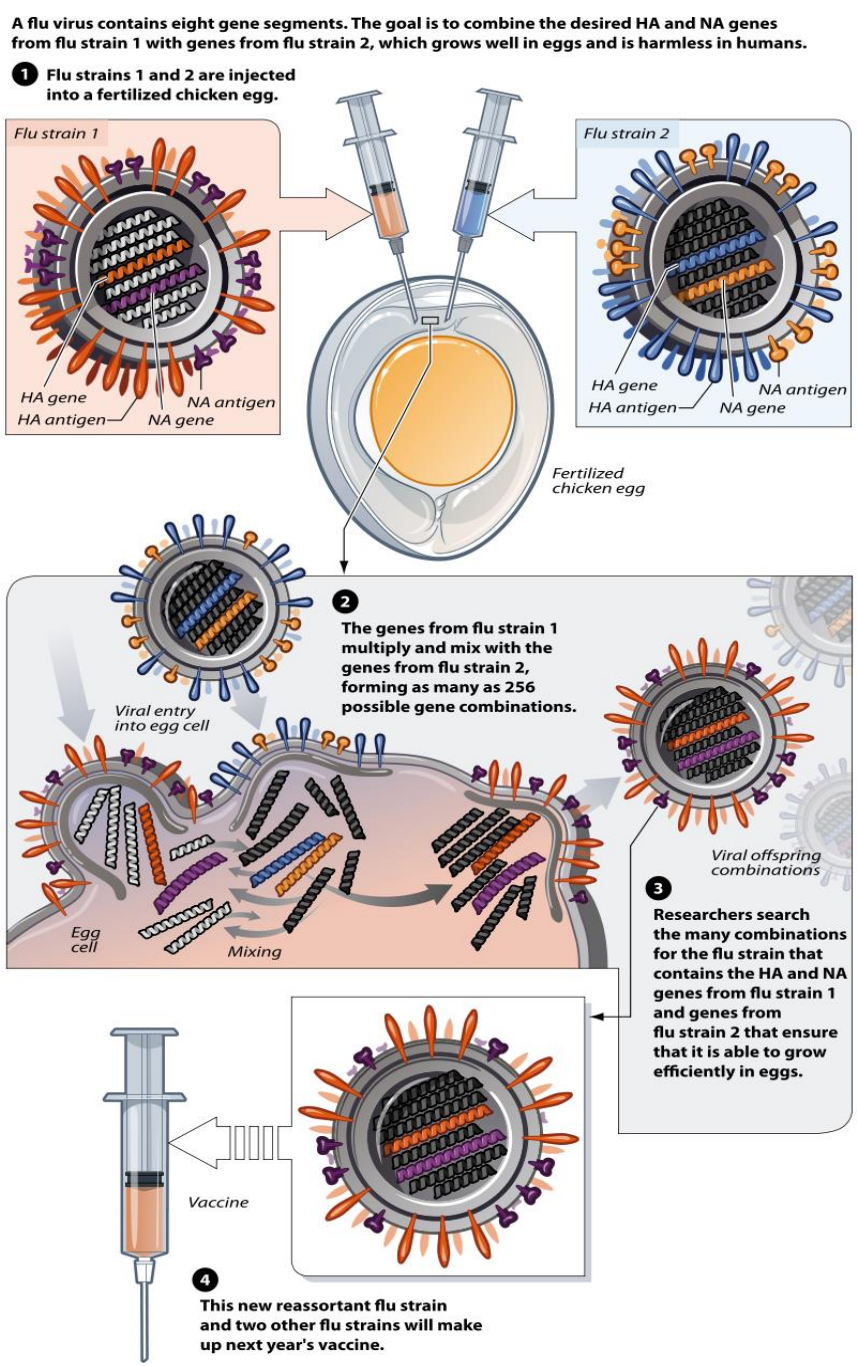
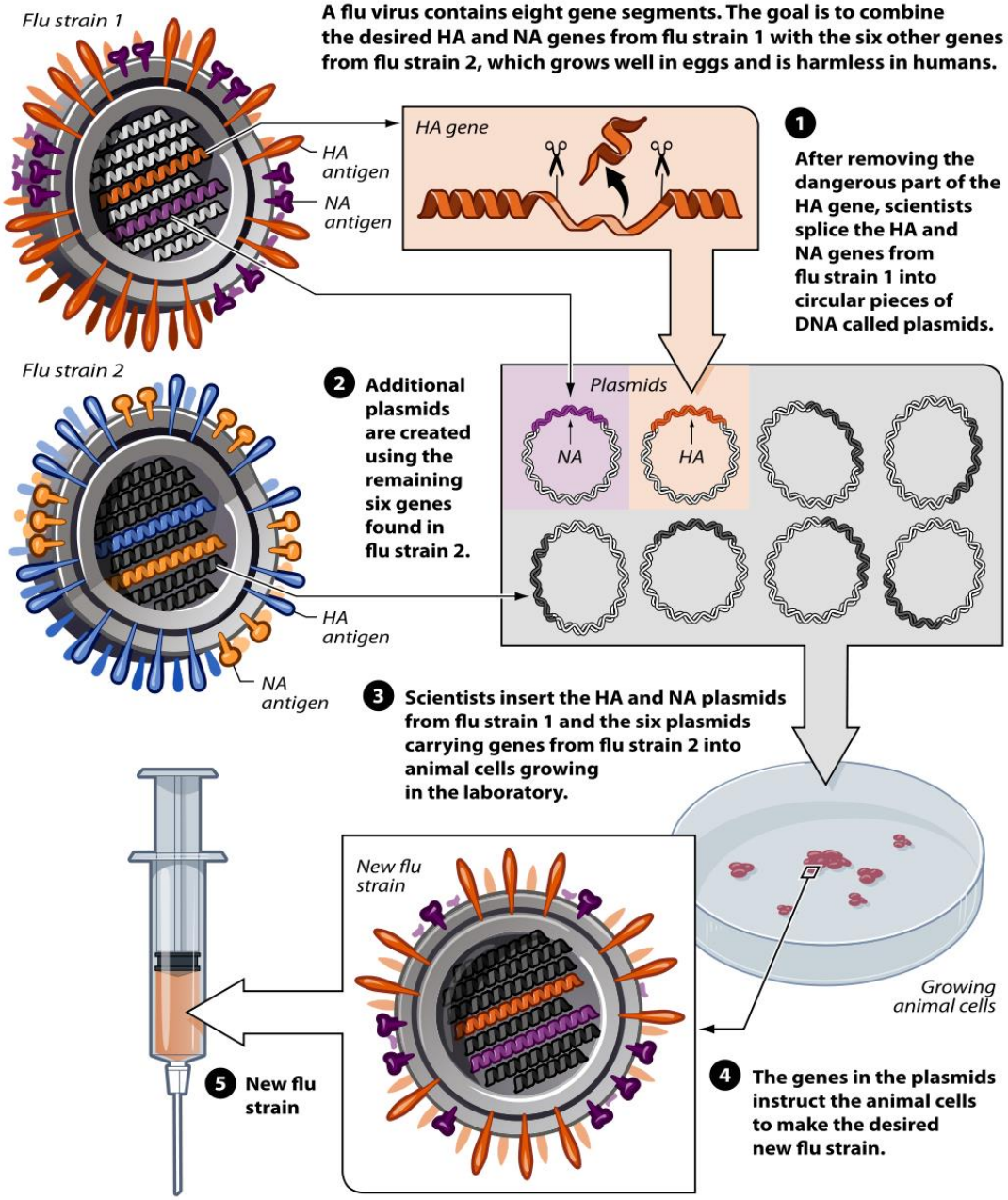


