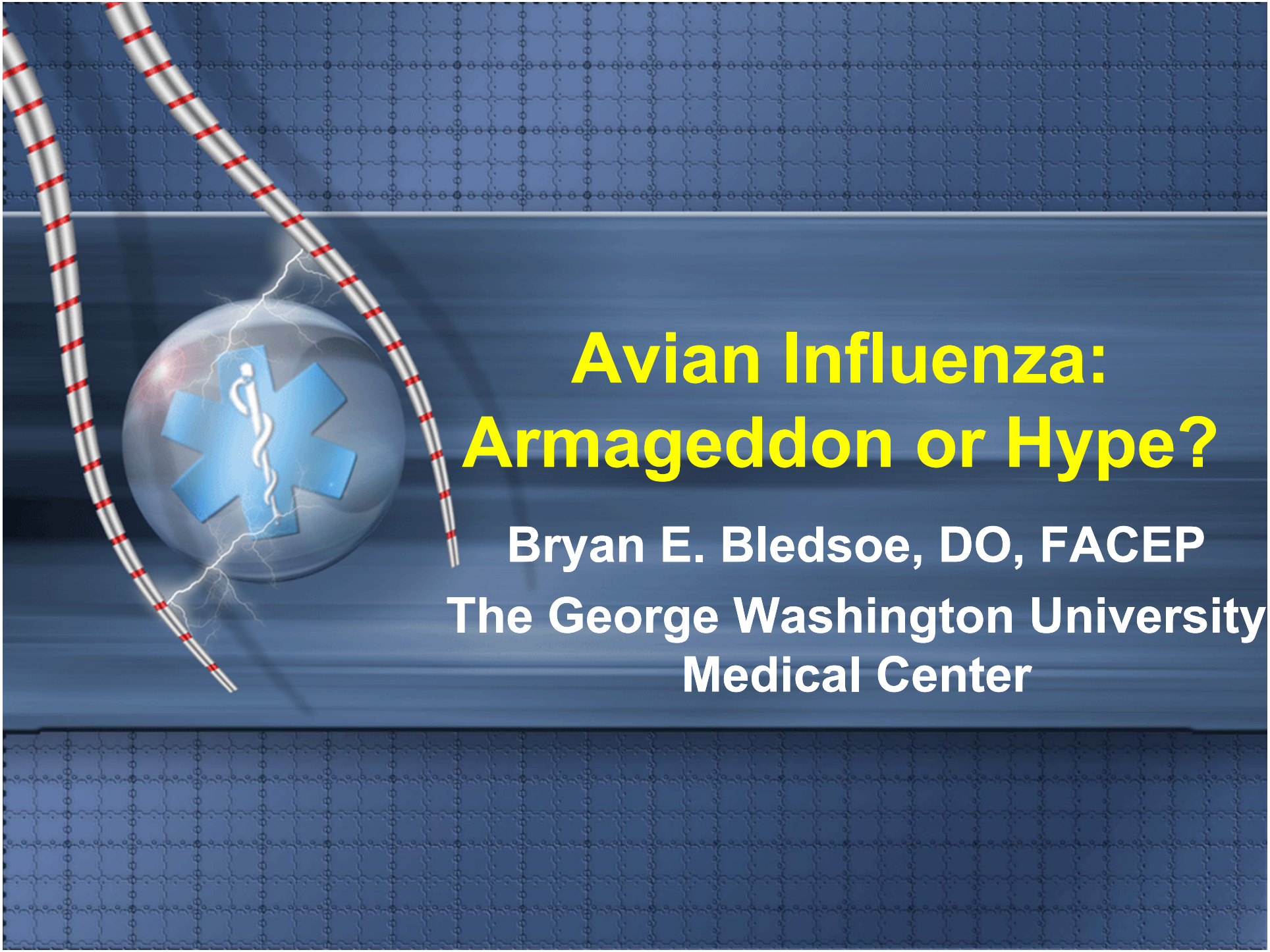

Avian Influenza:
Armageddon or Hype?
Bryan E. Bledsoe, DO, FACEP
The George Washington University
Medical Center

Avian Influenza

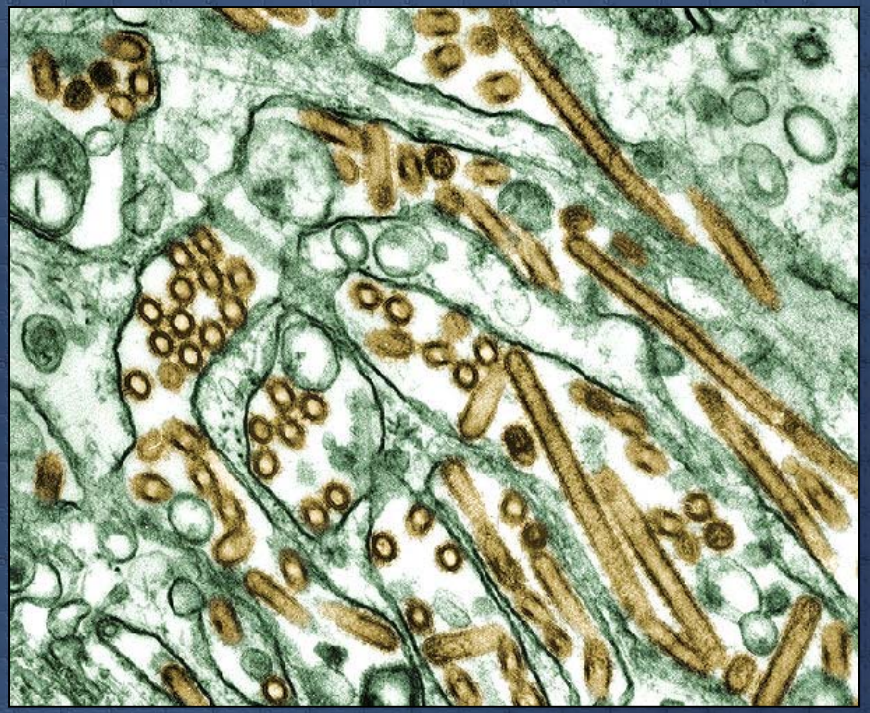
- Definitions:
  - Epidemic—The occurrence of cases of an illness in a community or region which is in excess of the number of cases normally expected for that disease in that area at that time.
  - Pandemic—An epidemic that strikes a very wide area, usually hemisphere-wide or world-wide.

Avian Influenza

- Three influenza pandemics during the last century:
  - 1968 (H3N2)
  - 1957 (H2N2)
  - 1918 (strain uncertain)
- Each cased by emergence of a new virus that contained components of previous human influenza viruses and avian influenza viruses.

Avian Influenza

- Avian influenza is causes by the H5N1 influenza virus.
- Influenza A virus.



Avian Influenza

- Avian influenza H5N1:
  - Sporadic transmission to humans in 2004-2005 killed 114 people and raises concern that next pandemic is imminent.
  - Two striking features:
    - Predominance of children and young adults.
    - High mortality rate.

Avian Influenza

- Highly-pathogenic N5H1 influenza virus now endemic among bird and poultry populations in Asia.

Avian Influenza

- Sporadic transmission from birds to humans of H5N1 raises concerns:
  - H5N1 may mutate.
  - H5N1 may combine with genetic material from human influenza virus creating a new strain capable of human-to-human transmission and potential pandemic.
- WHO describes the H5N1 as a “public health crisis” and declared that the world is as close as ever to the next pandemic.

