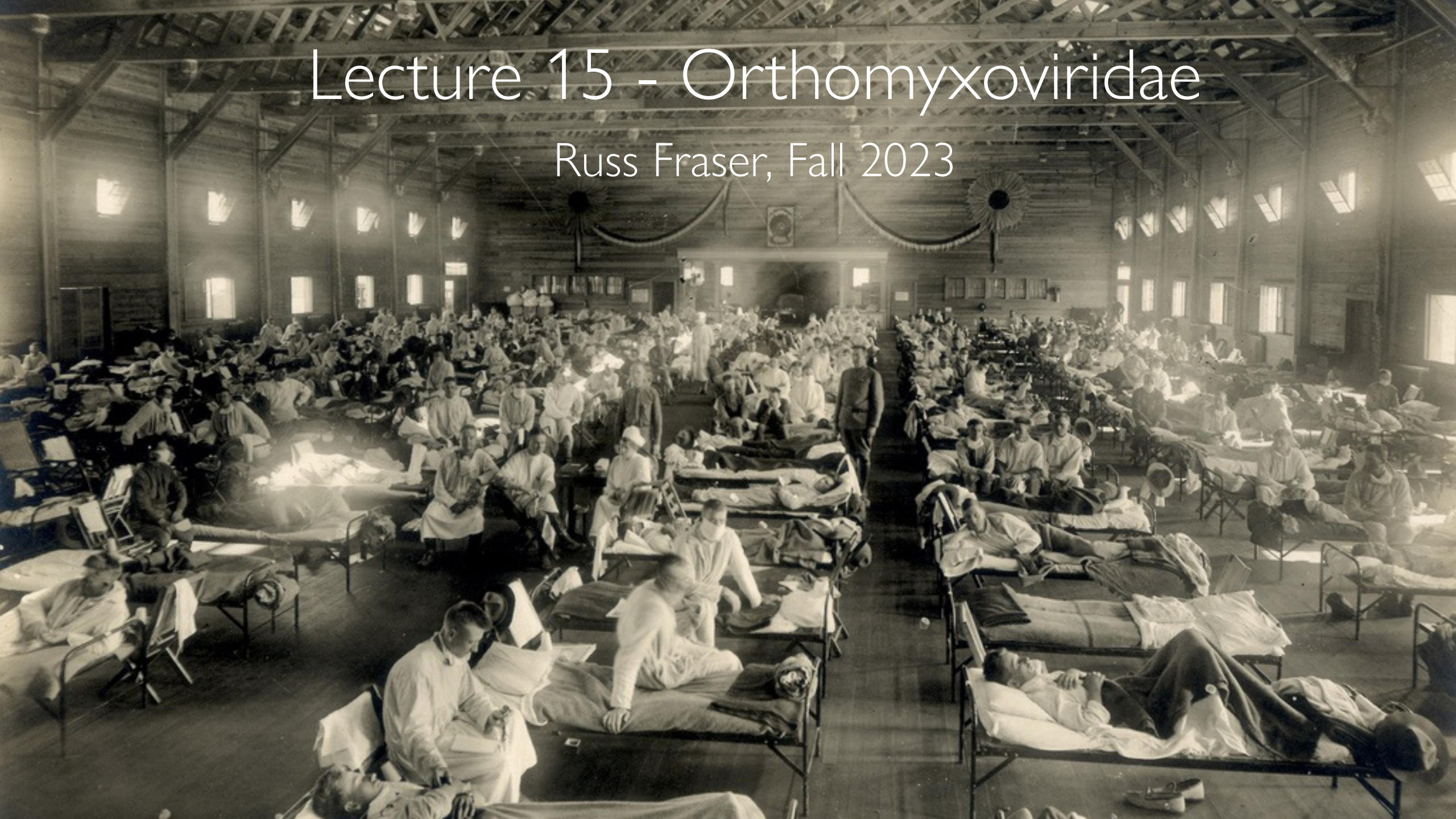
Lecture 15 - Orthomyxoviridae

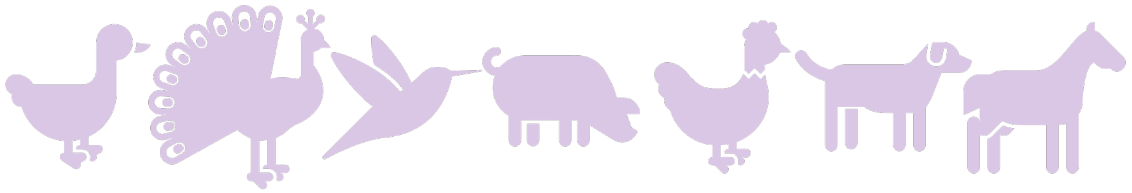
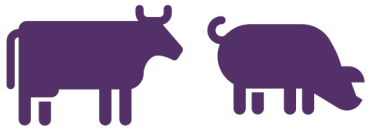
Russ Fraser, Fall 2023



Orthomyxoviridae

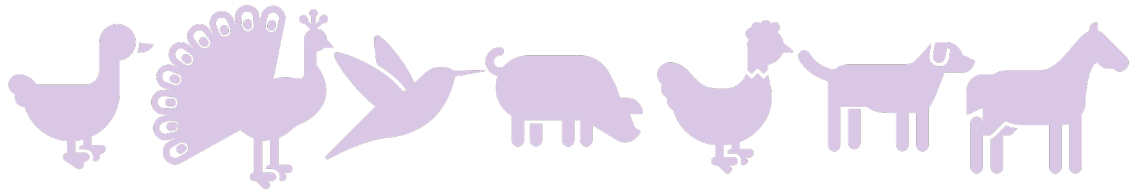
Size	80 - 120 nm
Morphology	Enveloped
	Several different shapes (spherical, filamentous)
Genome	• Segmented • ssRNA
Site of Replication	• Nucleus (!)
Properties	• Doesn't survive well in the environment. • Antigenic drift and shift are important contributors to pathogenicity and immune evasion.