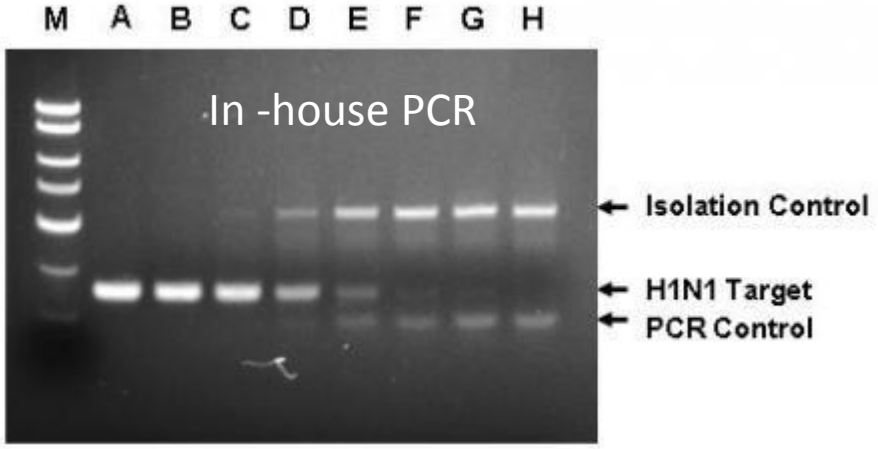
Flu vaccine is usually grown by vaccine manufacturers in fertilized chicken eggs

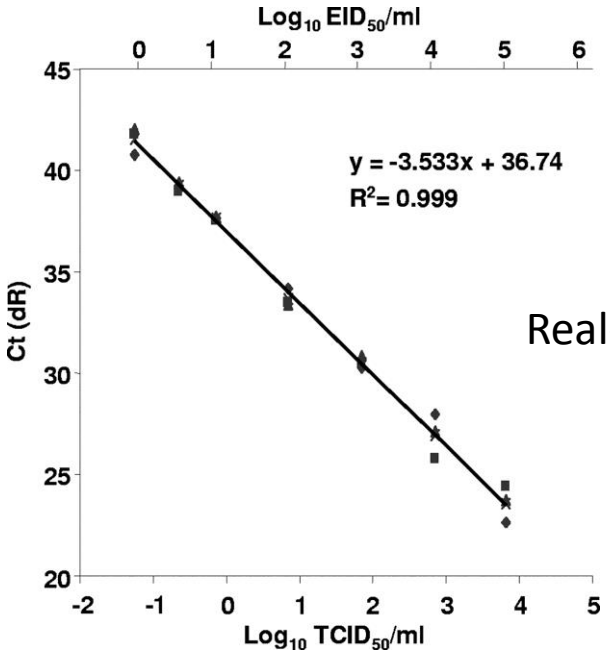
Avian flu vaccine development by reverse genetics technique



