CLINICAL PRESENTATION AND MANAGEMENT OF HPAI

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Outline of Presentation

- Avian Influenza virus, reservoir, types: , HPAI, LPAI
- Avian Influenza : Clinical manifestation and treatment

2017

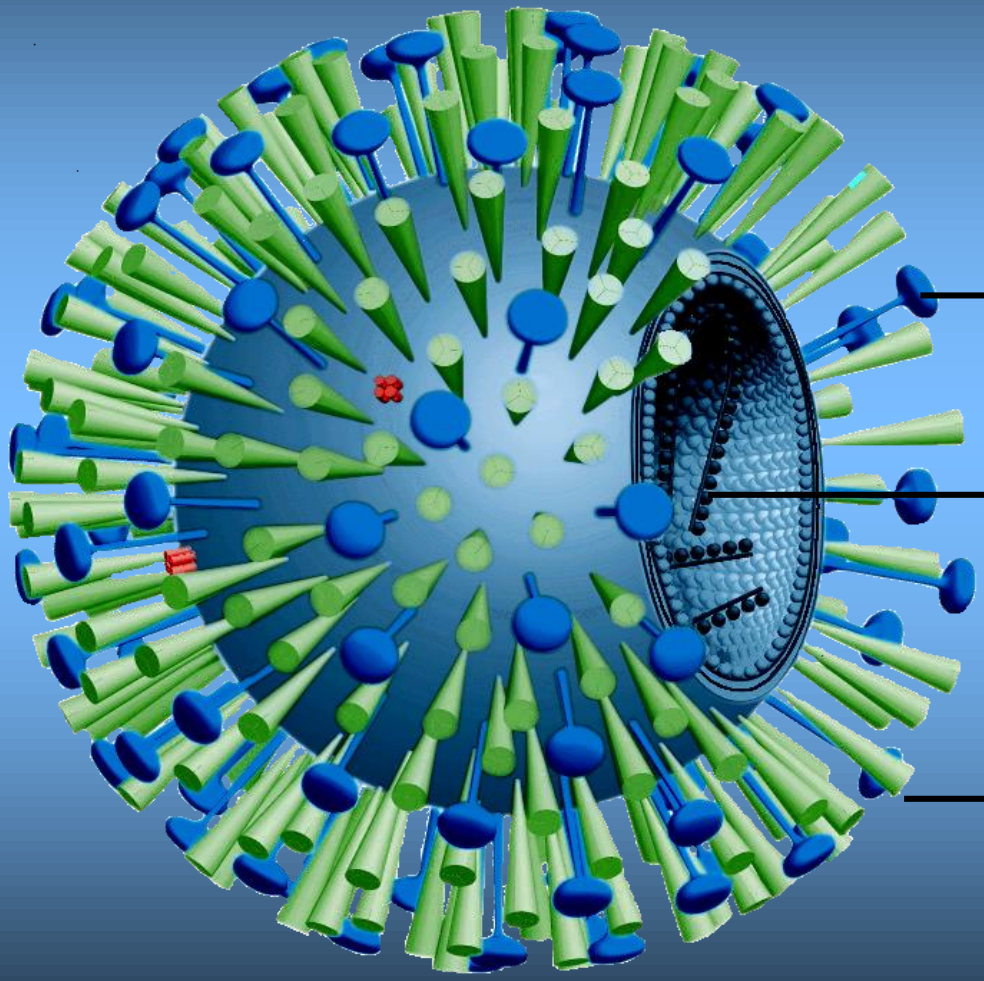

鶏
ROOSTER

FLU TERMS DEFINED

Avian (or bird) flu **is caused by influenza viruses that occur naturally among wild birds.**

- **The H5N1 variant is deadly to domestic fowl and can be transmitted from birds to humans.**
- **There is no human immunity and no vaccine is available.**