Orthomyxoviridae

- Influenza A 
- Influenza B 
- Influenza C 
- Influenza D 

Orthomyxoviridae

- Influenza A



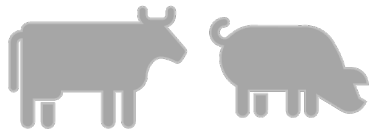
- Influenza B



- Influenza C



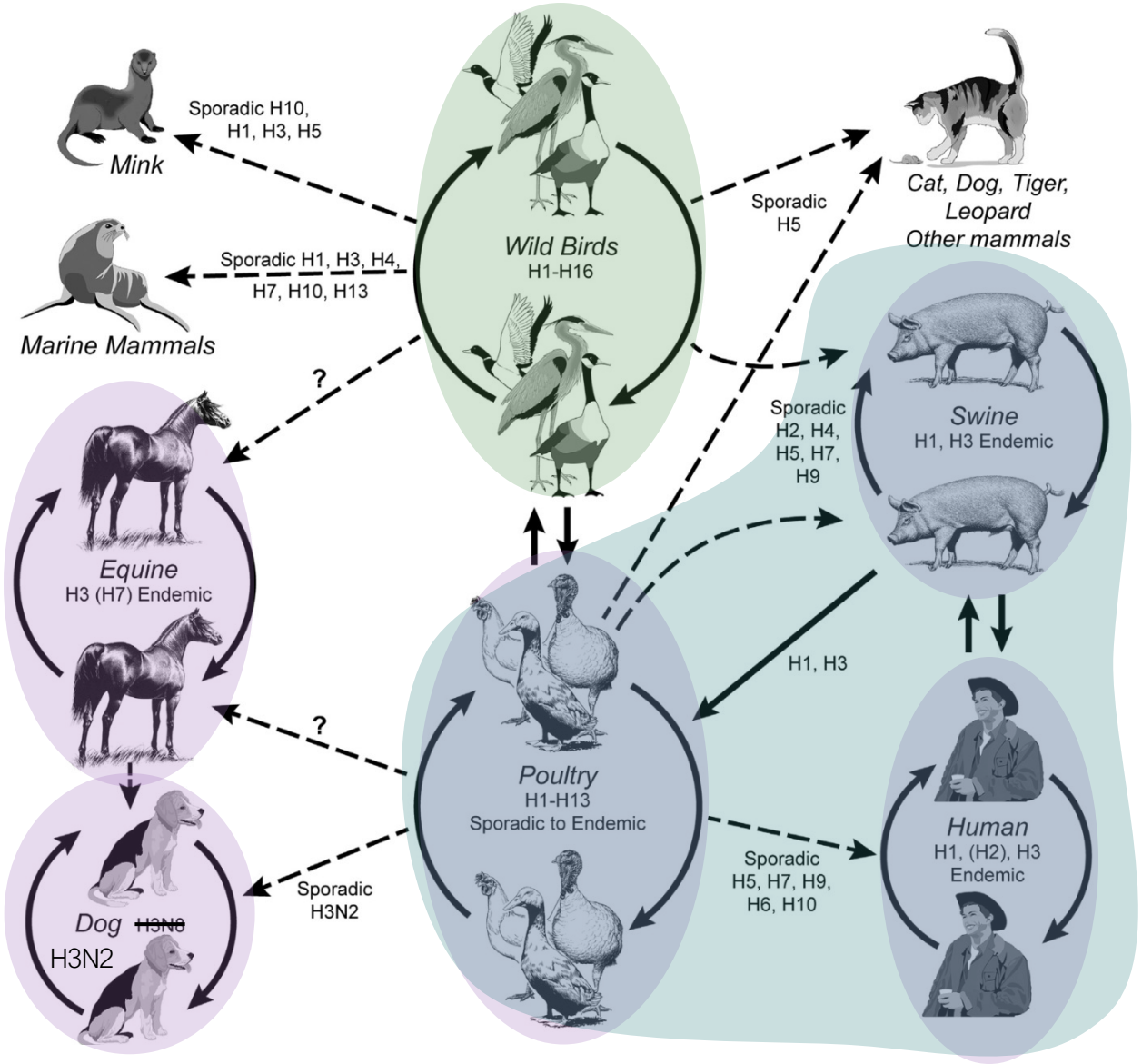
- Influenza D



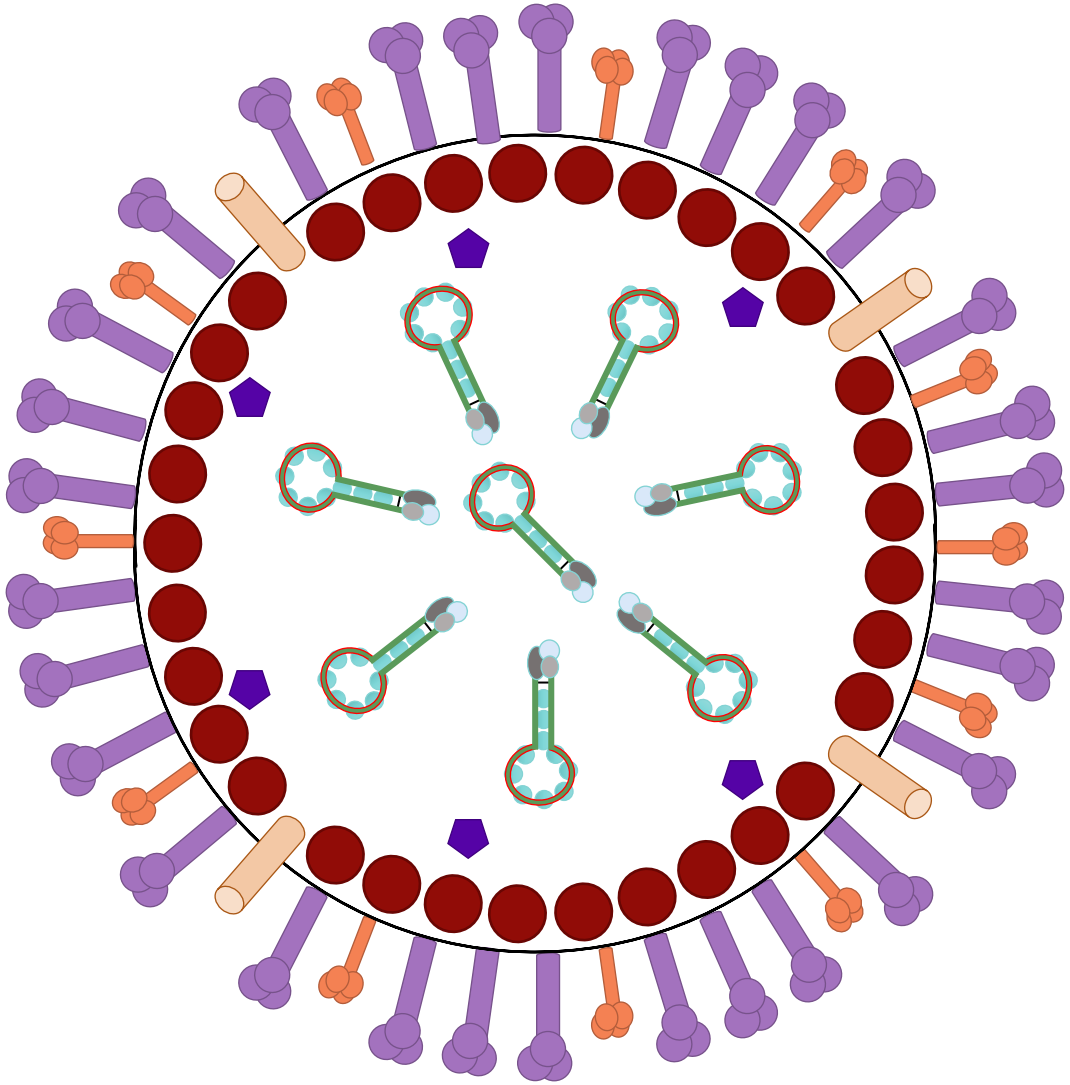
Influenza A virus: nomenclature

- WHO has a specific system for naming influenza viruses:
    - Genus/host species/geographic origin/month/year/(H and N subtype)
    - E.g. A/equine/Miami/1/63 (H3N8)

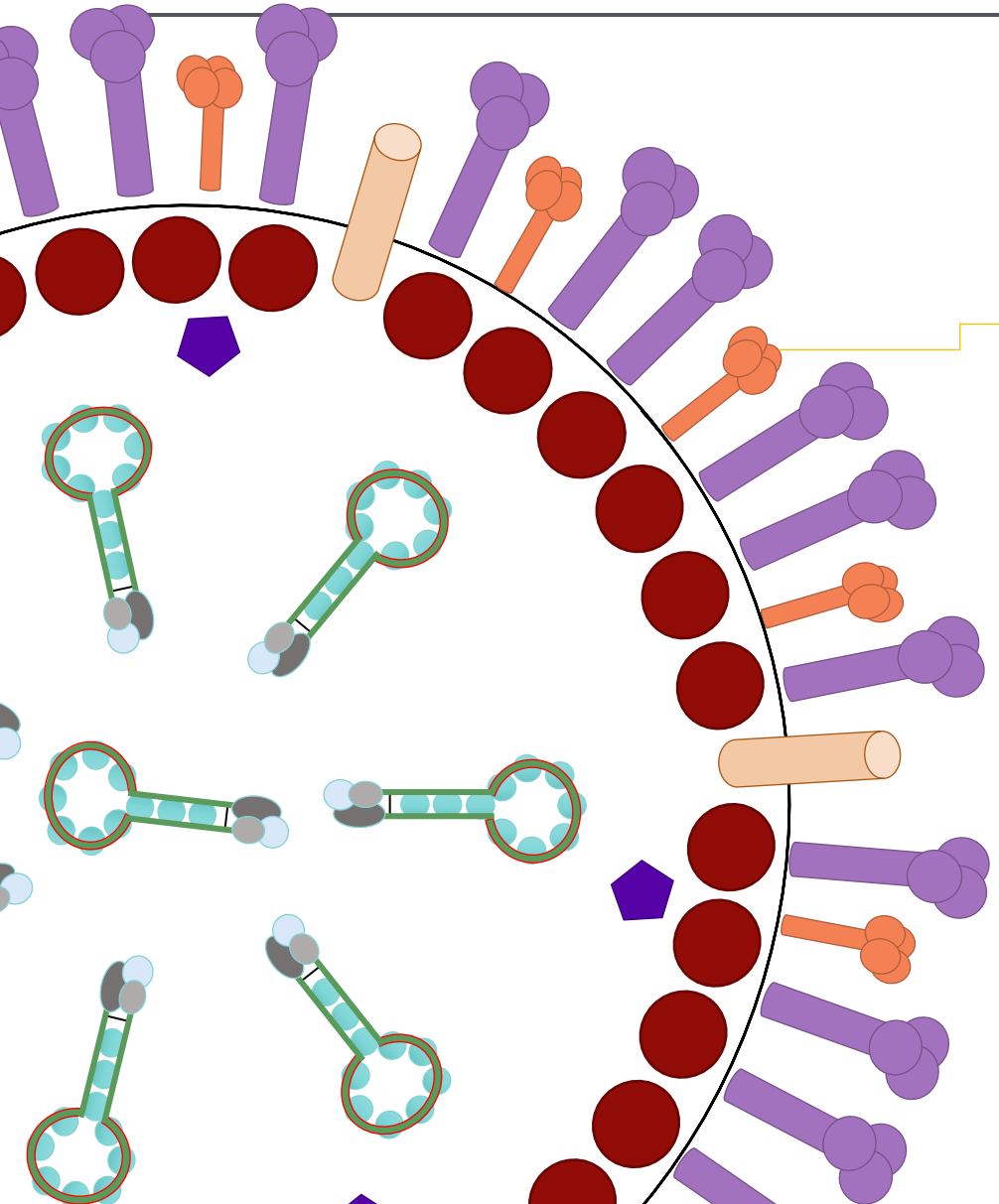
Influenza A virus: epidemiology



Influenza A virus: general



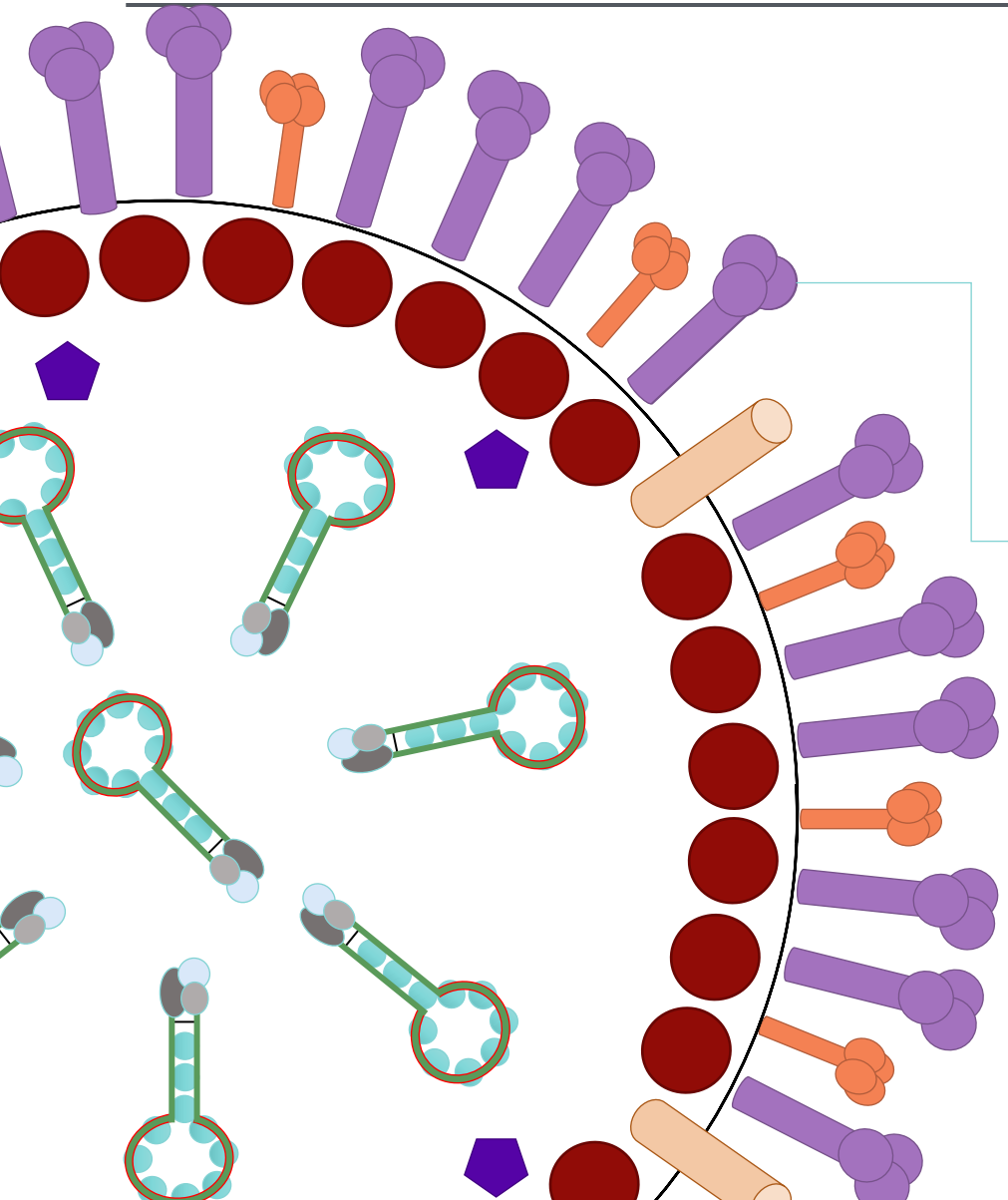
Influenza A virus: general



Neuramidase:

- Responsible for releasing budding virions from the host cell.
- 9 subtypes exist.
  - N1, N2, …, N9

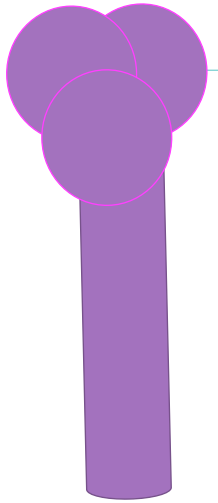
Influenza A virus: general



Hemagglutinin:

- 16 subtypes exist (plus another 2 in bats)
  - H1, H2, …, H16
- Binds receptors on host cell surface
  - This has an important role in determining which species IAV can infect
- Requires cleavage *before* the virion is infectious
  - $HA_0 \rightarrow HA_1 + HA_2$
  - This has an important role in the pathogenicity of the virus

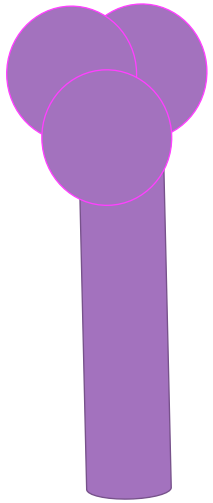
Influenza A virus: general

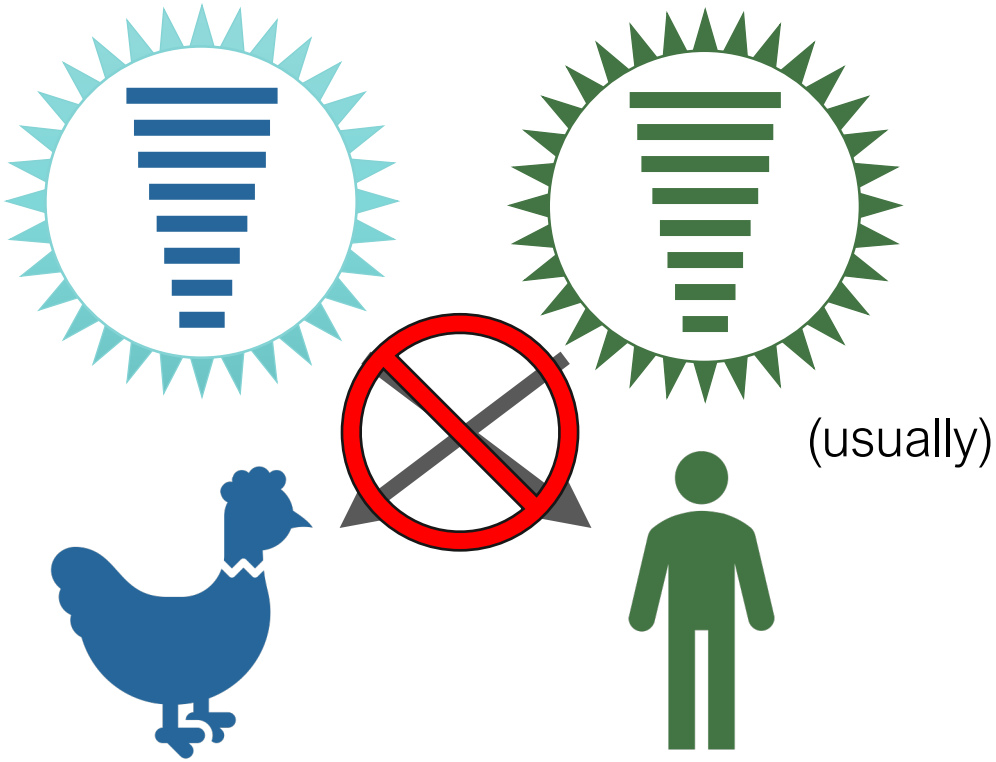


Hemagglutinin:

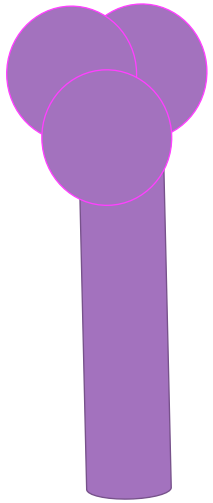
- Binds sialic acid on the surface of host cells
- The specific linkage of sialic acid to the underlying galactose is critical
  - Birds generally have α2-3 linkage
  - Mammals generally have α2-6 linkage
  - **Pigs have both – "mixing vessel"**

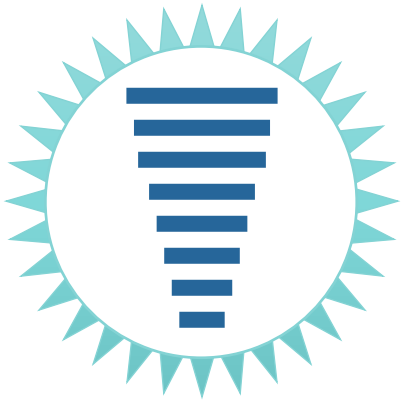
Influenza A virus: general

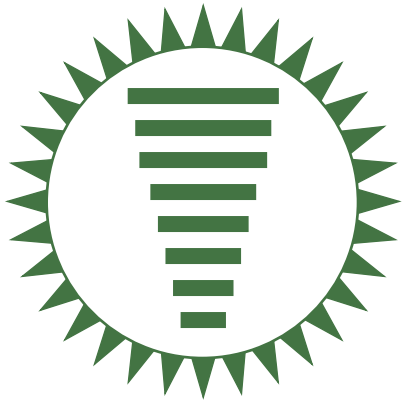


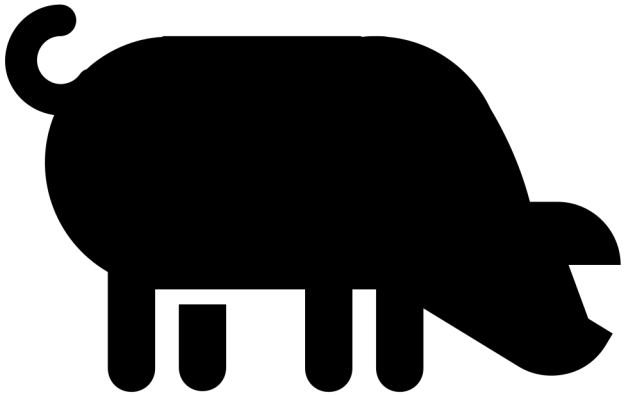


Influenza A virus: general

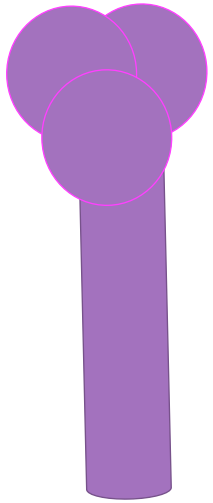


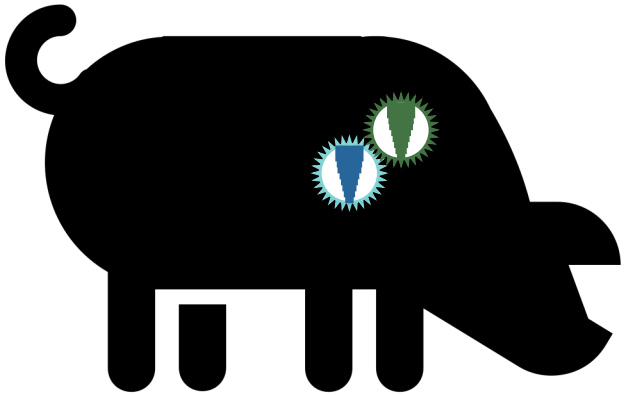






Influenza A virus: general





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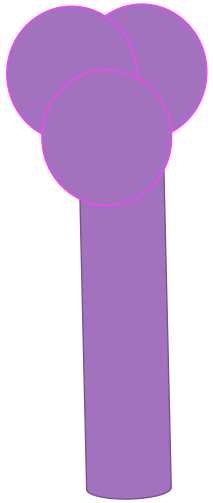
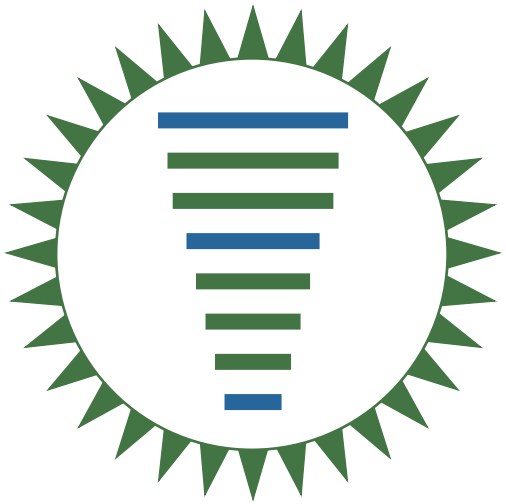
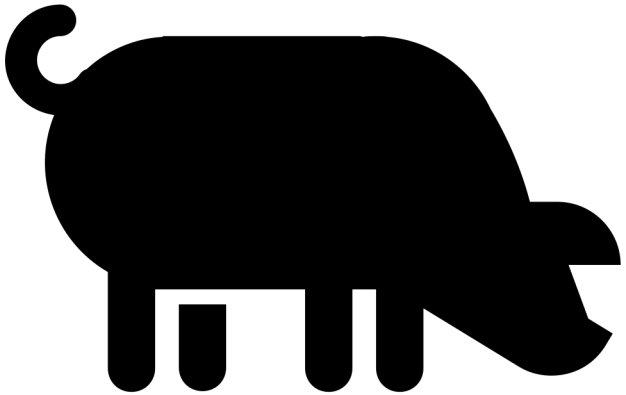
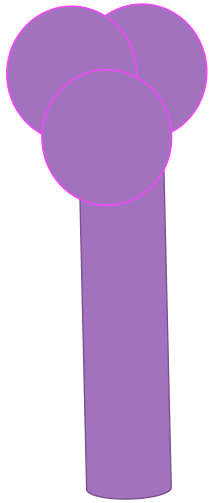
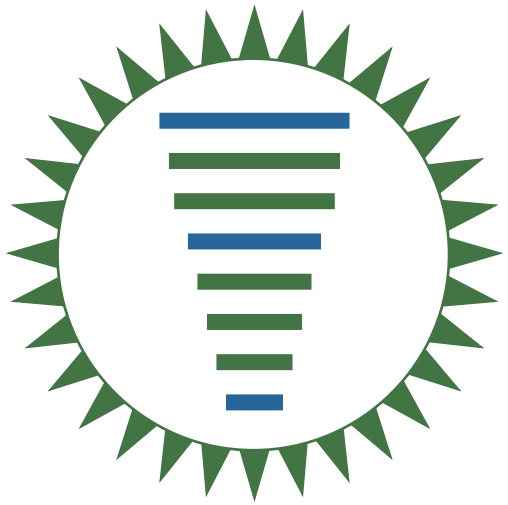