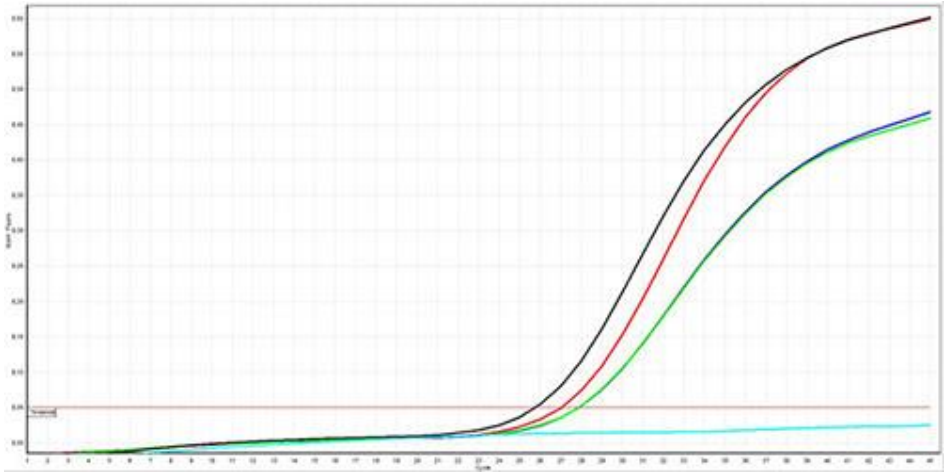
Detection of virus from respiratory secretions is the most convincing way of proving a viral aetiology:

- 1. Detection of virus infected cells by immunofluourescence or ELISA
- 2. Detection of virus by culture or multiplex PCR