Avian Influenza

Avian H3

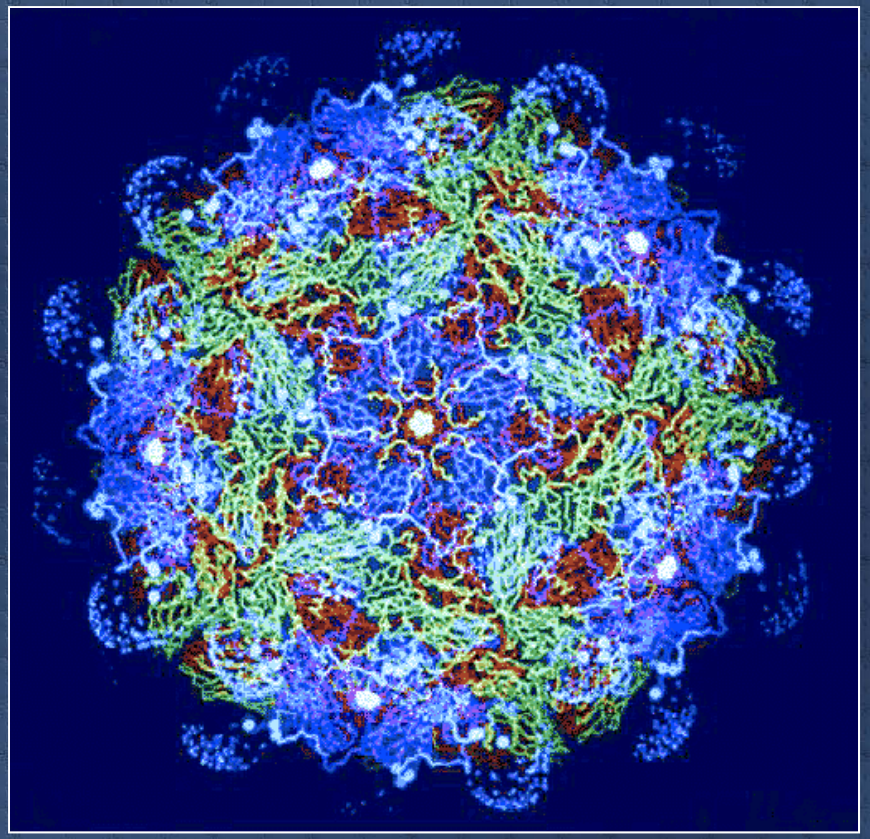
Human H2

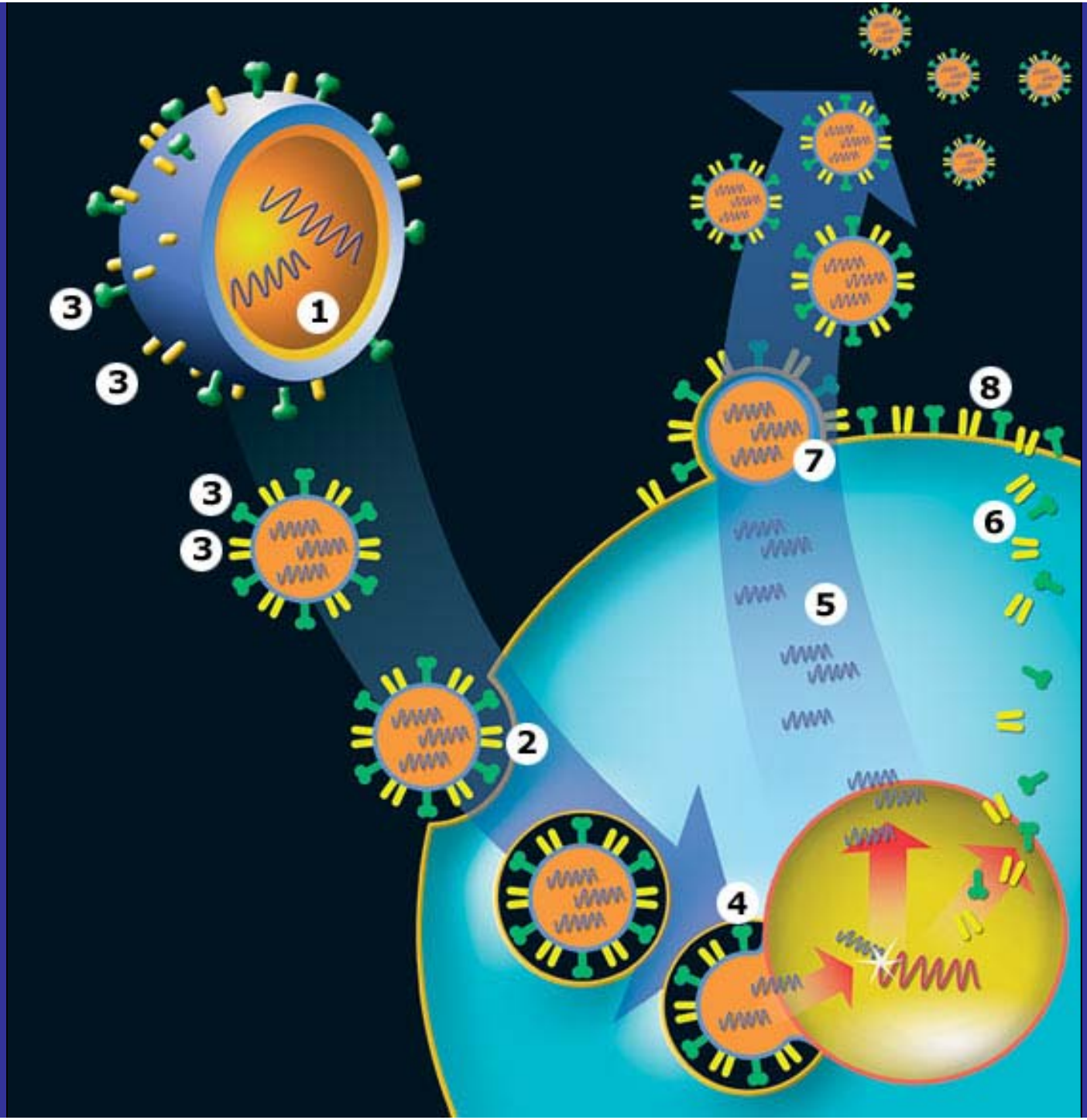
Human H3

Evolution of 1968 H3N2 Influenza Pandemic

Avian Influenza

- **Virus:**
  - Ultramicroscopic infectious agent that replicates itself only within cells of living hosts.
  - Many are pathogenic.
  - A piece of nucleic acid (DNA or RNA) wrapped in a thin coat of protein.

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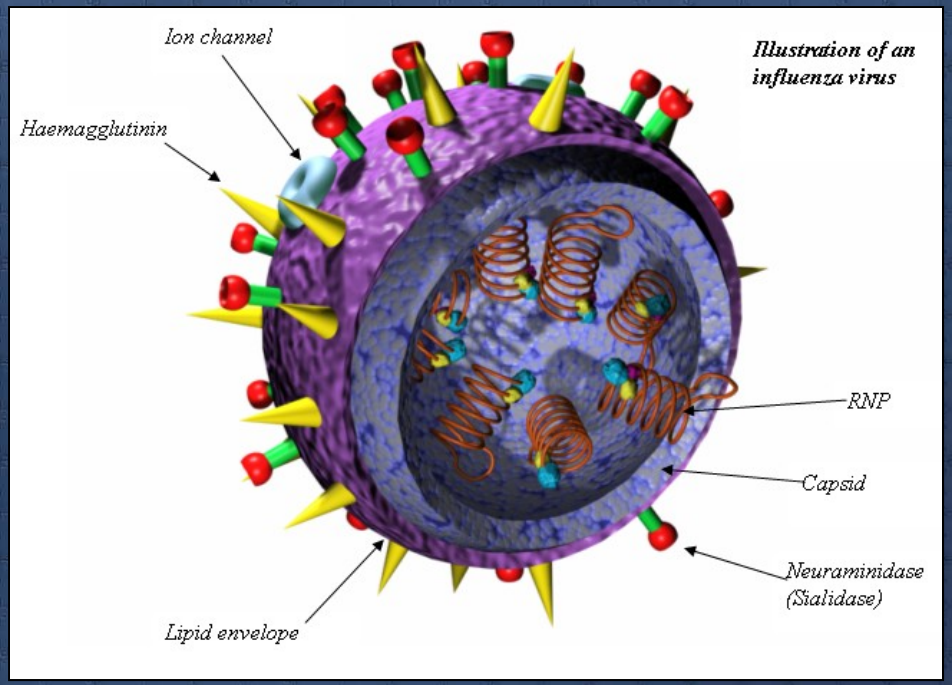
Avian Influenza

- Influenza viruses are RNA viruses.
- Segmented genome thus great antigenic diversity.