Influenza A virus: general





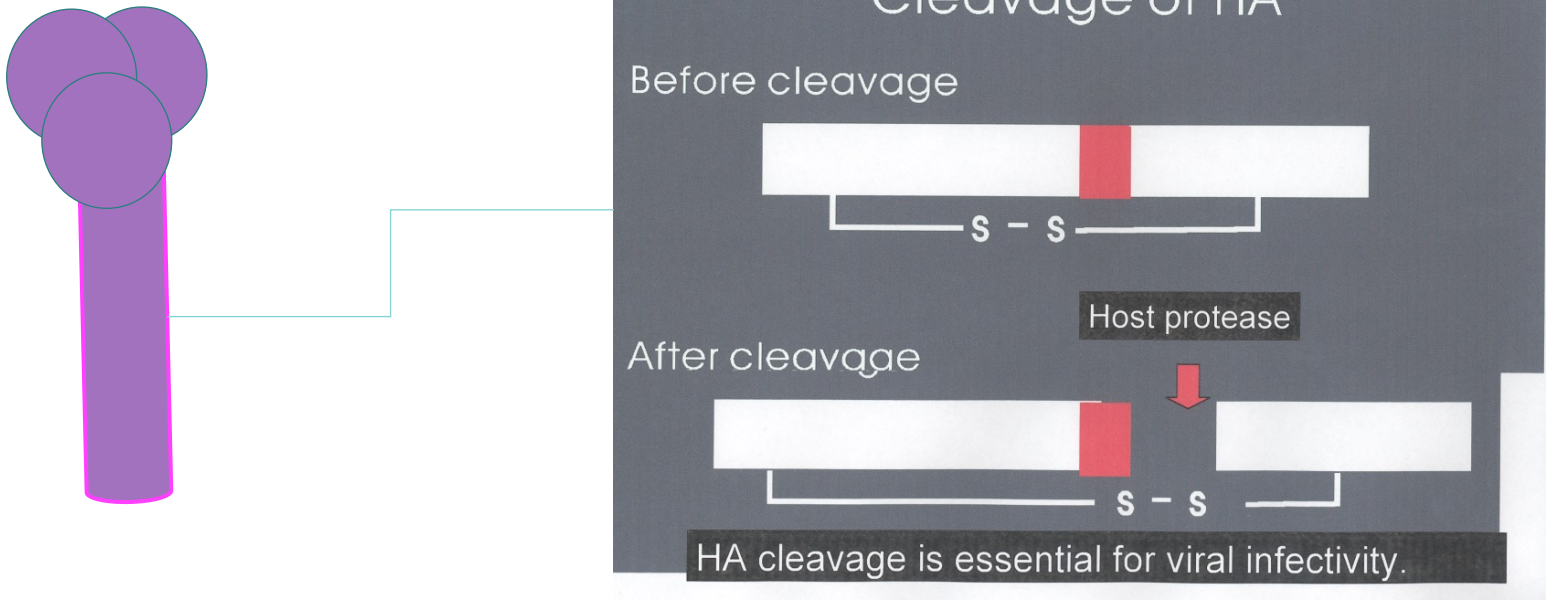
- The reassortment of segments from different strains of influenza results in viruses with novel pathogenicity and antigenicity.
- This process is also known as antigenic shift.
- ~256 new combinations are possible (but not all are viable).

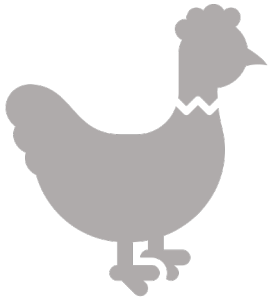
Antigenic drift

- Point mutations that accumulate slowly over time → changes in antigenicity (and potentially pathogenicity)

- Antigenic drift and shift are two methods by which influenza A viruses are able to escape the immune system and maintain a wide range of circulating strains.

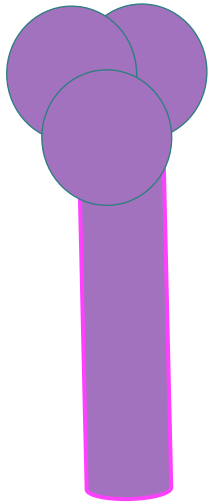
Influenza A virus: general

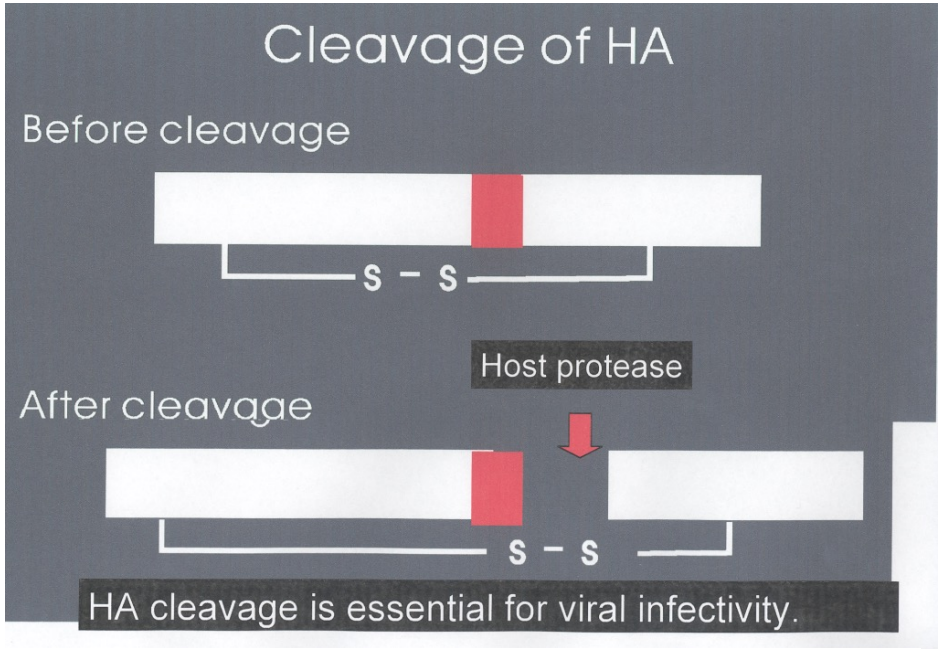


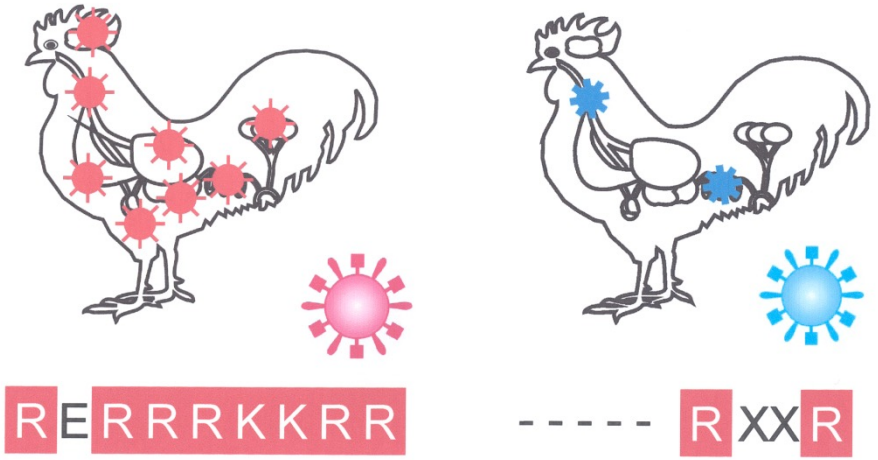


- Host enzyme cleaves the hemagglutinin protein.
- The composition of the cleavage site is what determines whether a virus is “high” or “low” pathogenicity:
  - Low pathogenicity viruses are cleaved only by enzymes within the respiratory or digestive tract
  - High pathogenicity viruses are cleaved by an enzyme (furins) within many cell types

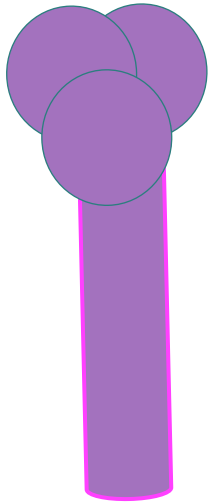
Influenza A virus: general

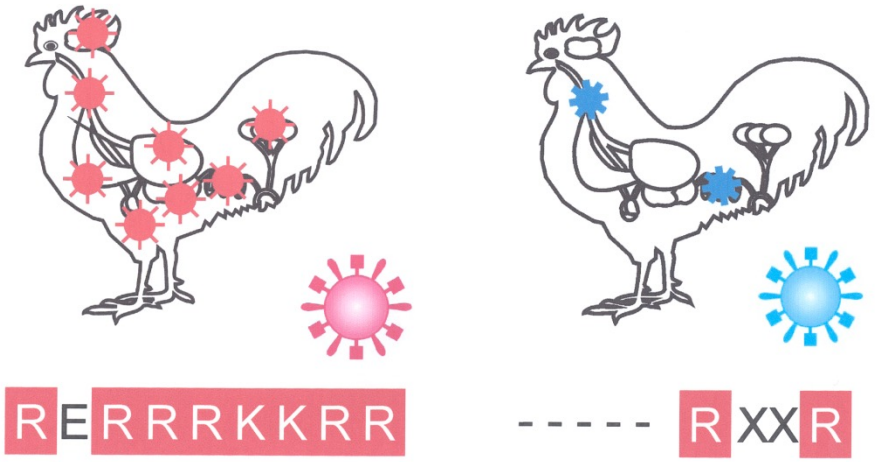






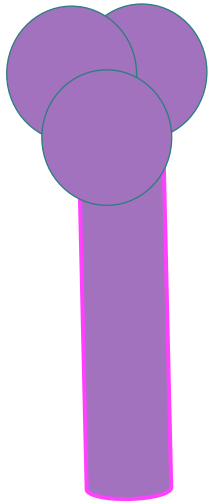
Influenza A virus: general

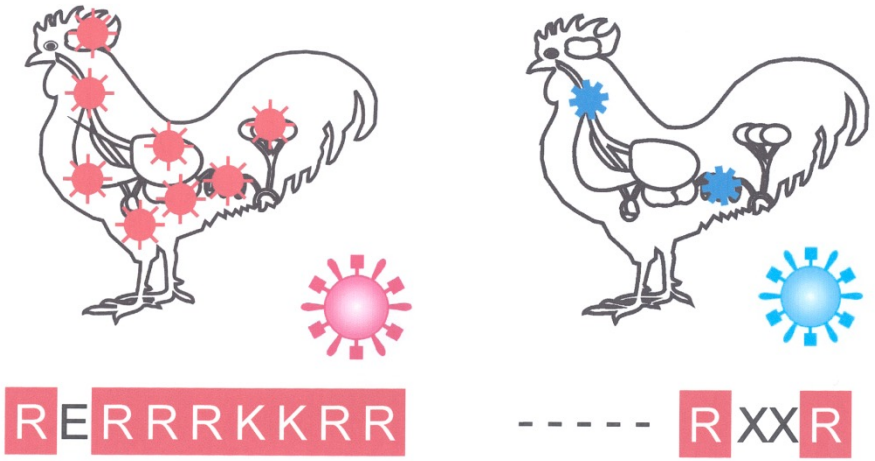




- H5 and H7 viruses more commonly acquire a polybasic cleavage site
- In general, they arise *de novo* in circulating low path strains