Real-time PCR



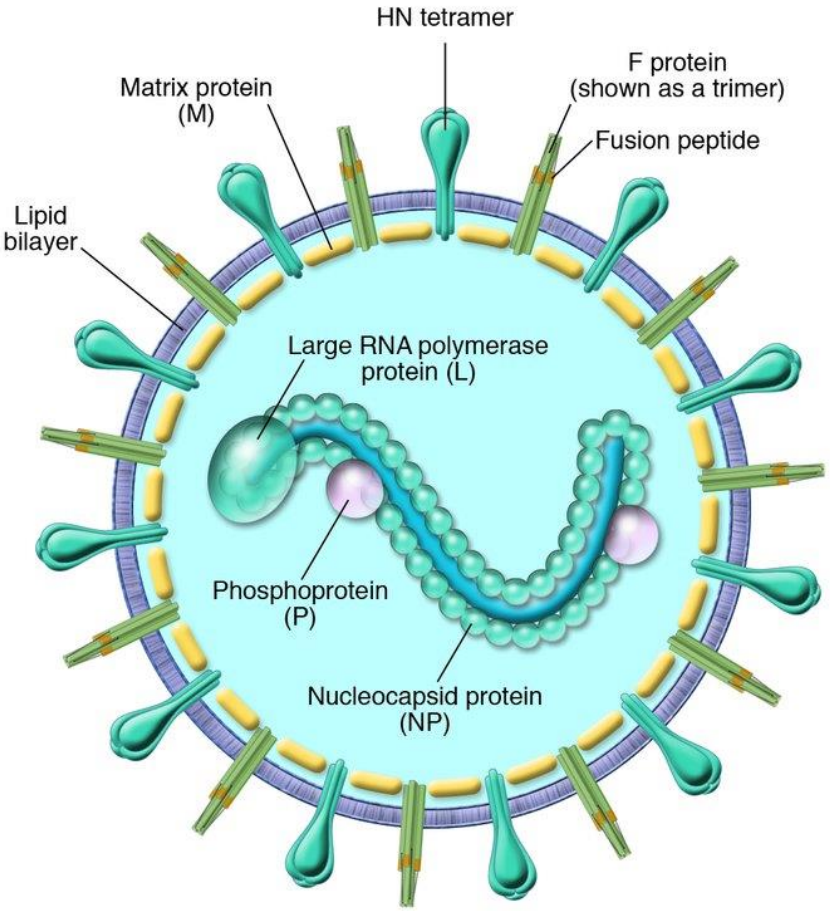
Biosafety level of influenza viruses

BIOSAFETY LEVEL 3

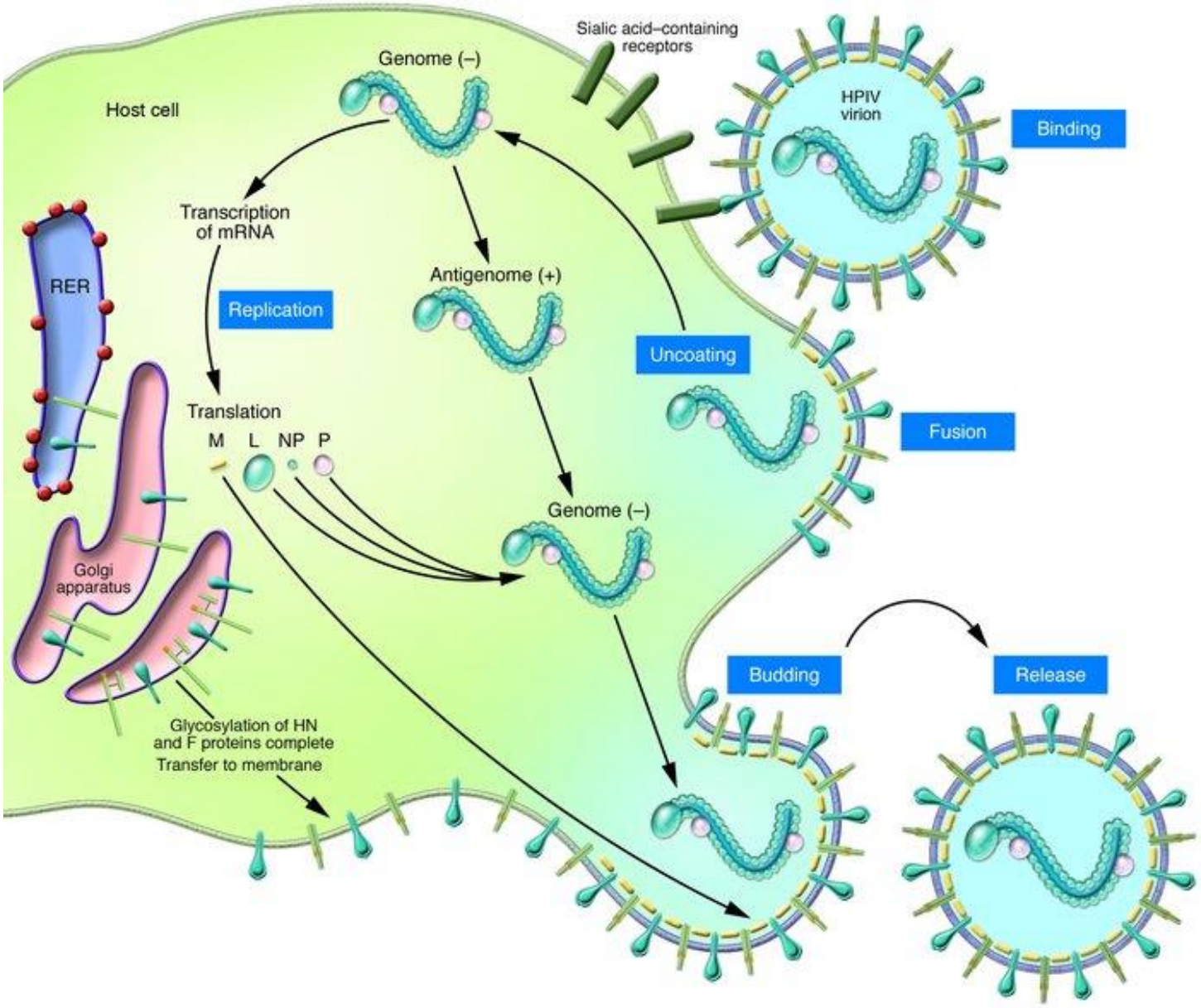
Para-influenza viruses 1, 2, 3 and 4

Virology

- Para-myxoviruses: pleomorphic, enveloped ssRNA viruses; approximately 150-200nm in diameter.
- There are two types of glycoprotein in the evnelope, namely the HN (haemagglutinin / neuraminidase) and the F (Fusion).
- They have an inner helical core that protects the ssRNA genome.
- Haemagglutinin binds, agglutinates red blood cells. Neuraminidase enzyme that degrades sialic acid (detaches the virion from the cell surface) Fusion causes membrane fusion, syncitium formation

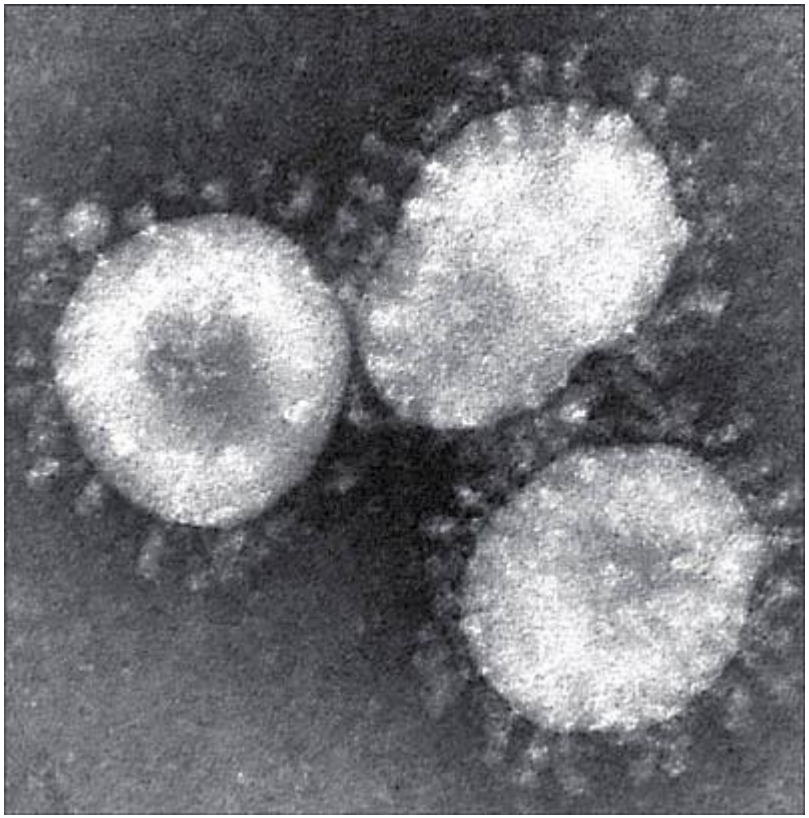


Entry of parainfluenza virus into cells as a target for interrupting childhood respiratory disease