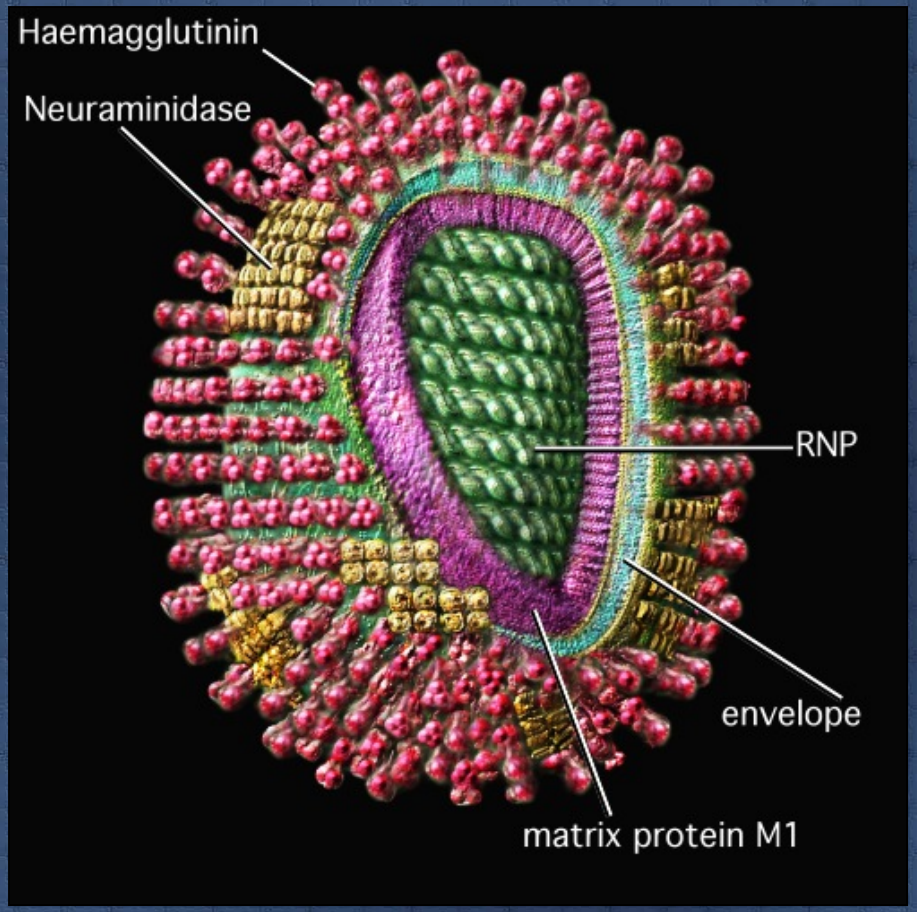


Avian Influenza

- Influenza virus classifications:
  - Core protein:
    - A
    - B
    - C
  - Species of origin (swine, avian, etc.)
  - Geographic site of isolation.
  - Serial Number
  - Glycoprotein subtypes (Influenza A only)

Avian Influenza

- Two major antigenic glycoproteins embedded in membrane:
  - Hemagglutinin (HA)
  - Neuramidase (NA)
- Induce antibody response in humans.

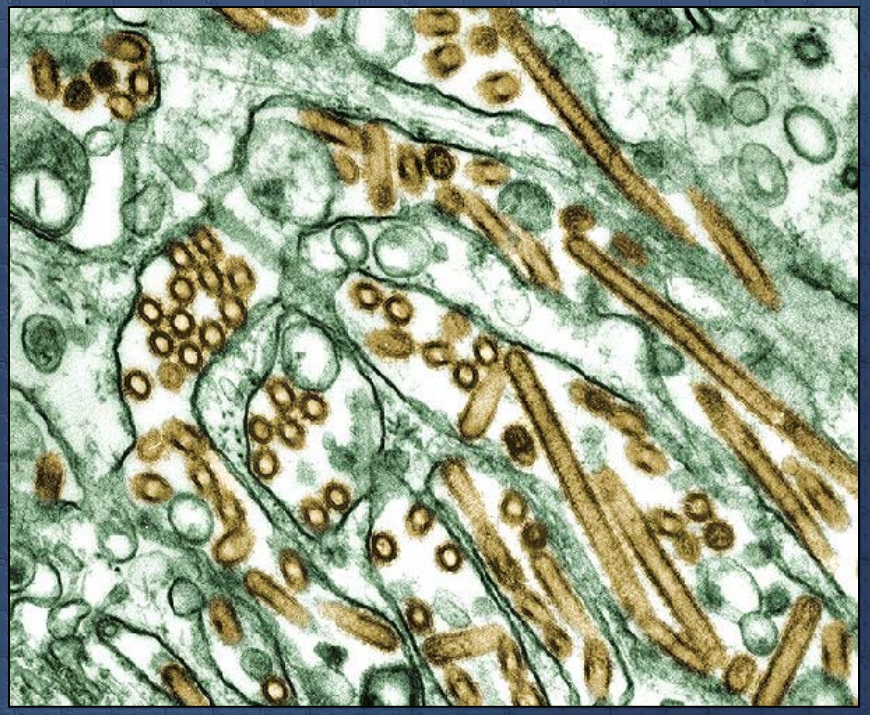


Avian Influenza

- Avian influenza:
  - 16 HA subtypes
  - 9 NA subtypes
  - Many subtypes possible.
  - All subtypes found in birds