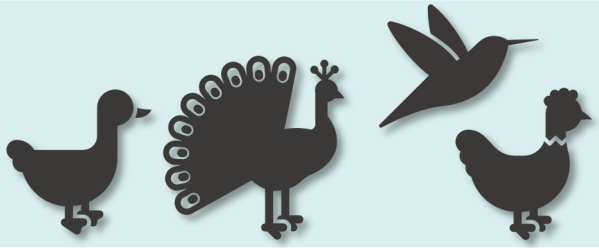
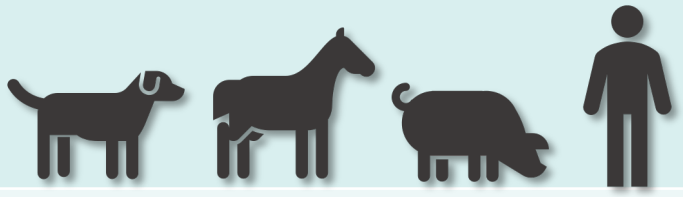
Influenza A virus: general





Any high pathogenicity strain and **all** H5 and H7 strains are **reportable**
"Notifiable **avian** influenza"

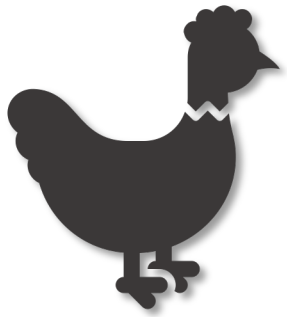
Influenza A virus: transmission & target organs

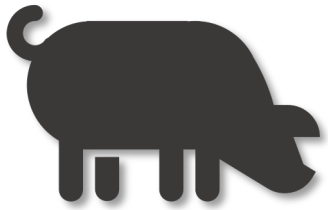
	

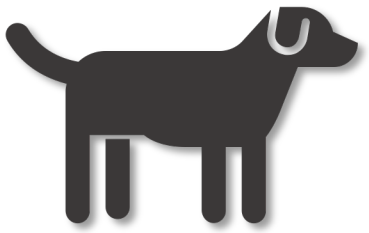
• Feco-oral (water is easily contaminated)
  • Maintains reservoir circulation
  • Factors into outbreaks
• Respiratory secretions (aerosol)
  • Mostly an issue within outbreaks
	• Aerosolized droplets (cough, sneeze)

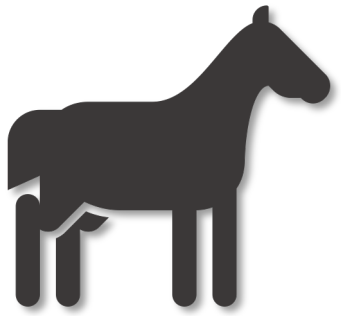
• Respiratory <u>and</u> gastrointestinal tracts • In poultry with HPAI, a wide range of organ systems	• Respiratory system • Systemic involvement with HPAI H5N1

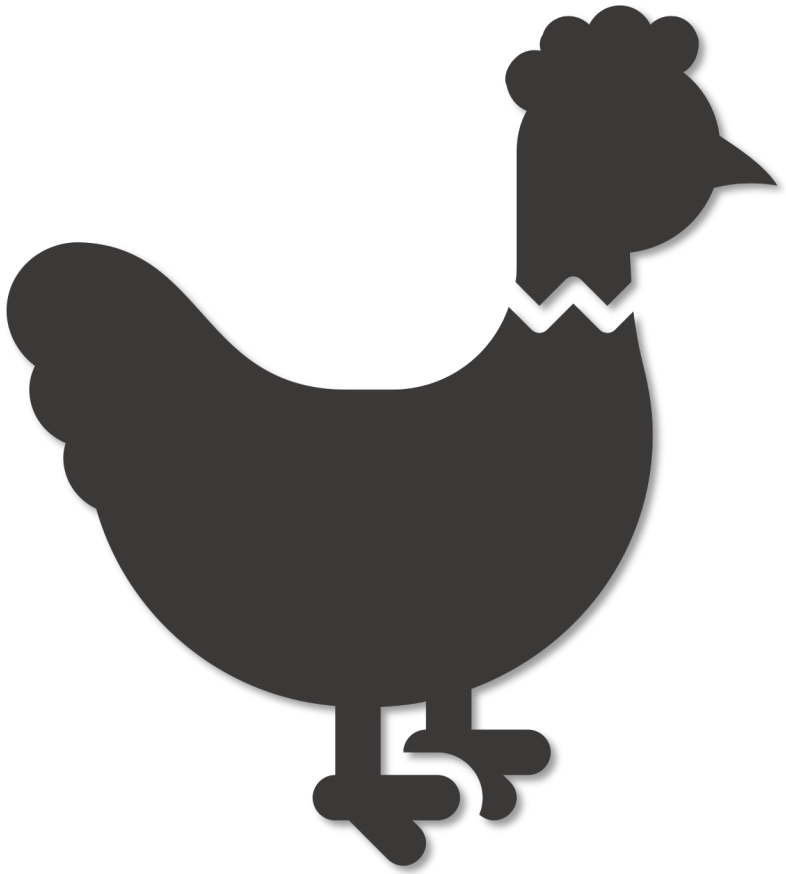
Influenza A virus: specific species









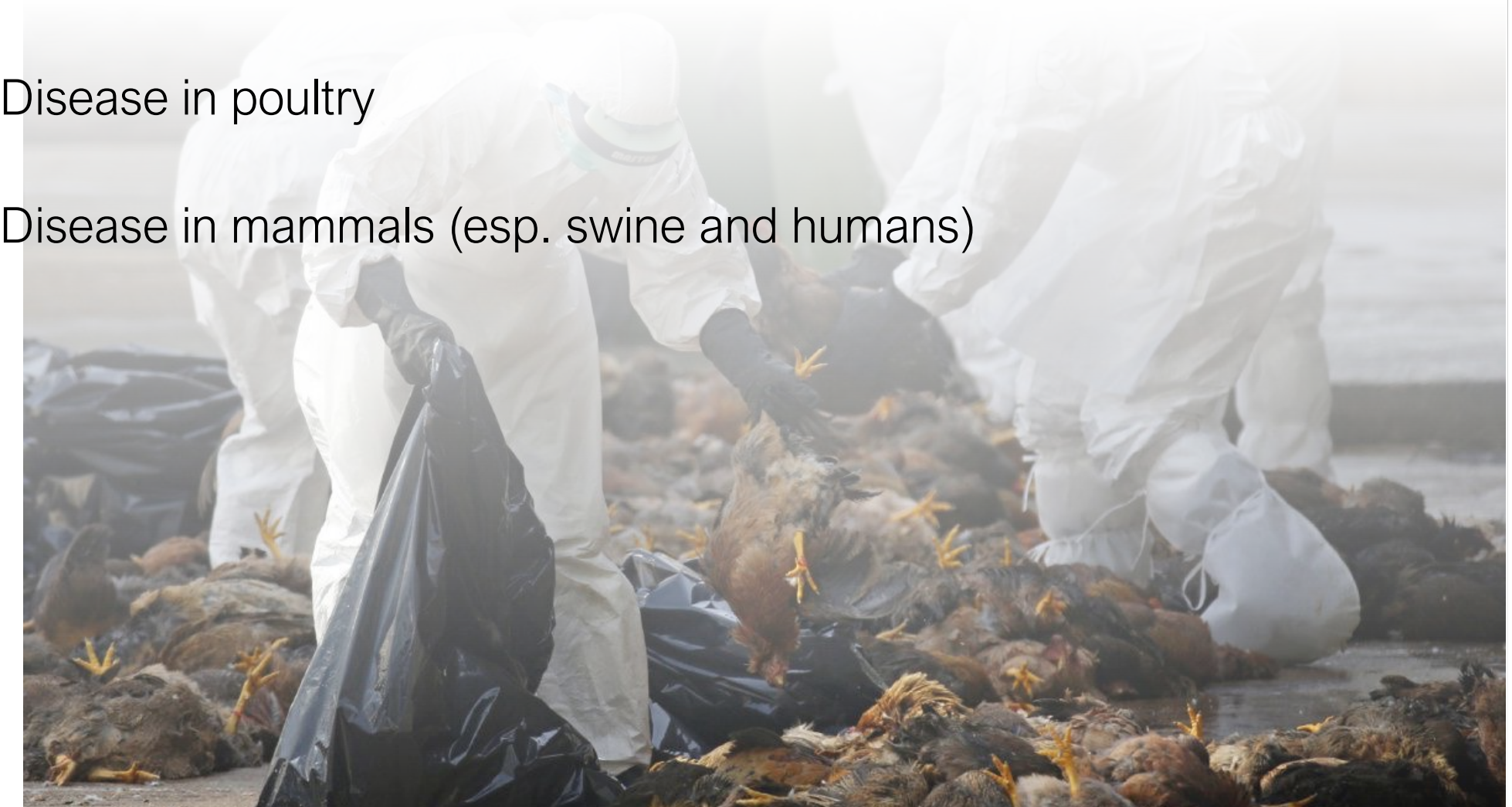


Avian influenza

"bird flu"

Avian influenza

- Two major concerns with AI:
  - Disease in poultry
  - Disease in mammals (esp. swine and humans)



Avian influenza: disease in poultry

- Chickens are usually infected by local or migrating waterfowl
- Once within the flock, spread is both feco-oral and respiratory
- Both LPAI and HPAI cause significant problems.
  - LPAI – asymptomatic → mild illness, but production may ↓
  - HPAI – ↑ ↑ mortality (90-100%), systemic illness