Parainfluenza

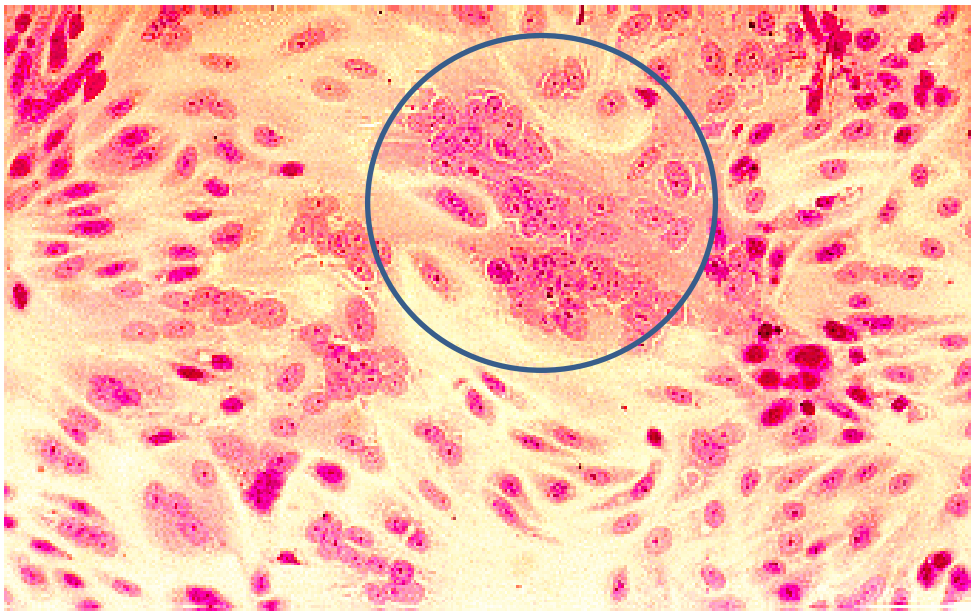
- **Spread:** Respiratory droplets, fomites (virus is delicate and does not survive long in the environment.)
- **Clinical Syndromes:** Acute laryngo-tracheo bronchitis (Croup), Bronchiolitis, Pneumonia Re-infections cause "common cold" symptoms.



Respiratory Syncitial Virus (RSV)

Virology

- Pneumovirus (sub-genus of paramyxoviridae) Enveloped, ssRNA viruses
- Lacks the HN glycoprotein typical of the para-myxovirus group, but contains the fusion protein.
- Gets its name from the fact that it causes large syncitia in cell culture.



Syncytial formation caused by RSV in cell culture

RSV

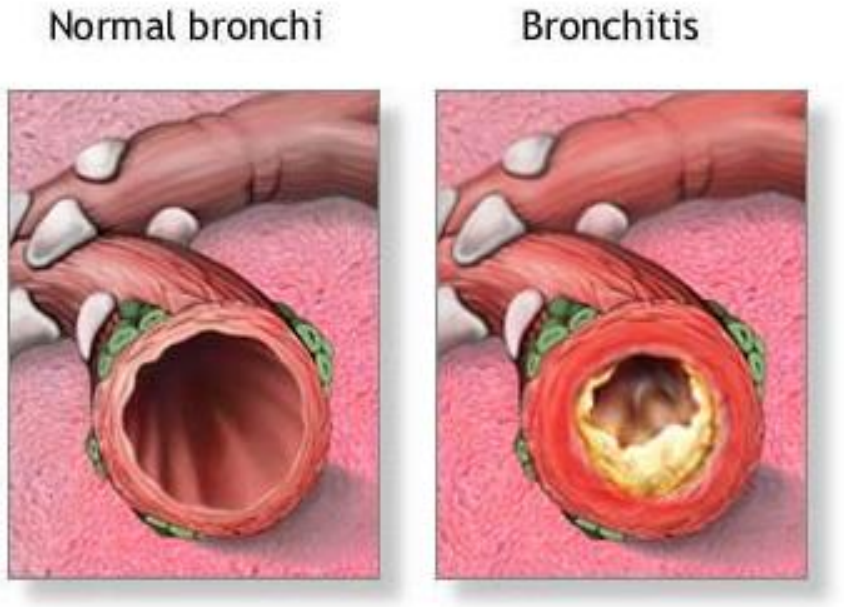
Epidemiology

- Spread: Respiratory droplets.
- It is the prime cause of bronchiolitis in young infants.
- There is no protection against RSV from maternal antibody and infants exposed in the first 6 months of life can develop life threatening disease.