Structure of Influenza A virus



Orthomyxovirus

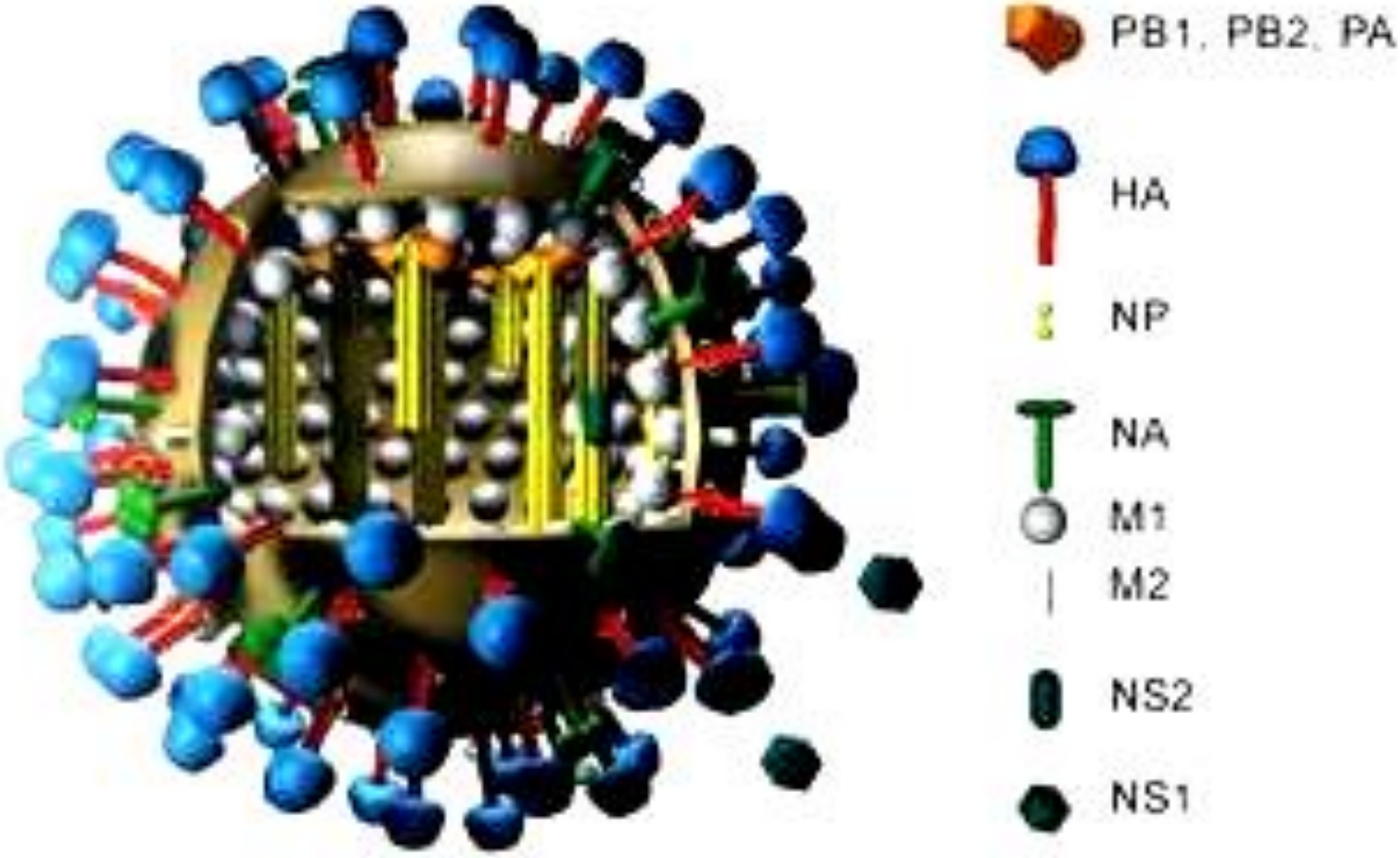