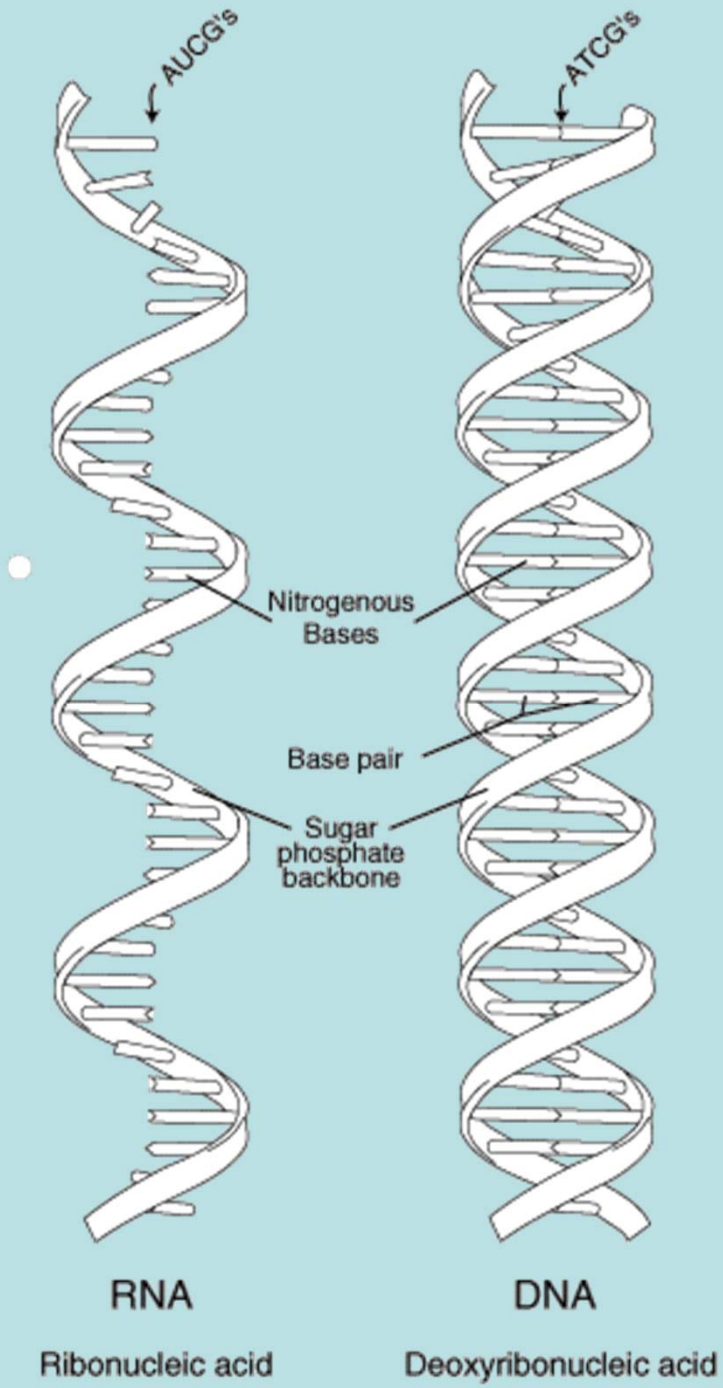
Avian Influenza

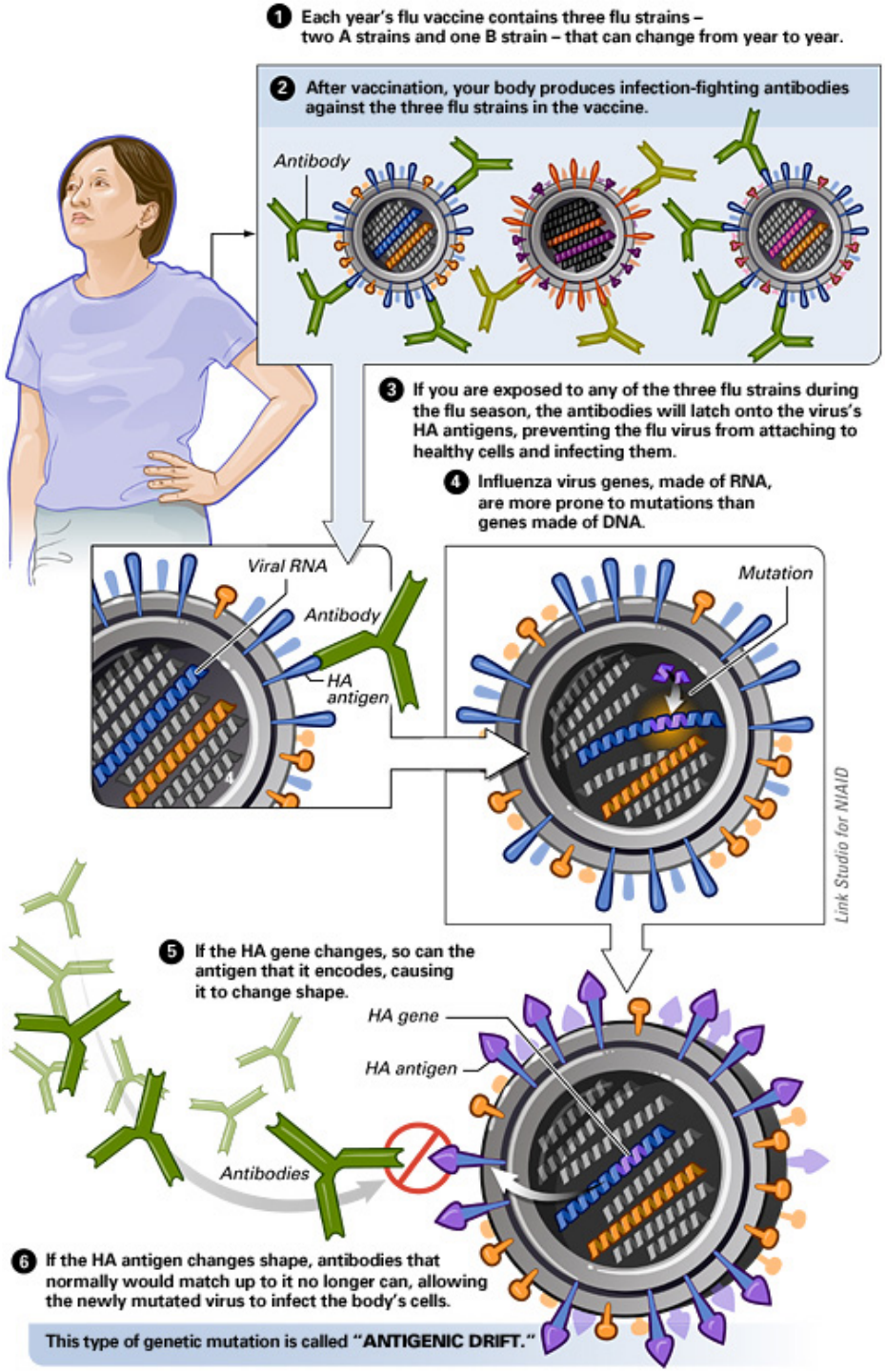
- **Influenza A:**
  - Responsible for frequent (usually annually) outbreaks or epidemics of varying intensity.
  - Occasional pandemics.
  - Subtypes circulating:
    - H1N1
    - N1N2
    - H3N2
- **Influenza B:**
  - Outbreaks every 2-4 years.