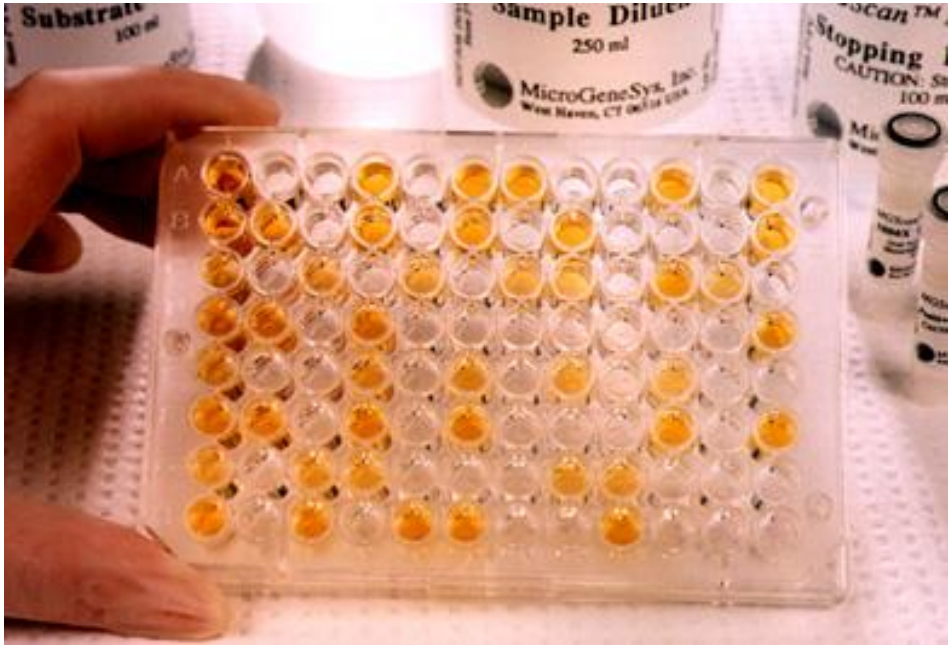
RSV

Clinical syndromes

- Bronchiolitis, Broncho-pneumonia infants < 6 months of age.
- Laryngo tracheo bronchitis infants, young children.
- Acute bronchitis adults, especially the elderly.
- Common cold syndrome re-exposure in children and adults



Bronchitis is the inflammation of the bronchi, the main air passages to the lungs. It generally follows a viral respiratory infection.



Microplate ELISA: coloured wells indicate reactivity. The darker the colour, the higher the reactivity

Human Metapneumovirus (hMPV)*

Virology

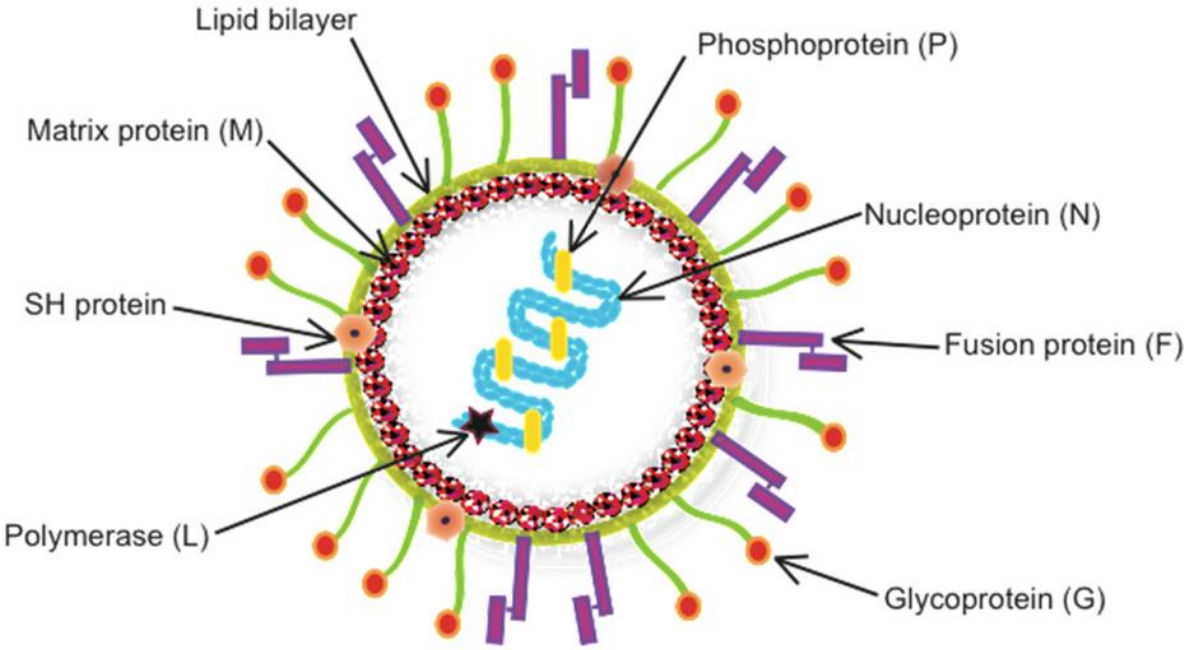
- Pneumovirus (subgenus of paramyxoviridae)
- Enveloped, ssRNA viruses Lacks the HN glycoprotein typical of the paramyxovirus group, but contains the fusion protein.
- Will not growth in cell culture. Amplification of PCR for detection (specimen: nasal swab)

Epidemiology

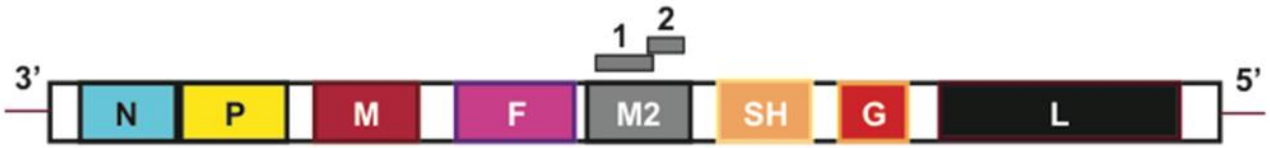
- Causes seasonal epidemics mainly in early Spring.
- Spread is via respiratory droplets
- Clinical syndromes (very similar to RSV) Bronchiolitis, Broncho-pneumonia infants < 6 months of age (95% of cases). Laryngo Tracheo bronchitis infants, young children Acute bronchitis adults, especially the elderly. Common cold syndrome re-exposure in children and adults

