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)

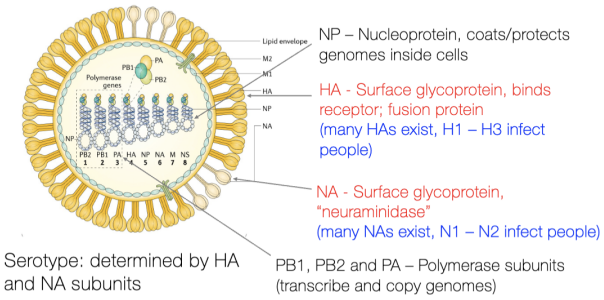

Figure 1: Orthomyxoviruses

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 attatched 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

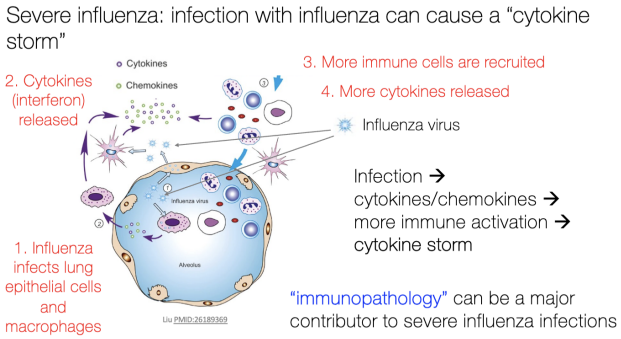

Figure 2: Cytokine Storm: Immune system causes more pathology than virus itself

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

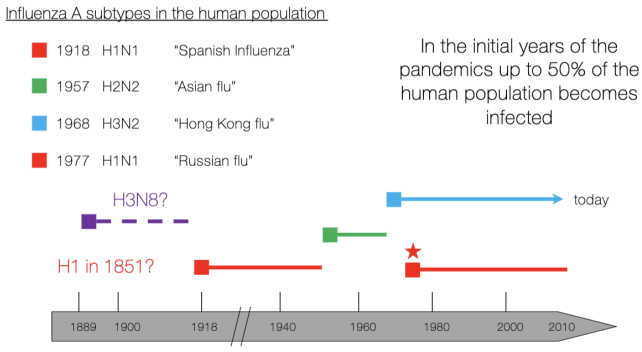

Figure 3: Historic Influenza

2 1918 'Spanish Flu'

First case was in Kansas, spread in US troops

How do we know?

1. Influenza-infected tissues were collected and stored in 'fixative'
2. Permafrost can recover viral sequences
3. Influenza RNA could be sequenced from stored samples

1918 segments are closely-related to avian viral sequences

2.1 Pandemic

First Kansas Flu cases in January of 'unusual severity'

→ Big wave of severe influenza in late fall 1918 (195,000 influenza deaths in the US during October)

2.1.1 Scale

20-40 million influenza deaths world-wide during 1918-19

Indigenous peoples (Alaska) were hit particularly hard, losing most of their adult population

Large decreases in life expectancy (worst in younger age groups)

An H1 virus circulated in 1851 leading to cross-protective immunity in seniors

Unusually high death rate among adults

An H3 virus circulated in late-1800s, leading to cross-reactive immunity in adults

3 Influenza Surface Proteins

HA is important in viral evolution including shifts, drift, and for vaccination

HA mediates receptor binding and is the major target for antibody recognition

→ Viral mutation leads to antibody / immune escape

Orthomyxoviruses have a high rate of 'antigenic evolution'

Good at mutating to escape immune responses, leading to necessity for annual flu vaccine

Influenza HA is 'rapidly evolving' (almost all mutations happen in HA and NA proteins)

Accelerated evolution due to a constant need for innovation (Red Queen Hypothesis)

3.1 Antigenic Drift and Shift

Drift:

1. Point mutations in HA and NA in existing human variants
2. Annual epidemics
3. Some cross-protection
4. Selection for escape from neutralizing antibodies

Shift:

1. Reassortment of new NA or NA segments from other strains into humans
2. Global pandemic
3. Little cross-protection
4. Up to 30% of the human population becomes infected

3.1.1 Antigenic Drift

Mutations in the sequence accumulate over time (ladder-like phylogenies)

Seasonal drift is why we need a new influenza vaccine each year

3.2 Seasonal Influenza Vaccine

1. Both inactivated and live attenuated vaccine
2. Given in October / November (before seasonal influenza peak)
3. A good flu vaccine has around 60% effectiveness
4. Flu vaccines can reduce severity even if you do get sick
5. Trivalent vaccine (H1N1, H3N2, Influenza B)

    Used to be quadrivalent but one influenza B strain is no longer circulating

Flu vaccine historically made in eggs

Disadvantages:

1. Need many eggs
2. Not all flu strains grow well in eggs

Cell-culture based flu vaccines / mRNA vaccines

Advantages:

1. Doesn't require eggs
2. Faster

Main influenza vaccine strains must be chosen 6+ months ahead due to vaccine manufacturing timelines

Influenza mortality usually highest in the very young and very old

High-dose vaccines are recommended for older adults because of increased effectiveness

4 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

4.1 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)

4.2 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 huamns

→ 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

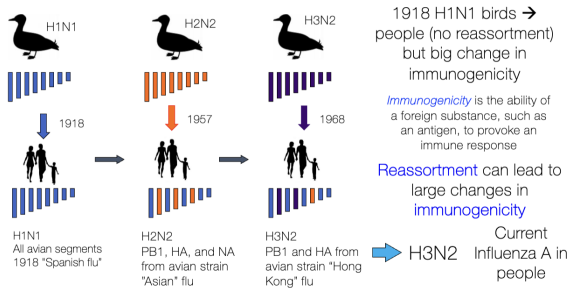

Figure 4: Avian influenza segments transferred to humans

4.3 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

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

2009 H1N1 still circulates as a seasonal influenza

5 Where Might The Next Pandemic Influenza Come From?

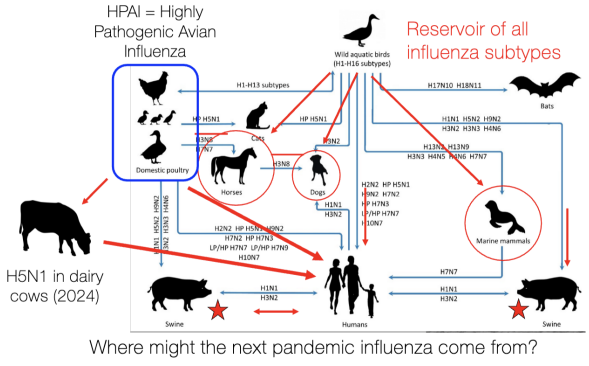

Figure 5: Influenza Reservoirs

5.1 H7N9

New influenza serotype 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)

5.2 H5N1

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 (Preventing reassortment)

→ H5N1 vaccine currently under development (only 10m doses)