Avian influenza: disease in poultry

LPAI

Replication in GI and respiratory tract

↓

Damage mostly to upper respiratory tract

↓

Sinusitis, rhinitis, congestion, tracheitis

Pneumonia is rare

HPAI

Replication in GI and respiratory tract

↓

Systemic viremia

↓

↑ ↑ ↑ cytokines

↓

Vasculitis, thrombosis, lymphoid necrosis

↓

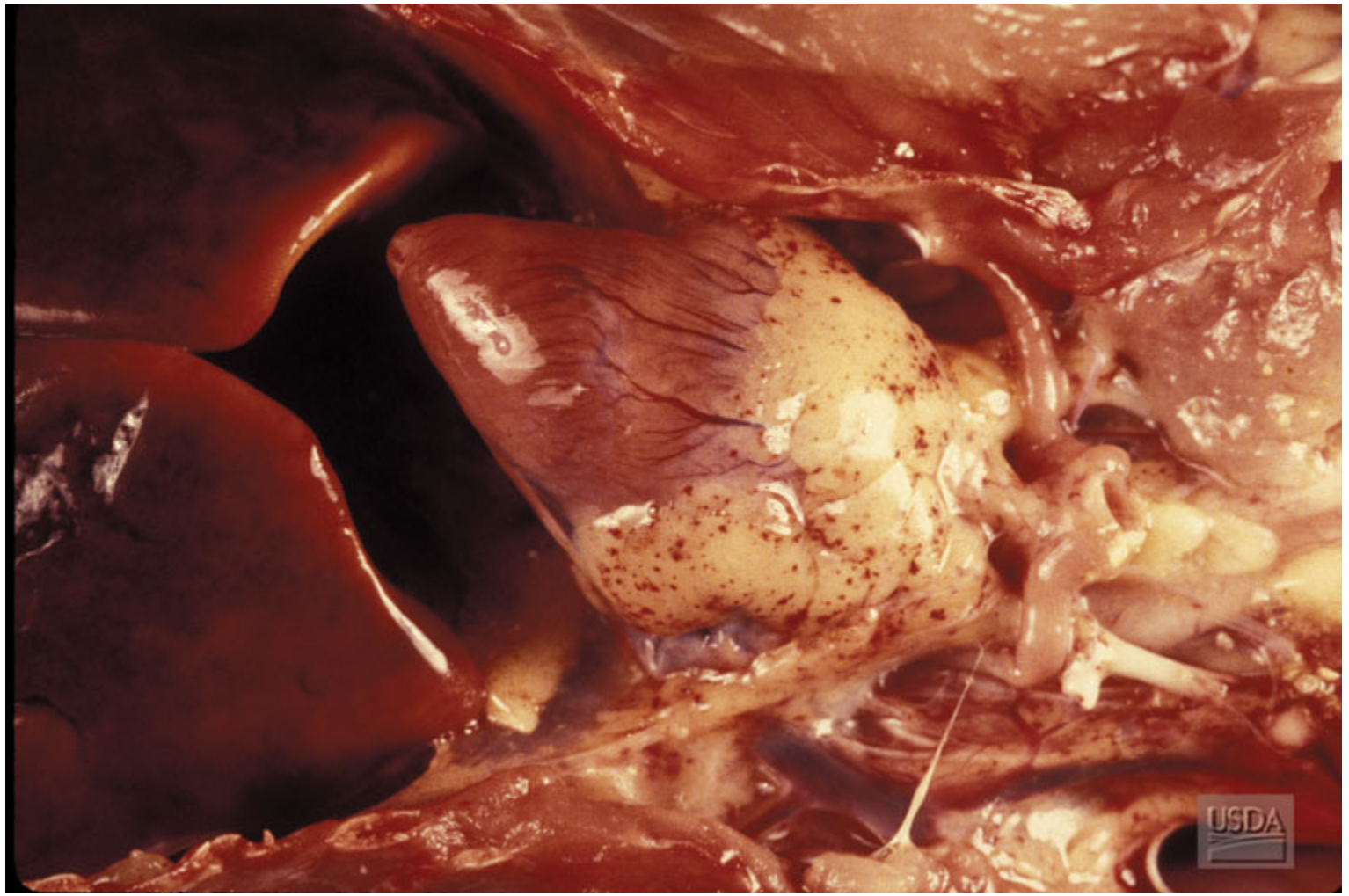
Multiorgan petechia, hemorrhage, necrosis (heart, pancreas, brain, muscle, skin, respiratory tract, GI), death

Avian influenza: disease in poultry



http://www.cfsph.iastate.edu/DiseaseInfo/disease-images.php?name=avian-influenza&lang=en

Avian influenza: disease in poultry



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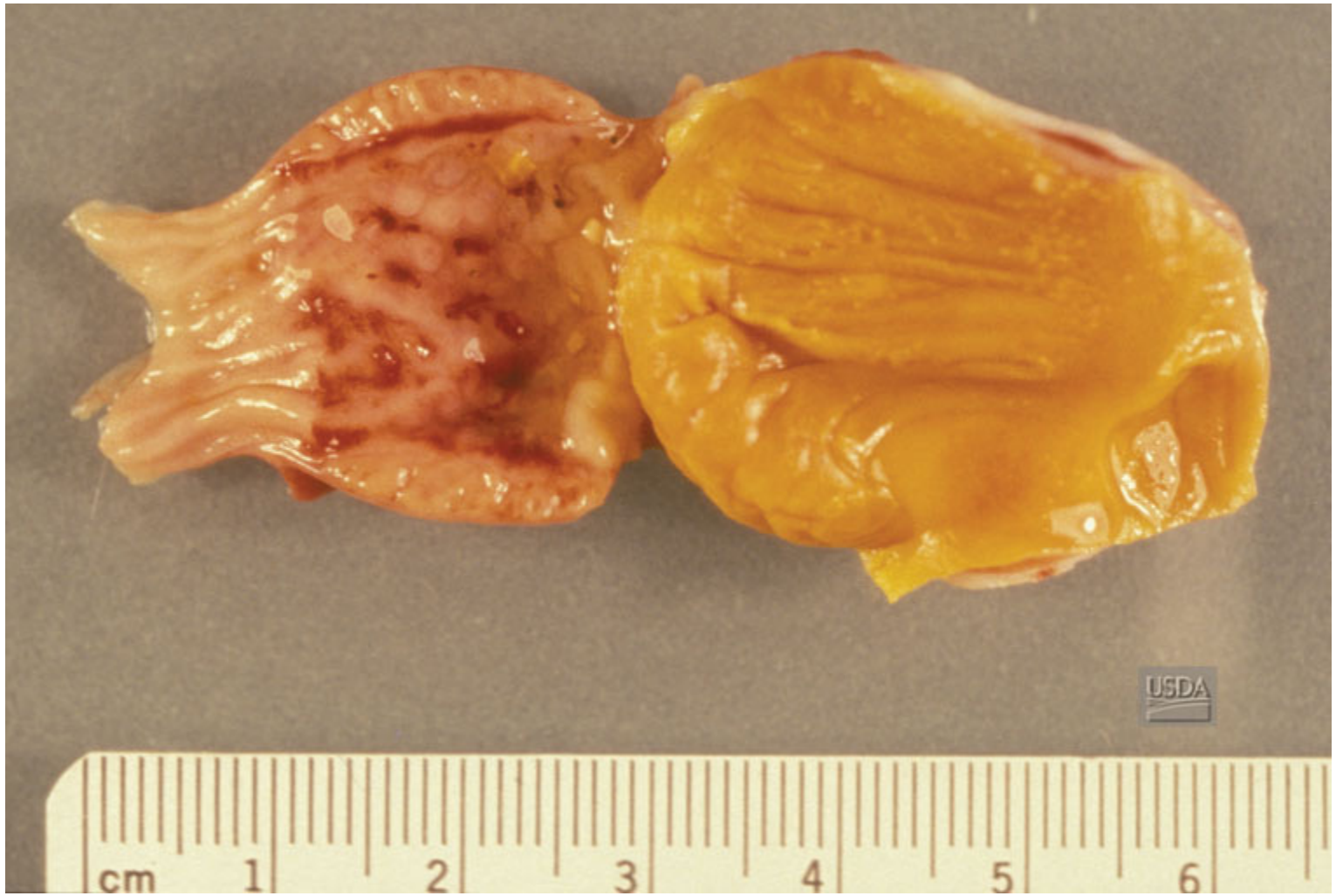
Avian influenza: disease in poultry



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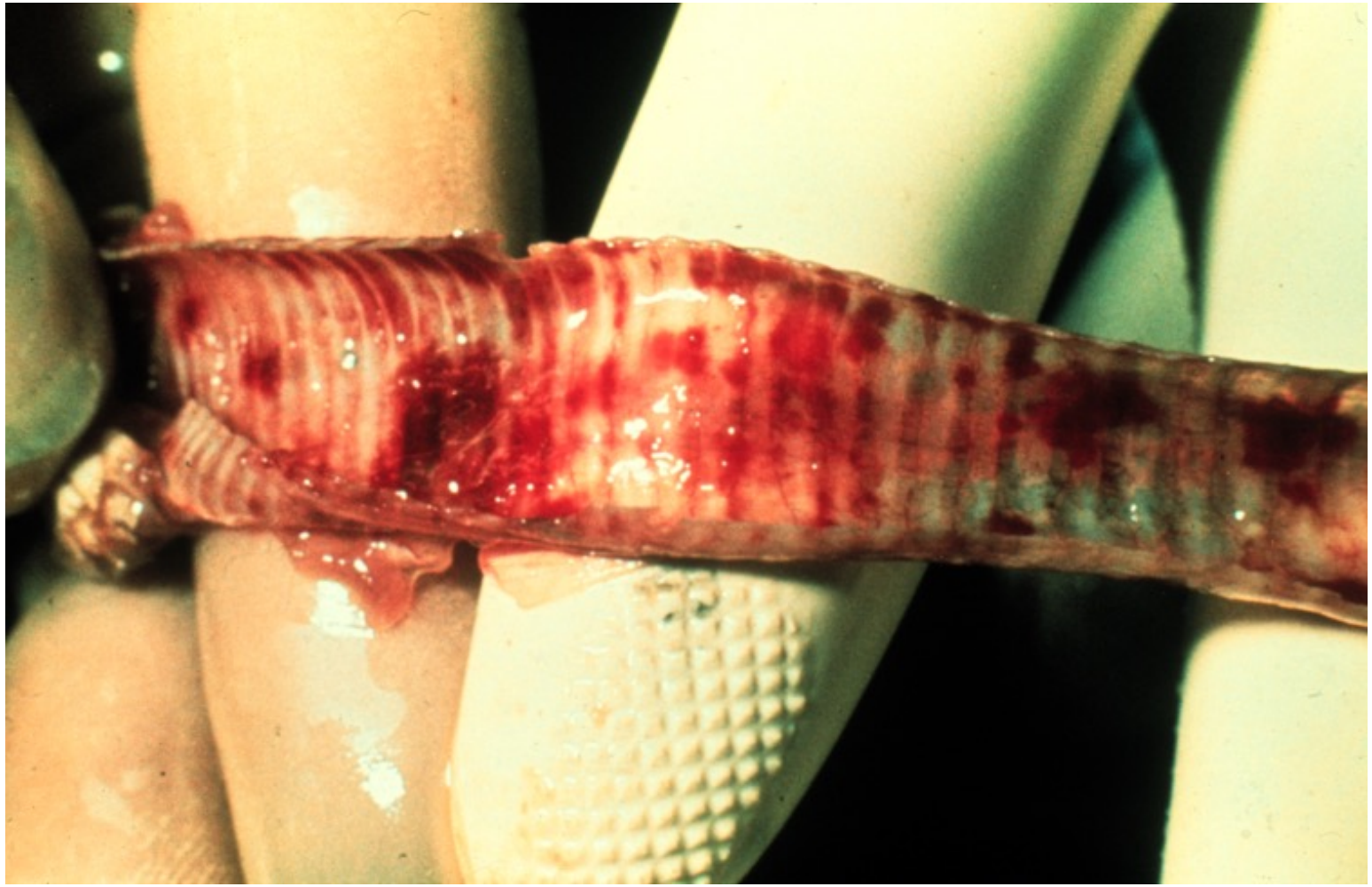
Avian influenza: disease in poultry