*First recognized in 2001

a. Model structure of hMPV



b. Proteins encoded by hMPV genome



L - Polymerase **M2-2** and **M2-1** - Matrix protein **M** - Matrix protein

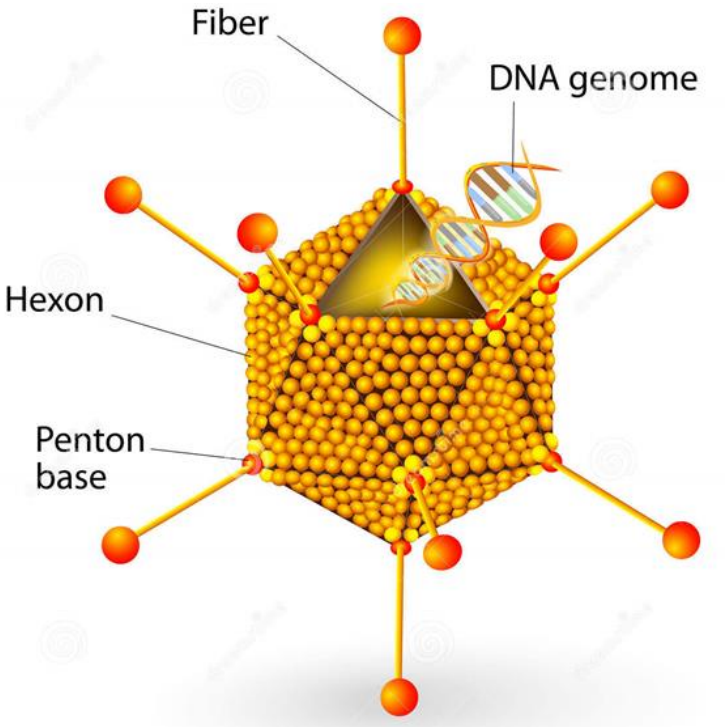
G - Glycoprotein **F** - Fusion protein **P** - Phosphoprotein

SH - Small hydrophobic protein **N**- Nucleoprotein

Virology

Adenovirus

- Family; Adenoviridae
- Unenveloped icosahedral ds DNA viruses,
- approximately 80 nm in diameter.
- There are 41 human adenoviruses which are divided into 6 sub-genera A-F



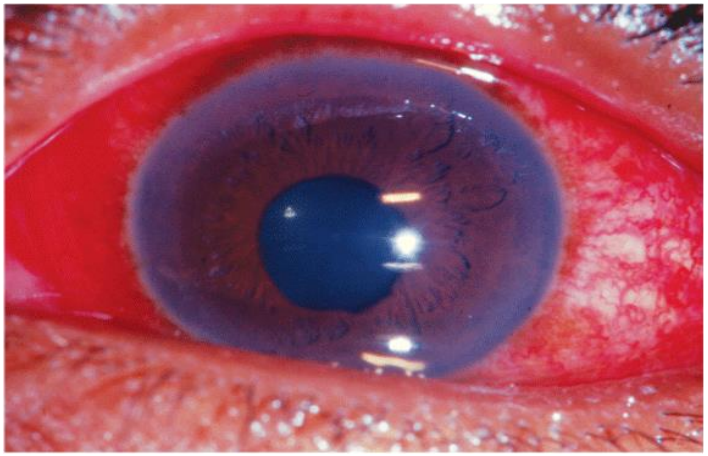
Epidemiology

- Adenovirus infections are not strongly seasonal.
- Infections occur throughout the year.
- The virus is highly resistant to inactivation and viable virus may remain on environmental surfaces.
- Nosocomial transmission of adenovirusleading to outbreaks is common in paediatric ICUs.
- Transmission is through respiratory droplets, fomites and ingestion. -

Clinical Features

- Adenoviruses infect the mucous membranes of the eye, respiratory and gastro intestinal tract, and occasionally the urinary tract.
- Local lymph nodes are often involved (enlarged and tender).
- Most infections remain localised to the body surface.
- Most infections are asymptomatic and those that do manifest clinically are usually acute and self-limiting. Some subtypes may be harboured asymptomatically for years.

Adenovirus Syndromes



Epidemic keratoconjunctivitis can be transmitted through close contact and non-sterile eye examinations.

- 1. Asymptomatic Infection
- 2. Acute pharyngitis with fever
- 3. Pharyngoconjunctivical fever
- 4. Acute follicular conjunctivitis
- 5. Epidemic kerato-conjunctivitis
- 6. Pneumonia
- 7. Epidemic acute respiratory disease
- 8. Gastro-enteritis, diarrhoea
- 9. Mesenteric adenitis
- 10. Immunocompromised host In transplant, AIDS or other immunocompromised patients, adenoviruses may cause haemorrhagic cystitis.