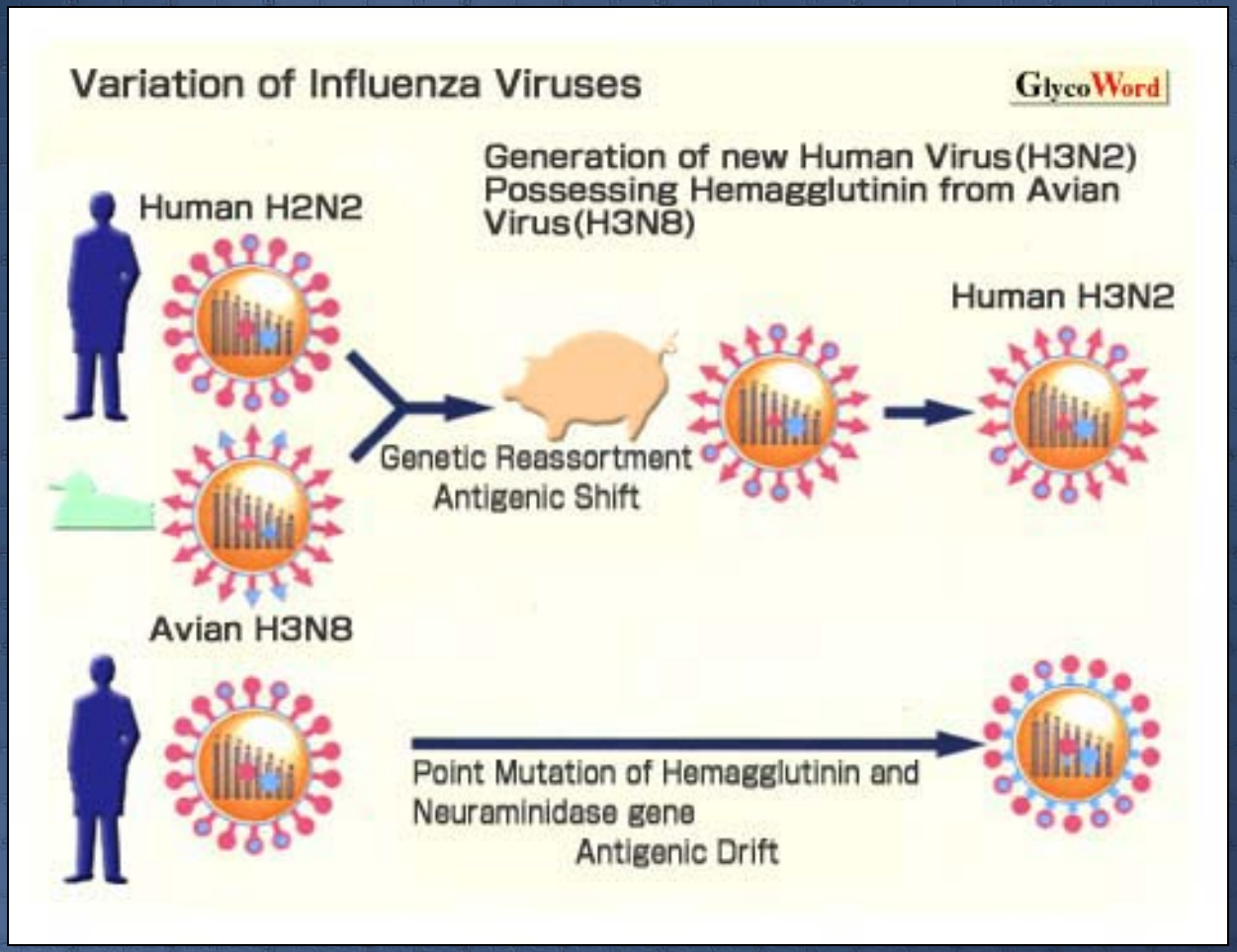
Avian Influenza

- Human influenza viruses (H1 & H3) circulate continuously and undergo antigenic drift.
- Inefficient proofreading during viral RNA replication causes transcription errors and amino acid substitutions in HA and NA.
- Allows new variants to evade pre-existing immunity thus causing outbreaks.


AUCG's
ATCG's
Nitrogenous Bases
Base pair
Sugar phosphate backbone
RNA
Ribonucleic acid
DNA
Deoxyribonucleic acid

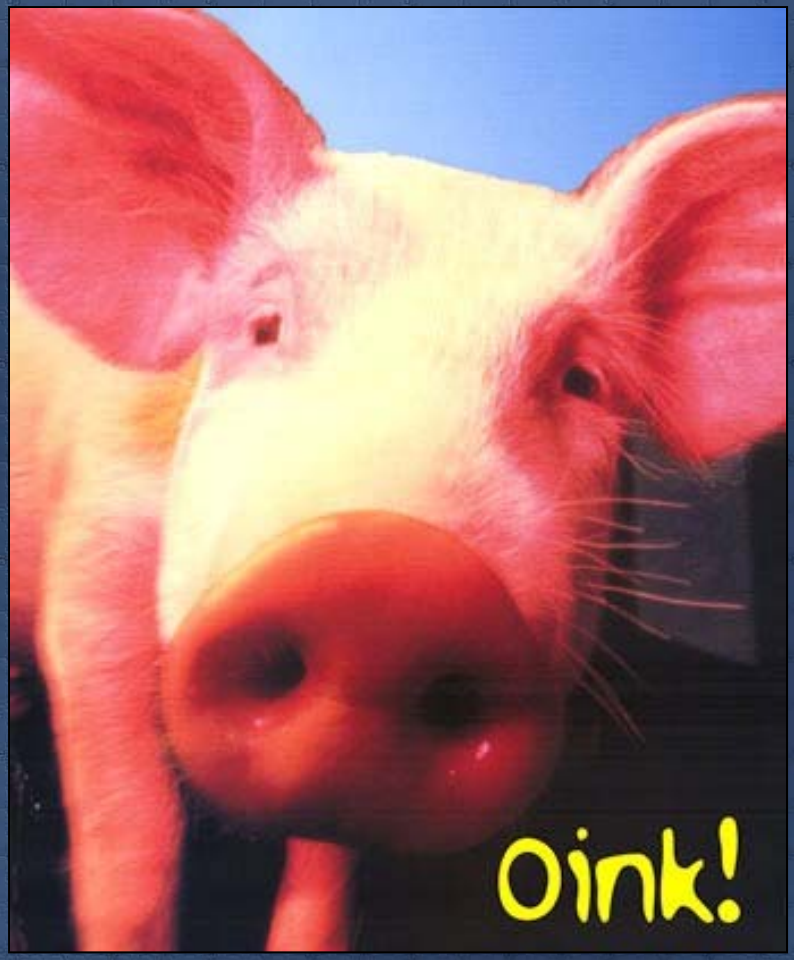

1 Each year's flu vaccine contains three flu strains – two A strains and one B strain – that can change from year to year.
2 After vaccination, your body produces infection-fighting antibodies against the three flu strains in the vaccine.
Antibody
3 If you are exposed to any of the three flu strains during the flu season, the antibodies will latch onto the virus's HA antigens, preventing the flu virus from attaching to healthy cells and infecting them.
4 Influenza virus genes, made of RNA, are more prone to mutations than genes made of DNA.
Viral RNA
Antibody
HA antigen
Mutation
Link Studio for NIAID
5 If the HA gene changes, so can the antigen that it encodes, causing it to change shape.
HA gene
HA antigen
Antibodies
6 If the HA antigen changes shape, antibodies that normally would match up to it no longer can, allowing the newly mutated virus to infect the body's cells.
This type of genetic mutation is called "ANTIGENIC DRIFT."

Avian Influenza



Avian Influenza

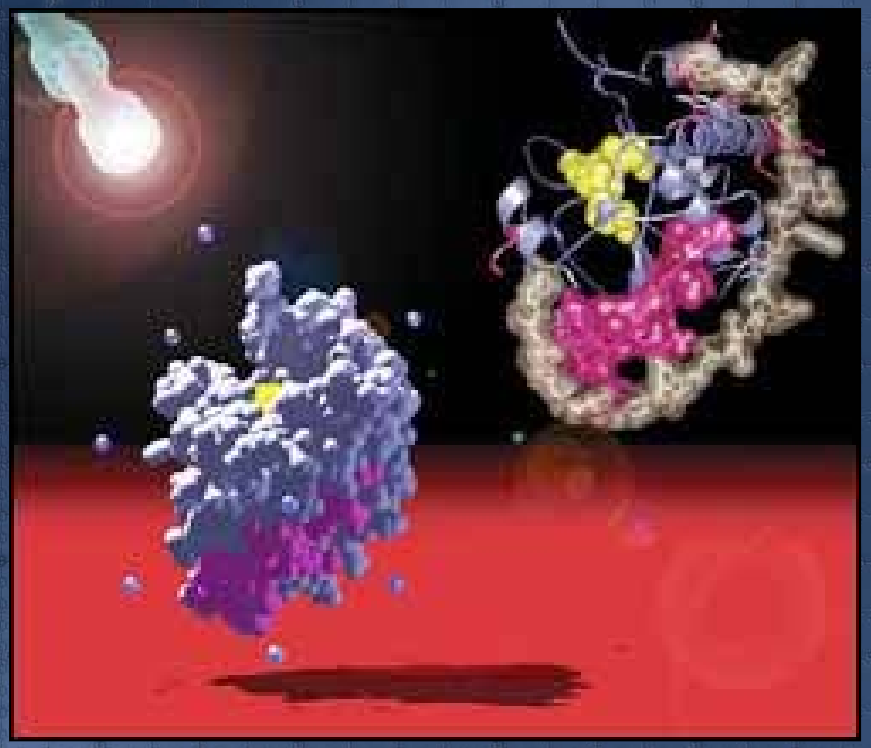
- Why are pigs involved?
- Pigs have receptors for both avian and human influenza viruses in their tracheas.
- Domestic pig supports the growth of both human and avian viruses.



