

1 Influenza Viruses

Family: *Orthomyxoviridae*

Single-stranded, negative-sense RNA genome

Genus: *Alphainfluenzavirus*, *Betainfluenzavirus*, *Gammainfluenzavirus*, *Deltainfluenzavirus*

1.1 Shapes

Influenza viruses form either enveloped, spherical, or filamentous particles

1.2 Life Cycle

1. Entry: HA glycoprotein
2. Gene segments imported to nucleus
3. mRNA are made
4. mRNA is exported from the nucleus and is translated
5. genome segments are packaged and virus buds from the cell

1.3 Characteristics of Orthomyxoviruses

1. Negative-sense RNA genome
2. Segmented genome
3. Genome: 13.5 kb in size
 - Encodes 11 proteins
4. HA (Hemagglutinin) and NA (Neuraminidase) surface proteins: targets of antibodies
5. Hosts: Aquatic birds, humans, pigs, horses, seals, cows, etc.
6. Transmission: Respiratory (mammals), Fecal-oral (birds)

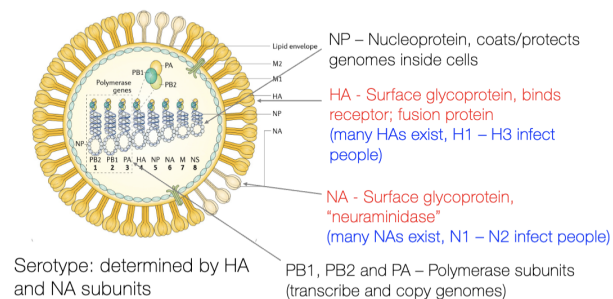


Figure 1: Orthomyxoviruses

Fish may have been ancient hosts

→ Fish influenza viruses are closely related to all influenzas that infect mammals

1.4 Types of Influenza

4 general types of Influenza Viruses

1. A and B viruses cause the flu season

A viruses are the only influenza viruses known to cause flu pandemics

2. C viruses cause mild illness and are not thought to cause human flu epidemics
3. D viruses primarily affect cattle and are not known to infect or cause illness in people

1.5 Influenza A

Most important influenza virus for human health

Can cause local epidemics or pandemics with significant infection rates

Wide host range and epidemiology involves close contact of humans, farm animals, and birds

Zoonotic spillover plays an important role of influenza virus biology

1.6 Neuraminidase (NA)

Needed for release of virions from the infected cell

Virions have NA on their surface which allows for cleavage of sialic acid on the cell surface

Target for the major antiviral agents against influenza

1.6.1 Sialic Acid

Sugars attached to proteins (glycoproteins) and lipids (glycolipids)

Glycocalyx: dense, gel-like meshwork surrounding the cell (physical barrier)

Sialic acid: sugar component of the glycocalyx that influenza uses to bind to and enter cells

1.7 Infection

Influenza infects the respiratory epithelium in the lungs

Upper respiratory tract infection: less severe

Lower respiratory tract infection: more severe

Virus replication peaks ~48 hours after infection and declines slowly thereafter

→ Little shedding of virus after days 6 to 8

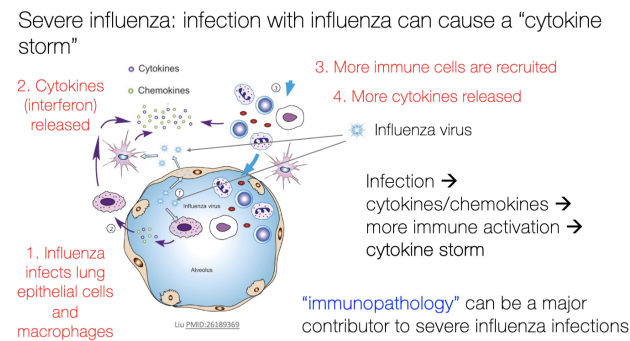


Figure 2: Cytokine Storm: Immune system causes more pathology than virus itself

1.8 Mortality

Influenza has over 1 billion cases of seasonal flu annually

3-5 million severe cases

Half a million deaths globally

10s of thousands die each year from influenza in the US

Influenza mortality in the US has declined

Likely due to behavior, hygiene, and vaccination

1.9 Seasonality

More Flu A than Flu B

Lowest rates of infection in summer, rises through fall and winter (like RSV)

Dependent on temperature (northern and summer hemisphere are offset)

Influenza is less seasonal near the equator

→ Viruses at the Equator seed seasonal epidemics in N and S hemisphere

1.10 Reassortment

Influenza genes are broken into 8 segments

If 2 different influenza viruses infect the same cell, new viruses can be made of gene segments from both viruses

→ Segmentation of the genome allows for reassortment

1.10.1 Reassorted Viruses Can Cause Major Pandemics

Ex: The 1918 flu looked different than influenza A viruses that were circulating in the population before