Classification of human adenoviruses and their associated clinical syndromes:

Sub group	Viruses	Target organ of disease
A	12, 18, 31	GIT
B	3, 7, 11, 21	Pharynx, lungs, conjunctiva, Urinary tract
C	1, 2, 5, 6	Pharynx
D	8, 9, 19	Eye (keratoconjunctivitis)
E	4	Upper respiratory tract, eye
F	40, 41	GIT

Diseases caused by Adenoviruses

Group Affected	Syndromes	Serotypes
Neonates	Fatal disseminated infection	3, 7, 21, 30
Infants	Coryza, pharyngitis	1, 2, 5 (C)
Children	Upper respiratory disease Pharyngoconjunctival fever Hemorrhagic cystitis Diarrhea Intussusception Meningoencephalitis	1, 2, 4-6 3, 7 (B) 7, 11, 21 (B) 2, 3, 5, 40, 41 (F) 1, 2, 4, 5 2, 6, 7, 12
Young adults	Acute respiratory disease and PNA	3, 4, 7
Adults	Epidemic keratoconjunctivitis	8, 19, 37 (D)
Immunocompromised patients	PNA with dissemination Liver infection Urinary Tract Infection Intestinal Infection CNS disease including encephalitis	5, 31, 34 1, 2, 5 (C) 35, 39 42-51 (D) 7, 12, 32

LABORATORY DIAGNOSIS

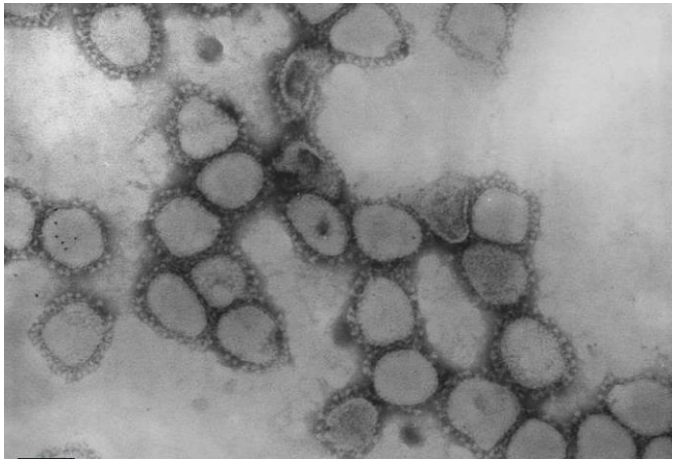
- **Virus Isolation**
  - Adenovirus may be isolated from most body fluids and secretions; eye swabs, NPA, throat swabs, urine, faeces, and CSF.
  - Human embryonic kidney cells — Hep-2 cells
  - Primary monkey kidney cells — 293 cells
  - **CPE includes rounding, clustering of cells with refractile intranuclear inclusion bodies**
- **Detection of antigen by Immunoflurescence (IF)**
- **Serology**
  - Infection of humans with any adenovirus type stimulates a rise in complement-fixing antibodies to adenovirus group antigens shared by all types. ***A four-fold or greater rise*** in these antibodies between acute phase and convalescent phase sera indicates recent infection.
  - **The fastidious (no growth on cell cultures) enteric adenoviruses can be detected by direct examination of fecal samples by ELISA or latex agglutination tests.**

In my laboratory, we diagnose Adenovirus with Enterovirus and Parceho virus together in a one sample by multiplex PCR technigue.

Rhinoviruses

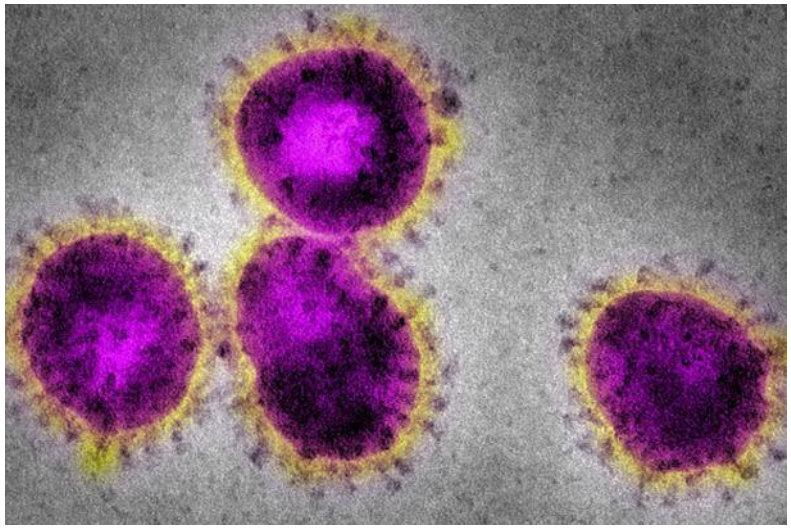
Virology

- Family; Picornaviruses
- Small, un-enveloped ssRNA viruses
- 100 antigenically distinct serotypes
- Responsible for cold syndrome



Severe acute respiratory syndrome (SARS)

- **Severe acute respiratory syndrome** (SARS) is an acute viral lower respiratory tract infection with a high mortality.
- It is a new disease of humans, caused by a novel **coronavirus**.
- The first cases occurred in November 2002 in Guangdong province (China).



Transmission:

- Respiratory droplets, fomites and stool.
- Effective infection control measures include: hand hygiene, contact precautions, eye protection, environmental cleaning and airbourne precautions (**N95 masks**, negative pressure room).

Origin of infection; Guangdong