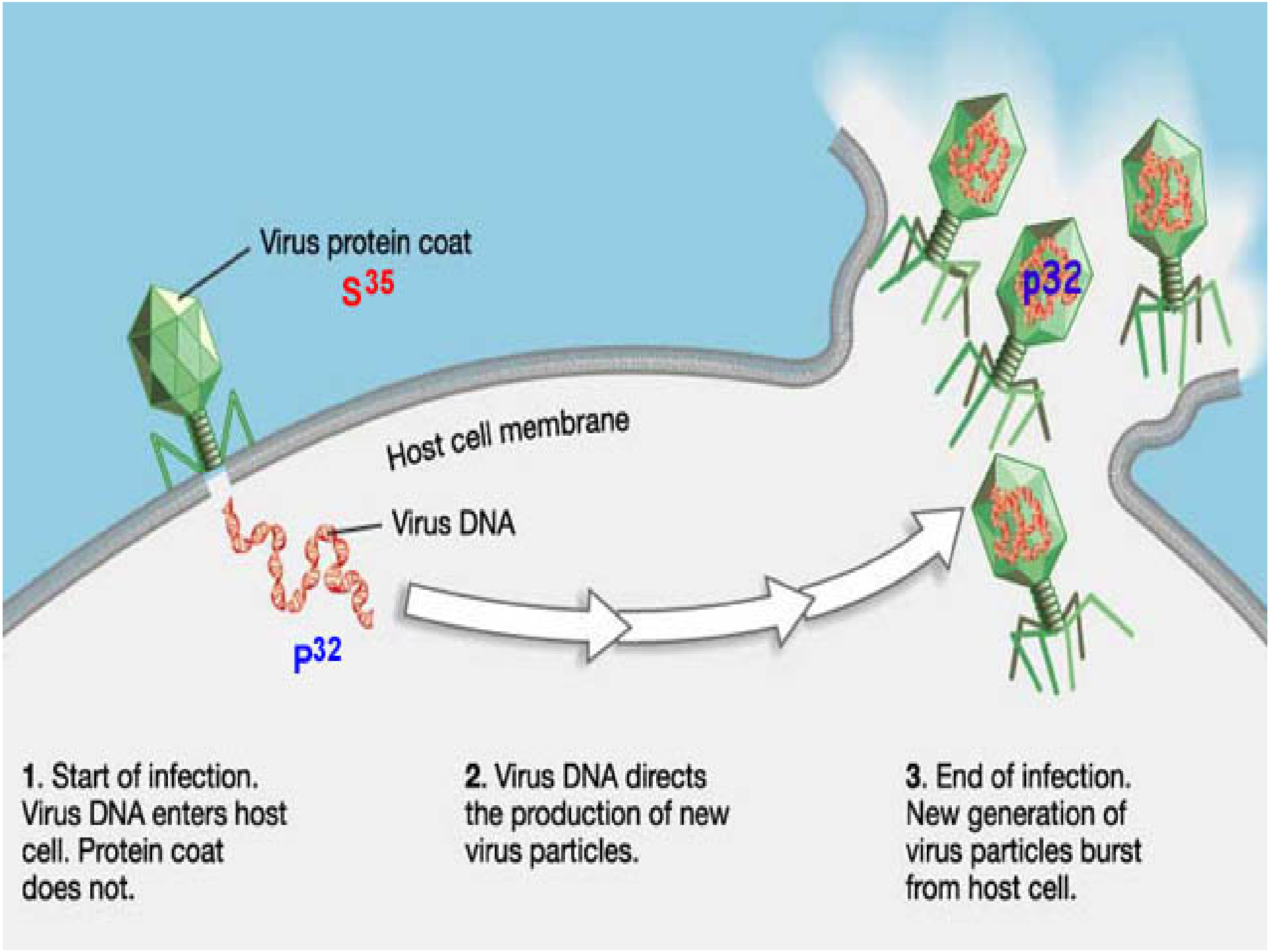
Avian Influenza

- Why does influenza always seem to come from Southeast Asia?
- Agricultural practices .
- Humans, birds and swine are in close proximity.

Avian Influenza



- Avian viruses replicate inefficiently in humans.
- However, some subtypes can replicate in the human respiratory tract and cause disease.


Virus protein coat
S35
Host cell membrane
Virus DNA
P32
p32
1. Start of infection. Virus DNA enters host cell. Protein coat does not.
2. Virus DNA directs the production of new virus particles.
3. End of infection. New generation of virus particles burst from host cell.

Avian Influenza

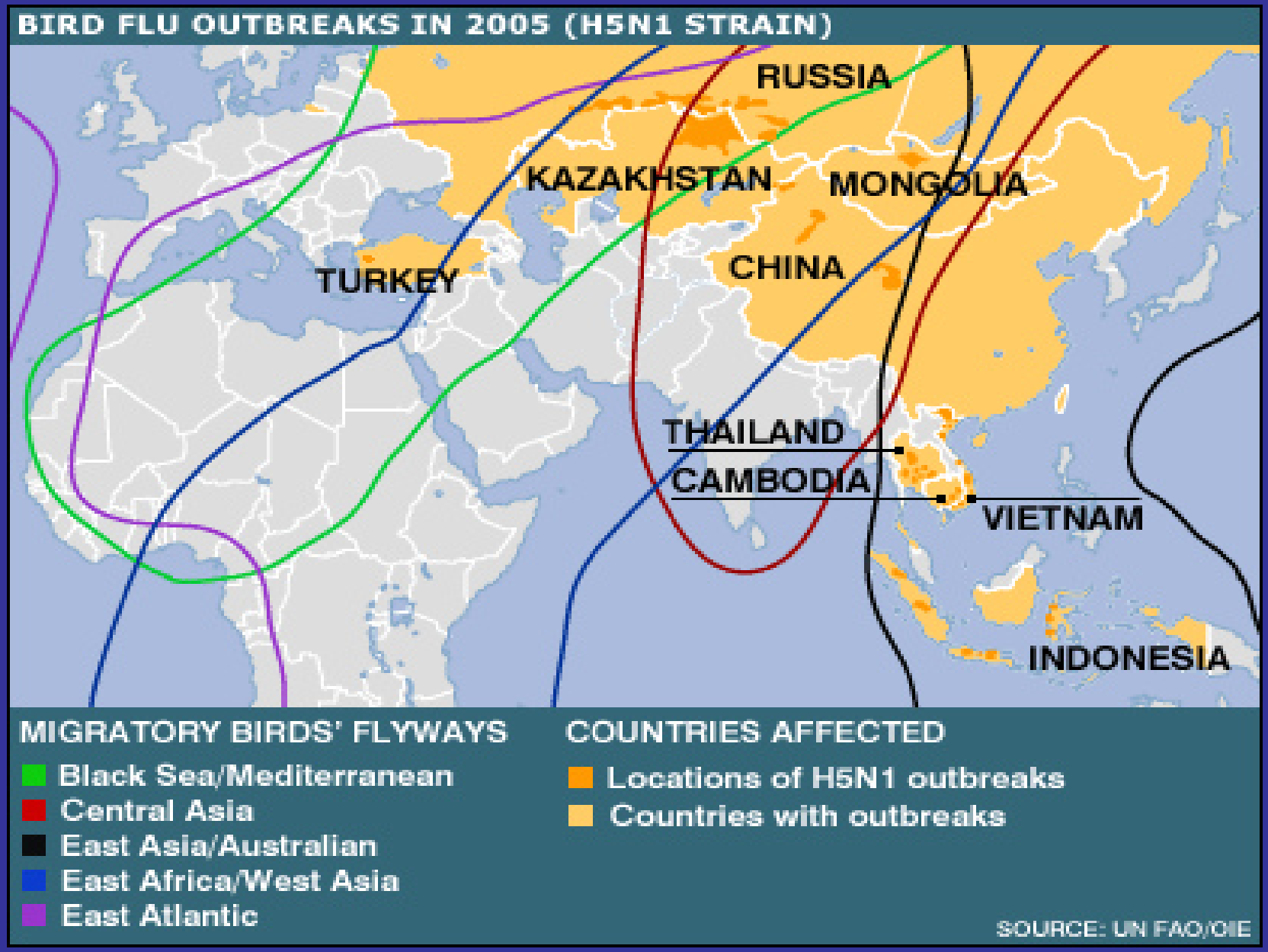
- Avian influenza virus types:
  - H5N1
  - H9N2
  - H7