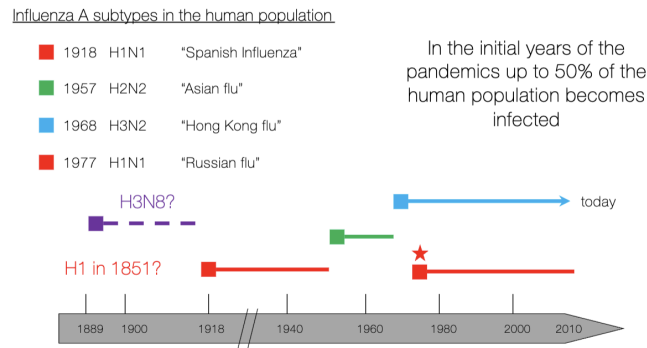


Figure 3: Historic Influenza

2 Zoonoses

The reservoir of influenza A diversity resides in aquatic birds

All subtypes of HA and NA are found in waterfowl / bats

→ 16 subtypes of HA; 9 subtypes of NA

Only H1, H2, H3, N1, N2 have become endemic in humans

2.1 Transmission Differences

Influenza grows in the intestinal tract of aquatic birds and causes little to no disease

Influenza binds to different types of sialic acid, determining what cells can be infected

Types of sialic acid are determined by mutations in HA (receptor binding)

2.2 Avian Influenza

Avian HA uses a slightly different sialic acid compared to human-infecting influenza HAs

Sialic acid used by birds is limited to the lower airways in humans

→ Leads to lower transmission efficiency but higher virulence

'Avian Flu' infections typically see higher viral loads and increased levels of chemokines / cytokines (cytokine storm) produced by bronchial epithelial cells and alveolar macrophages

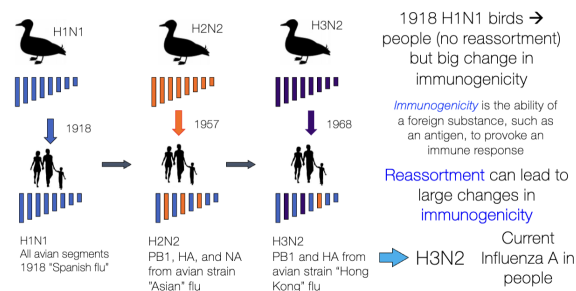


Figure 4: Avian influenza segments transferred to humans

2.3 2009 H1N1 'Swine Flu' Pandemic

Unusual cluster of illnesses very late in the flu season (March-April)

Spread world-wide by fall of 2009

Vaccine came late but severity was not super high

Came about as a hybrid from human, avian, and swine viruses

Unusual due to lack of morbidity in persons >65 years old

Cross-reactive immunity: Some antigenic similarity with much older strains

~ $\frac{1}{3}$ had neutralizing antibodies

2009 H1N1 still circulates as a seasonal influenza

3 Where Might The Next Pandemic Influenza Come From?

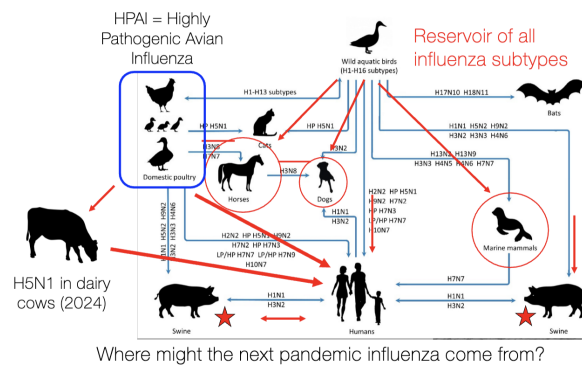


Figure 5: Influenza Reservoirs

New influenza serotype (H7N9) in China (2013-2017) due to direct contact with poultry

1. Closing of poultry market
2. High morbidity and mortality
3. Some human-human transmission but primarily direct contact with poultry
4. Complex reassortment with segments from wild birds, domestic waterfowl, and chickens
5. Controlled by culling birds and immunizing chickens
6. May have been a pandemic averted

H5N1 Avian influenza (Avian segments only, without reassortment)

1. VERY virulent in domestic poultry
Highly-Pathogenic Avian Influenza (HPAI)
2. Dramatic and unpredictable spread among wild and domestic birds
3. Can, but does not always, have exceptionally high mortality rate
4. None / limited human-to-human spread (so far)

Significant increases in H5 infections since 2019 in poultry and wild birds

H5N1 is a panzootic virus: Widely distributed infectious disease of animals

HPAI has recently become widespread in 25 wild mammalian species

Most recently dairy cows (with mild symptoms)

Reassortment or mutations are cause for worry

→ Seasonal flu vaccines are given to workers in close contact with dairy cows