Neuraminidase

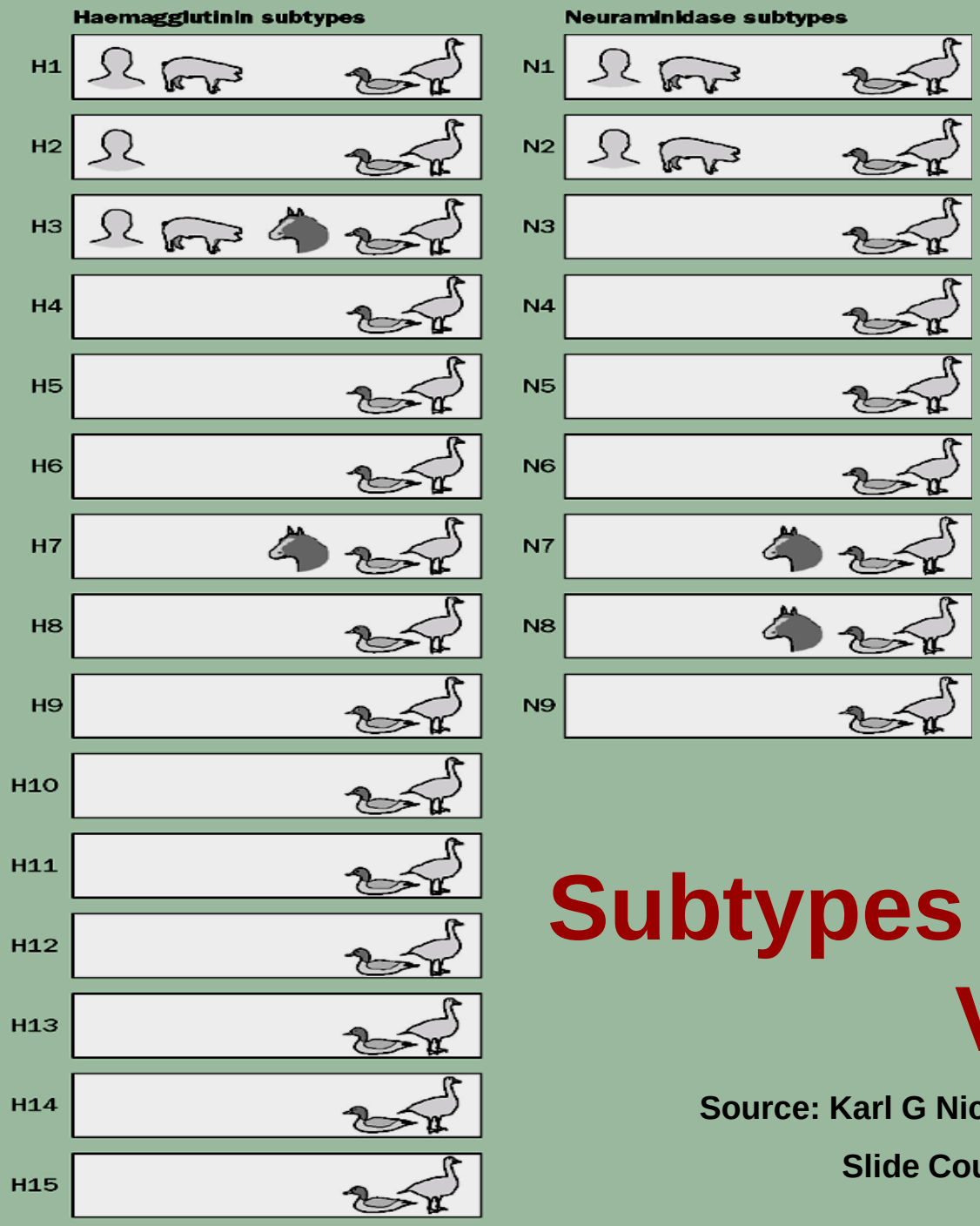
Viral RNA (segmented genome)