Avian Influenza

- H5N1
  - 1997: 18 human cases (Hong Kong)
    - 33% mortality
    - 61% pneumonia
    - 51% needed ICU care
    - All genes of avian origin showing virus had "jumped species."
    - Little evidence of human-to-human transmission.

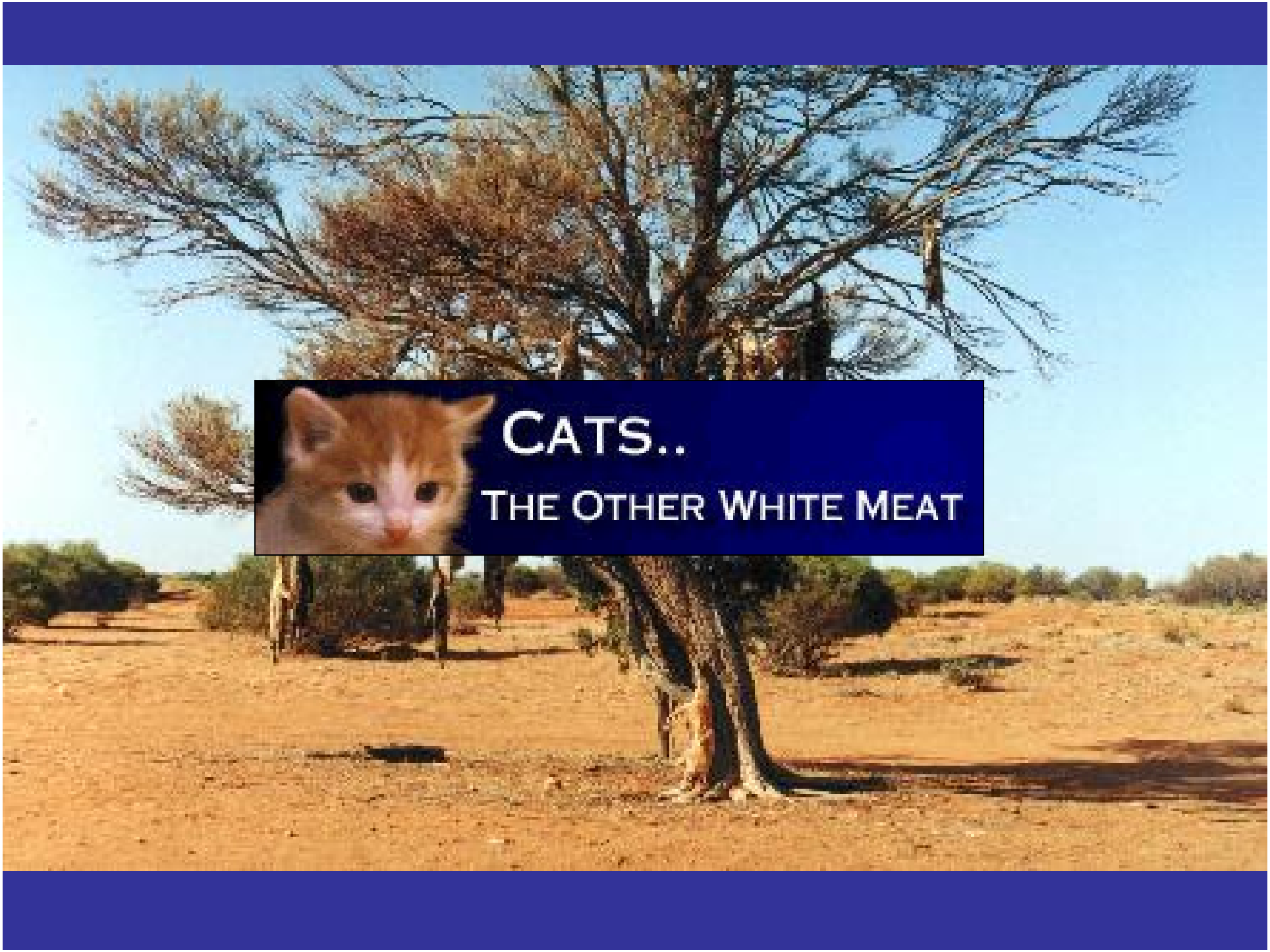
Avian Influenza

- H5N1
  - 2003: Reemerged in a family group returning from Hong Kong to China.
  - 2003-2006: Highly pathogenic variant caused extensive outbreaks in Asia.
    - Cambodia
    - China
    - Indonesia
    - Laos
    - Malaysia
    - Thailand
    - Vietnam
    - Russia
    - Kazakhstan
    - Mongolia


BIRD FLU OUTBREAKS IN 2005 (H5N1 STRAIN)
RUSSIA
KAZAKHSTAN
MONGOLIA
CHINA
TURKEY
THAILAND
CAMBODIA
VIETNAM
INDONESIA
MIGRATORY BIRDS' FLYWAYS
Black Sea/Mediterranean
Central Asia
East Asia/Australian
East Africa/West Asia
East Atlantic
COUNTRIES AFFECTED
Locations of H5N1 outbreaks
Countries with outbreaks
SOURCE: UN FAO/OIE

Avian Influenza

- **H5N1:**
  - Human cases = 130 (>50% mortality)
  - Locations:
    - Thailand
    - Cambodia
    - Vietnam
    - Indonesia
    - China
  - Spread to domestic cats.


Cats..
The Other White Meat

Avian Influenza

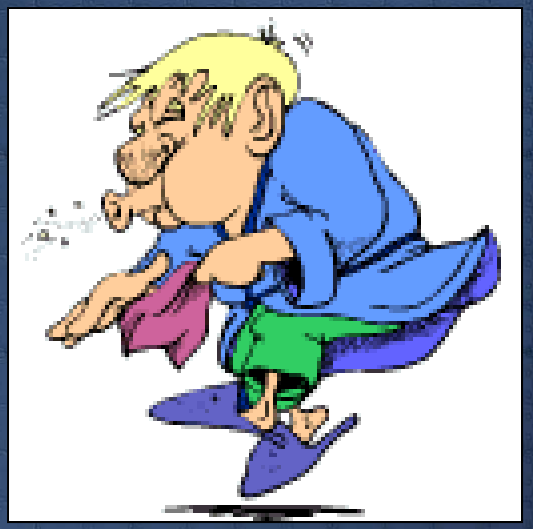
- H9N2:
  - 1999: Hong Kong
  - 2003: Hong Kong
    - Caused mild, self-limited respiratory infection in children.