Avian influenza: disease in poultry

- Diagnosis:
  - Top DDx is Newcastle disease virus
  - Clinical signs are non-specific: need ancillary testing.
    - PCR is routinely used on cloacal or tracheal swabs
    - Whole genome sequencing of the virus is performed
    - Virus isolation is performed regularly
    - Subtyping can be done with specific hemagglutinin inhibition assays

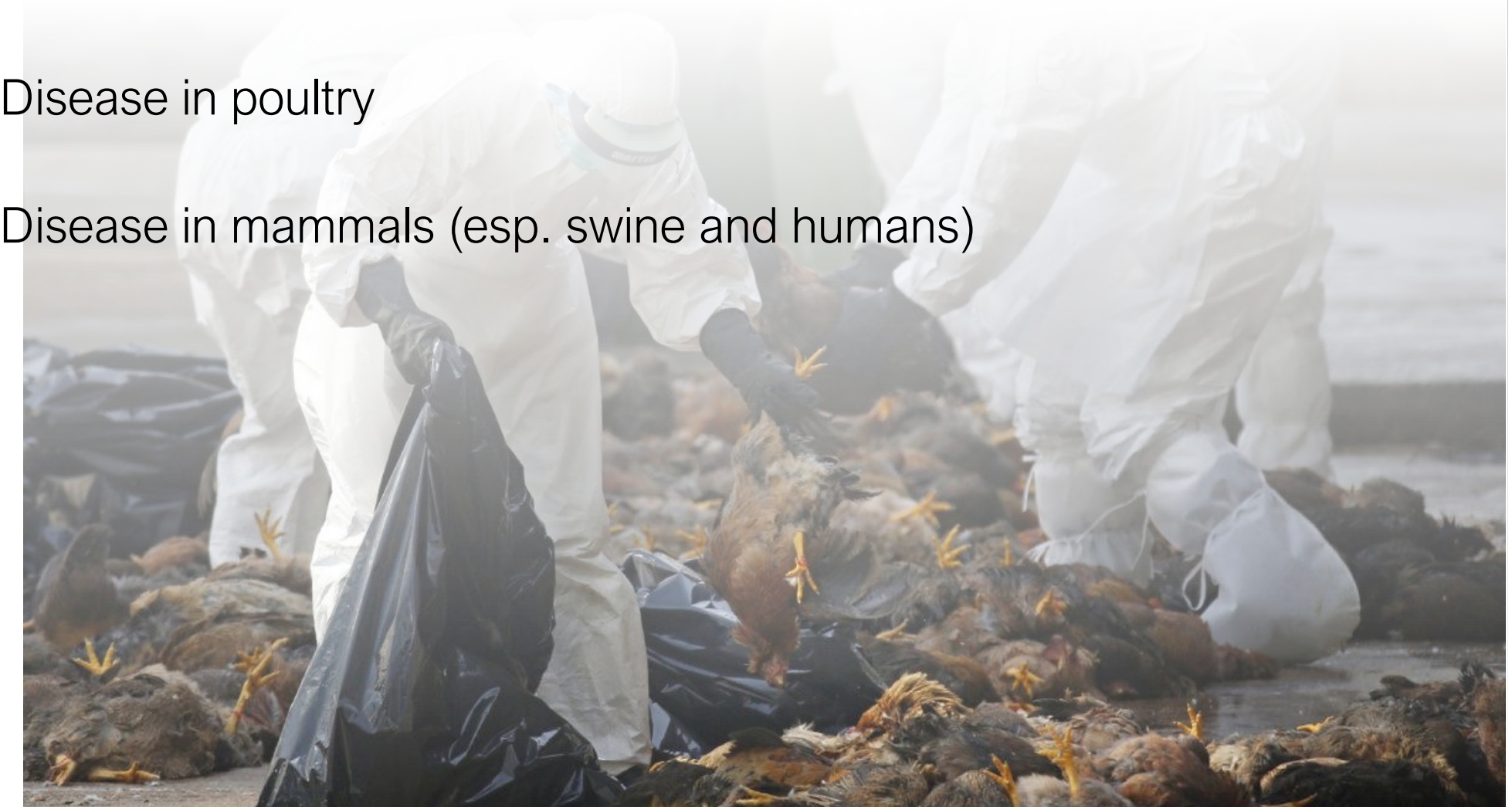
  - HP vs LP
    - Dictated in large part by the polybasic cleavage site, but other factors play a role.
    - Strict (OIE) definition of HP:
      - Intravenous pathogenicity in 6 week old chicks > 75 %
      - Any H5 or H7 with a polybasic cleavage site

Avian influenza: disease in poultry

- Control:
  - Biosecurity
    - Keep waterfowl away from chickens
  - Depopulation of flocks with HPAI
  - Vaccination is available but interferes with international trade (cannot differentiate between infected/vaccinated)

Avian influenza

- Two major concerns with AI:
  - Disease in poultry
  - Disease in mammals (esp. swine and humans)



Avian influenza: disease in humans

- HPAI is a potentially zoonotic infection
- Since 2003: 878 cases of H5N1, 458 deaths (wow!)
  - Systemic disease
  - These are individual cases: human-to-human transmission ha
  - Other strains can also be zoonotic – H5N7, H5N6, H3N8, H7
  - Often the result of contact with infected birds at live/wild mar
- Reassortment with circulating swine or human influenza strains has the potential for deadly pandemic
  - 2009 H1N1 swine flu was composed of avian, swine, and human strains

CONFIRMED CASES

771 407 825

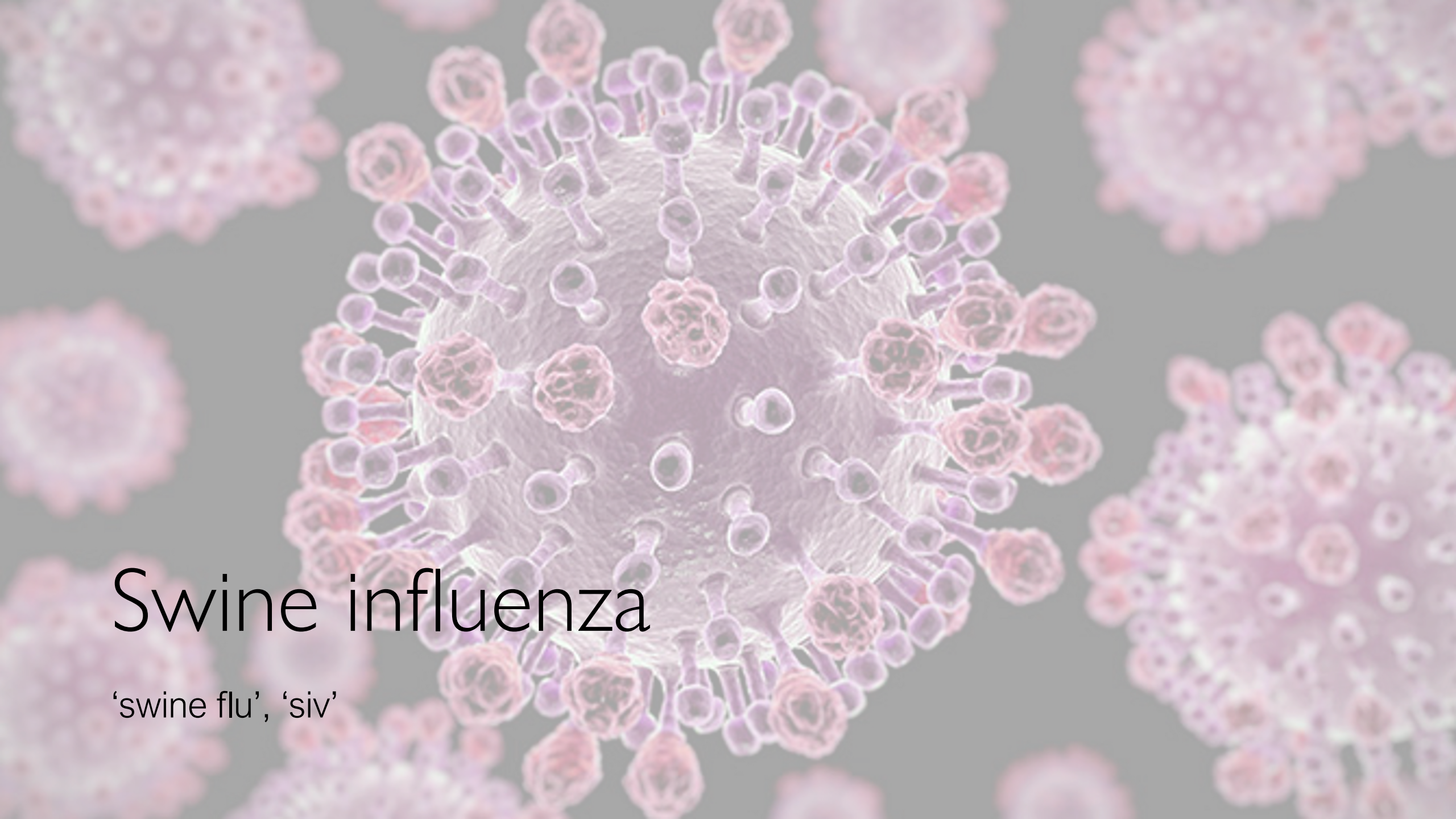
Last update: 17 October 2023 at 21:00 GMT-3

CONFIRMED DEATHS

6 972 152

Last update: 17 October 2023 at 21:00 GMT-3





Swine influenza

‘swine flu’, ‘siv’

Swine influenza A virus (SIV)

- Occurs worldwide

- Pigs can serve as a mixing vessel:
  - They possess the receptors recognized by both avian and mammalian adapted IAV
  - Despite that, most swine IAV are H1 or H3

- Host range:
  - Pigs
  - (Turkeys were infected through AI in the 2009 pandemic)
  - Humans (e.g., pandemics of 1918 and 2009, & recently with variant viruses H1N1v, H3N2v & H1N2v).

- Usual route of introduction is the addition of an infected pig.

Swine influenza A virus: pathogenesis

Inhalation/contact

↓

Replication in respiratory tract

↓

Necrosis of epithelial cells of the airway, inflammation

↓

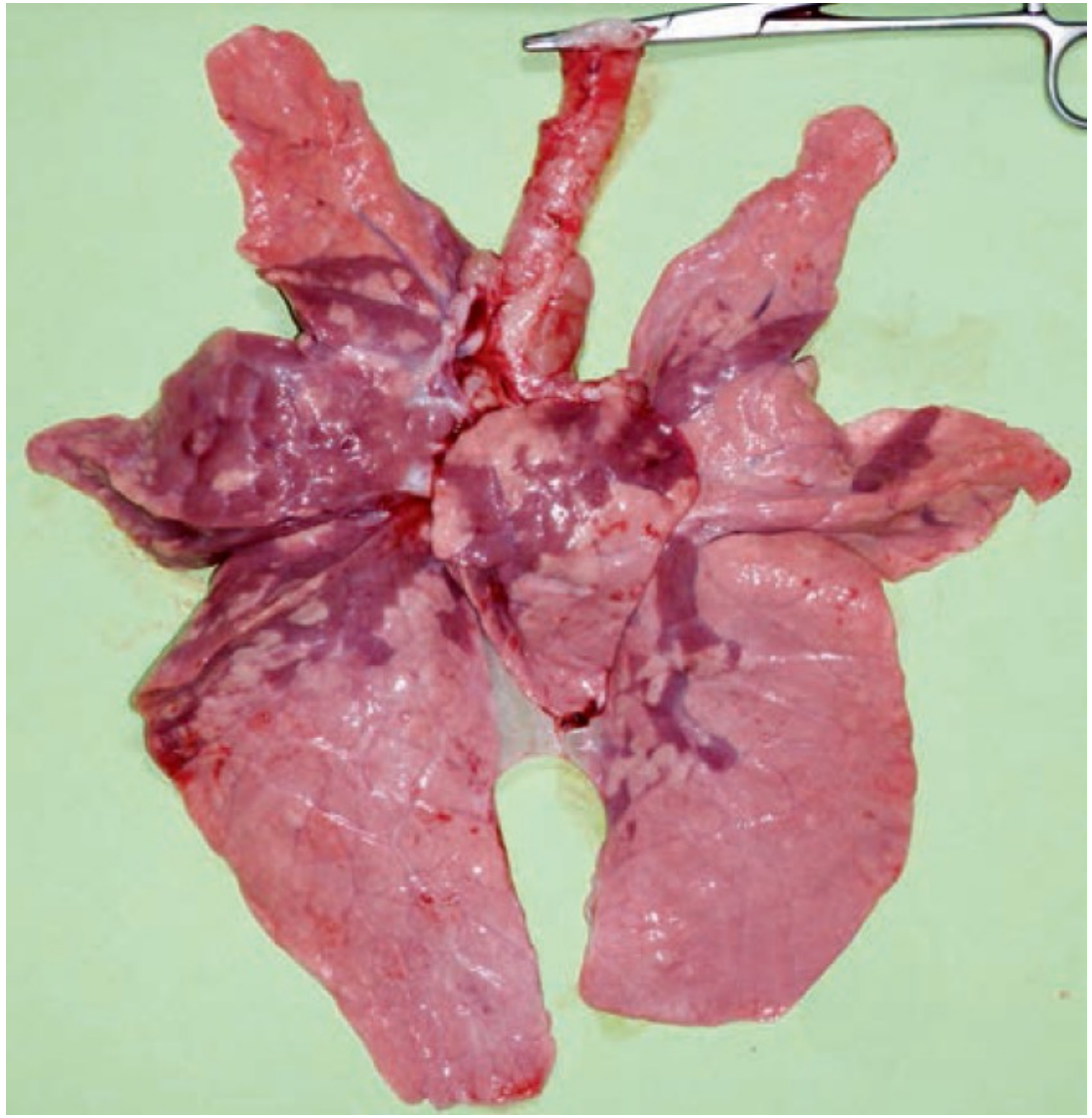
Bronchopneumonia

± secondary bacterial infection

Swine influenza A virus: clinical signs

- Rapidly spreading outbreak
- Clinical signs appear rapidly and affect pigs of all age groups
  - Fever
  - Anorexia
  - Coughing, sneezing, and rhinitis
- Most pigs recover in ~ 7 days
- Mortality is low (< 1 %)
  - Secondary bacterial infection may ↑ mortality
- Impact to production can have significant economic impact

Swine influenza A virus: gross lesions



Swine influenza A virus: diagnosis, control, and prevention

- Diagnosis:
  - DDx: PCV-2, Nipah virus
  - PCR on fresh lung tissue or nasal swabs

- Control
  - Good biosecurity, “all-in, all-out” is often enough
  - Vaccines are available
    - Do not prevent infection
    - ↓ shedding and clinical signs
    - Cannot differentiate between vaccinated and infected based on serology

- Zoonotic:
  - Those in close contact are at particular risk
  - 1918 and 2009 pandemics came from swine



Equine influenza virus

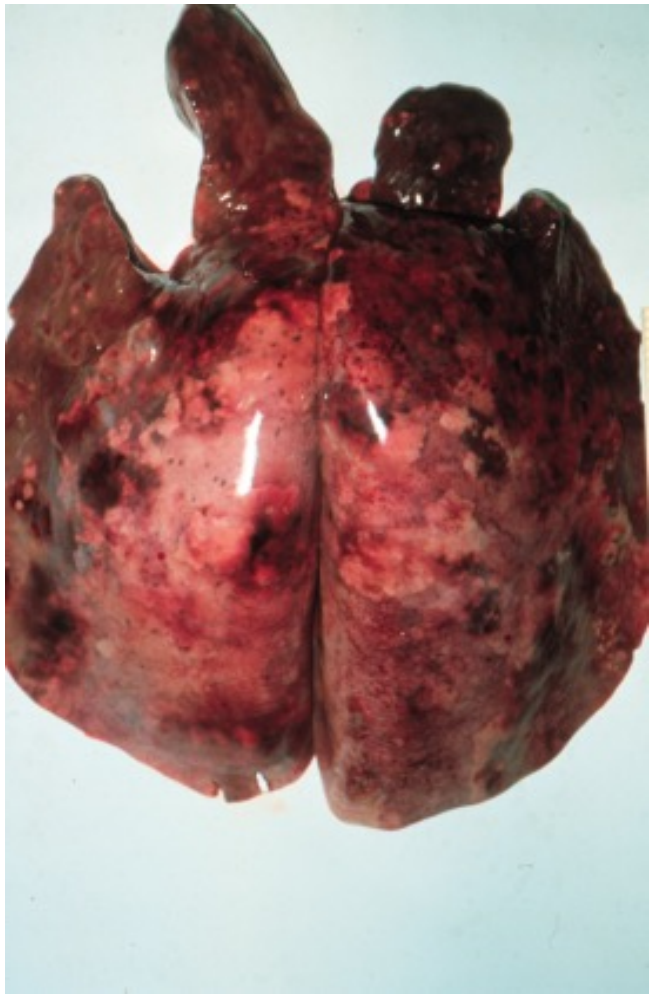
Equine influenza virus

- Occurs worldwide except in New Zealand, Australia, and Iceland.
- Exists only as H3N8 (H7N7 considered to be extinct)
- Important cause of respiratory disease in horses.
- Epizootics occur during racing season
  - Factors associated with risk of infection:
    - Age: 1-5 year olds are most susceptible
    - Frequent contact with large number of horses
- Transmission is through aerosolized droplets and contaminated fomites
- Pathogenesis is similar to swine: infection of epithelial cells of the airways

Equine influenza virus: clinical signs

- Fever
- Anorexia
- Rhinitis, conjunctivitis
- Dry, harsh paroxysmal cough
- Recovery within 2-3 weeks
- Secondary bacterial infections/mixed infections result in chronic cases:
  - Purulent nasal exudate
  - Bronchopneumonia

- Morbidity ↑ ↑, mortality ↓ ↓



Bacterial pneumonia secondary to equine influenza

Equine influenza virus

- Diagnosis:
  - DDx: EHV-1, EHV-4, rhinovirus
  - PCR on nasal swabs

- Control:
  - Vaccination is widely practiced
    - Most contain only H3N8
    - Vaccine strains haven't completely kept up with antigenic drift
    - Vaccines are not 100% protective
  - Biosecurity
  - Quarantine infected premises



Canine influenza virus

Canine influenza virus

- Two major strains:
- H3N8
  - Result of species jump from horses → dogs
  - First reported in Greyhounds in 2004 in Florida
  - Rarely identified nowadays

- H3N2
  - Avian influenza origin → dogs in Asia
  - Arrived in Chicago, USA via the importation of dogs from S. Korea and China



Canine influenza virus (CIV)

- Older dogs & puppies may be more severely affected.
- Incubation period: 2-5 days.
- Clinical disease:
  - 80% of dogs develop clinical signs; 20% do not show clinical signs of disease but can still shed the virus and can spread the infection
  - Low-grade fever
  - Coughing, dyspnea, mucoid to purulent nasal discharge
  - Anorexia, depression, & recovery in 1-3 weeks (80% are mild cases)
  - Pneumonia with secondary bacterial infection (*Pasteurella multocida*, *Mycoplasma* spp or *Streptococcus* spp) is the most common complication
- Commercial vaccines are available (against CIV H3N8 or both H3N8 and H3N2)
  - CIV vaccine is a “non-core” vaccine
  - Only dogs that are in contact with other dogs should be considered for the vaccine (should be healthy dogs ≥ 8 weeks of age).
  - Administered in 2 doses, 2-4 weeks apart
  - Recommended annual revaccination with a single dose.

Canine influenza virus

- Differential diagnosis:
  - Kennel cough syndrome (due to CAV-2, CPIV-5, Bordetella bronchiseptica, & mycoplasmas).
  - Avian influenza A virus (very rare)

- Confirm by PCR, serology, or by use of rapid human influenza A kit.

Feline influenza virus

- Newly recognized infection in domestic & zoo cats (in Asia & Europe) caused by avian influenza, subtype H5N1:
  - First reported in 2004 in 23 tigers and leopards in a Thailand zoo fed poultry carcasses infected with avian influenza (H5N1);
  - Horizontal transmission between tigers occurred in same zoo in 2005.
  - Domestic cats can be infected experimentally (horizontally) and develop severe diffuse alveolar damage.
  - A domestic cat in Germany was infected naturally in 2005; disease was possibly acquired from a wild bird.

- Thus, H5N1 virus should be considered a rare potential threat to domestic and captive felids.

Influenza D virus

- Major host seems to be cattle
- *Might* cause mild respiratory disease
  - *Most likely* significance is as a component of bovine respiratory disease complex