Avian Influenza

- H7:
  - 2003: H7N7 outbreak in the Netherlands
    - Influenza-like illness
    - Mild respiratory illness
  - H7N3 caused conjunctivitis in Canadian poultry workers.

Avian Influenza

- Transmission:
  - Inhalation of infectious droplets
  - Direct contact
  - Indirect (fomite) contact [possibly]



Avian Influenza

- Transmission:
  - H5N1:
    - Bird-to-human
    - Environment to human [possible]
    - Limited non-sustained human-to-human

Eat bird guts—make your skin so smooth.

Avian Influenza

- Pathogenesis:
  - H5 and H7 strains capable of evolving into highly pathogenic strains,
  - Recent H5 virus strains increasingly pathogenic.
  - Virulence related to HA molecules

Avian Influenza

- Clinical Features
  - H5N1:
    - 1997:
      - 8 of 18 < 12 years old
        - » All but one had mild disease
      - > 12 years old
        - » Fever (100%)
        - » Upper respiratory tract symptoms (67%)
        - » Pneumonia (58%)
        - » GI symptoms (50%)

Avian Influenza

- Clinical Features
  - H5N1:
    - 1997:
      - Risk factors
        - » Older age
        - » Delayed admission to hospital
        - » Pneumonia
        - » Leukopenia / Lymphopenia
      - Complications
        - » MODS
        - » Renal failure
        - » Cardiac compromise
        - » Pulmonary hemorrhage
        - » Pneumothorax
        - » Pancytopenia

Avian Influenza

- Primary cause of death is respiratory failure.

Avian Influenza

- Clinical features
  - H5N1
    - 2004-2005
      - Majority < 25 years of age
      - All presented with:
        - » Fever
        - » Lower respiratory symptoms and pneumonia
        - » Lymphopenia
      - Diarrhea developed in 7 of 10
      - All developed ARDS
      - All died between days 6-29 post-presentation

Avian Influenza

- Clinical features
  - H5N1
    - Incubation period 2-4 days (maximum of 8)
  - H7
    - Conjunctivitis
  - H5N2
    - Children show mild, limited URI symptoms

Avian Influenza

- Diagnosis
  - Viral culture
  - Polymerase Chair Reaction (PCR) assay for avian influenza A (H5N1) RNA
  - Immunofluorescence for antigen with use of H5 monoclonal antibody
  - Four-fold rise in H5-specific antibody

Avian Influenza

- Who should be tested?
  - High-risk patients
    - Patients with a history of travel within 10 days of symptom inset to a country with documented H5N1 avian influenza in poultry and/or humans
    - AND
    - Patients with pneumonia on CXR, ARDS, or other severe respiratory illness for which an etiology has not been established.

Avian Influenza

- Who should be tested?
  - Low-risk patients
    - Patients with history of contact with domestic poultry or a known or suspected human case in an H5N1-infected country within 10 days of symptom onset
    - AND
    - Documented fever ≥38° C
    - AND
    - One or more of the following:
      - Cough
      - Sore throat
      - Shortness of breath

Avian Influenza

- Vaccination
  - No licensed vaccine.
  - Area of intense research.
  - Biosecure facilities required because of viral pathogenicity.
  - Viruses are lethal to eggs which prevents mass vaccine production.
  - Avian vaccines available although inconsistently administered.

Avian Influenza

- Vaccination
  - Fast track process underway
  - Initial studies (Phase 1) of 450 patients:
    - Rochester, NY
    - Baltimore, MD
    - Los Angeles, CA

Avian Influenza

- Treatment
  - Effective drugs:
    - M2 channel blockers
      - Amantadine (Symmetrel)
      - Rimantadine (Flumadine)
    - Neuraminidase inhibitors
      - Oseltamivir (Tamiflu)
      - Zanamivir (Relenza

Avian Influenza

Treatment

- H5N1 in Thailand has developed mutations in the M2 protein which makes it resistant to amantadine and rimantadine (neuraminidase inhibitors remain effective).
- Oseltamivir (Tamiflu) effective when given ***early*** in the course of the infection.
- Oseltamivir (Tamiflu) ineffective when given ***late*** in the course of the infection.
- Treat for 5-8 days.

Avian Influenza

- Drug resistance:
  - Mutation of the hemaggultinin or neuraminidase genes.
  - Drug resistance has been documented in human strains—specifically in children.
  - Prophylactic treatment of a Vietnamese girl caused drug resistance for oseltamivir.

Avian Influenza

- Prevention
  - Poultry outbreak:
    - Quarantine
    - Depopulation
    - Area surveillance
  - Workers:
    - PPE (gowns, gloves, frequent hand washing)
    - N95 mask
    - Prophylaxis
    - Vaccination with current influenza vaccine

Avian Influenza

- Prevention
  - Avian influenza should be treated in the same manner as SARS.

Avian Influenza

- Post-Exposure Prophylaxis
  - Household contacts of H5N1 patients should receive oseltamivir daily for 7-10 days.
  - Monitor temperature.
  - Quarantine.

Avian Influenza

Summary

Epidemiology

- Highly pathogenic H5N1 influenza viruses are now endemic in bird populations in Asia and spreading west.
- Sporadic human-to-human transmission has occurred raising likelihood of reassorting with coinfecting human influenza virus producing novel strain capable of human-to-human transmission.
- Predominance of children
- High mortality rate

Avian Influenza

Summary

- Clinical symptoms and diagnosis:
  - Fever
  - Pneumonia
  - Diarrhea
  - Encephalopathy
- Diagnosis made by laboratory tests

Avian Influenza

- Treatment
  - No outcome trials to date
    - Oseltamivir (Tamiflu) may be of benefit (75 mg BID x 7 days)
  - Optimal dose and duration unknown.
- Prevention
  - No licensed vaccines
  - Appropriate biosafety precautions
  - Isolation precautions similar to that for SARS

Avian Influenza

"Experts at the WHO and elsewhere believe that world is now closer to another influenza pandemic than at any time since 1968, when the last of the previous century's three pandemics occurred. WHO uses a series of six phases of pandemic alert as a system for informing the world of the seriousness of the threat and of the need to launch progressively more intense preparedness activities."

Avian Influenza

Inter-pandemic phase New virus in animals, no human cases	Low risk of human cases	1
	Higher risk of human cases	2
Pandemic alert New virus causes human cases	No or very limited human-to-human transmission	3
	Evidence of increased human-to-human transmission	4
	Evidence of significant human-to-human transmission	5
Pandemic	Efficient and sustained human-to-human transmission	6

WHO Pandemic Alert

http://www.who.int/csr/disease/avian_influenza/phase/en/index.html

Avian Influenza

Summary

- North America has avoided H5N1 because current infected migratory birds have not entered North American flyways.
- With increasing human-to-human transmission, foreign air travel places North America at increased risk.
- If the virus mutates or reassorts with human influenza virus—then we are definitely facing a pandemic.

Avian Influenza

Avian Influenza

- Resources:
  - WHO:
    - [http://www.who.int/csr/disease/avian_influenza/en/]
  - CDC:
    - [http://www.cdc.gov/flu/avian/]
  - NIAID:
    - [http://www3.niaid.nih.gov]

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