Haemagglutinin

from ROCHE Philippines

Structure of Influenza A virus





Subtypes of influenza A Virus in Birds

H1	N1
H2	N2
H3	N3
H4	N4
→ H5	N5
H6	N6
→ H7	N7
H8	N8
→ H9	N9
H10	
H11	
H12	
H13	
H14	
H15	

Subtypes of Influenza A Virus

Source: Karl G Nicholson, et al Lancet 2003; 362: 1733-45

Slide Courtesy of Dr. Jean-Marc J. Olivé of WHO

Currently Circulating INFLUENZA VIRUSES

1) H1N1 = **Swine Flu**
2) H2N2
3) H3N2 =Seasonal flu
4) H5N1 = **Bird Flu**
5) H7N9
6) H5N6

TYPE A

7) TYPE - B

INFLUENZA

- **Currently, influenza A viruses are categorized into 18 hemagglutinin (HA) subtypes (H1 to H16 from wild waterfowl, and H17 and H18 from bats)**

and

- **11 neuraminidase (NA) subtypes (N1 to N9 from wild waterfowl, and N10 and N11 from bats)**

Hye Kwon Kim, Dae Gwin Jeong, Sun-Woo Yoon. Recent outbreaks of highly pathogenic avian influenza viruses in South Korea. Clin Exp Vaccine Res 2017;6:95-103

INFLUENZA

Influenzas do not just pop out of bowhere – they jumble their genes up , mixing one avian or swine flu with another to form something new and potentially dangerous”

The Year of the Flu. Laurie Garrett . February 14, 2015

Avian Influenza (AI) Virus

- **Wild birds** worldwide carry the viruses in their intestines but usually do not get sick from them
- **However** it is very contagious among birds and can kill domesticated birds like chickens, ducks and turkeys

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Avian Influenza (AI) Virus

- **Aquatic birds are the primary natural reservoir for most subtypes of influenza A viruses.**
- **Most cause asymptomatic or mild infection in birds, where the range of symptoms depends on the virus properties.**

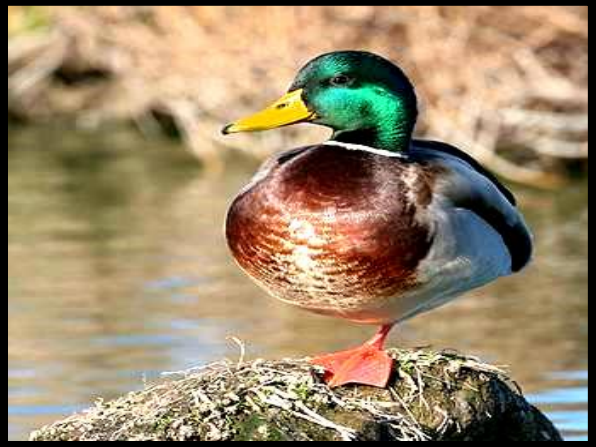
TYPES OF H5N1

- **HPAI H5N1, often referred to as the "Asian" H5N1, is the type causing worldwide concern.**

- **LPAI H5N1, often referred to as the "North American" H5N1, is of less concern.**

LPAI H5N1 ("North American" H5N1)

- 1975 – wild mallard duck and a wild blue goose (Wisconsin)
- 1981 and 1985 – sentinel ducks (the University of Minnesota)
- 1983 – ring-billed gulls (Pennsylvania)
- 1986 - wild mallard duck (Ohio)
- 2002 – turkeys (Michigan)
- 2005 - ducks (Manitoba, Canada)
- 2006 – mute swans (Michigan)




www.galleryofbirds.com

AVIAN INFLUENZA "BIRD FLU"

(Clinical Manifestation and Treatment)

AVIAN INFLUENZA

- **Highly Pathogenic or "high path" avian influenza (HPAI)**
  - **is often fatal in chickens and turkeys.**
  - **spreads rapidly and has a high death rate in birds than LPAI.**
  - **has been detected and eradicated three times in U.S. domestic poultry.**
  - **HPAI H5N1 is the subtype rapidly spreading in some parts of the world.**

www.usda.gov

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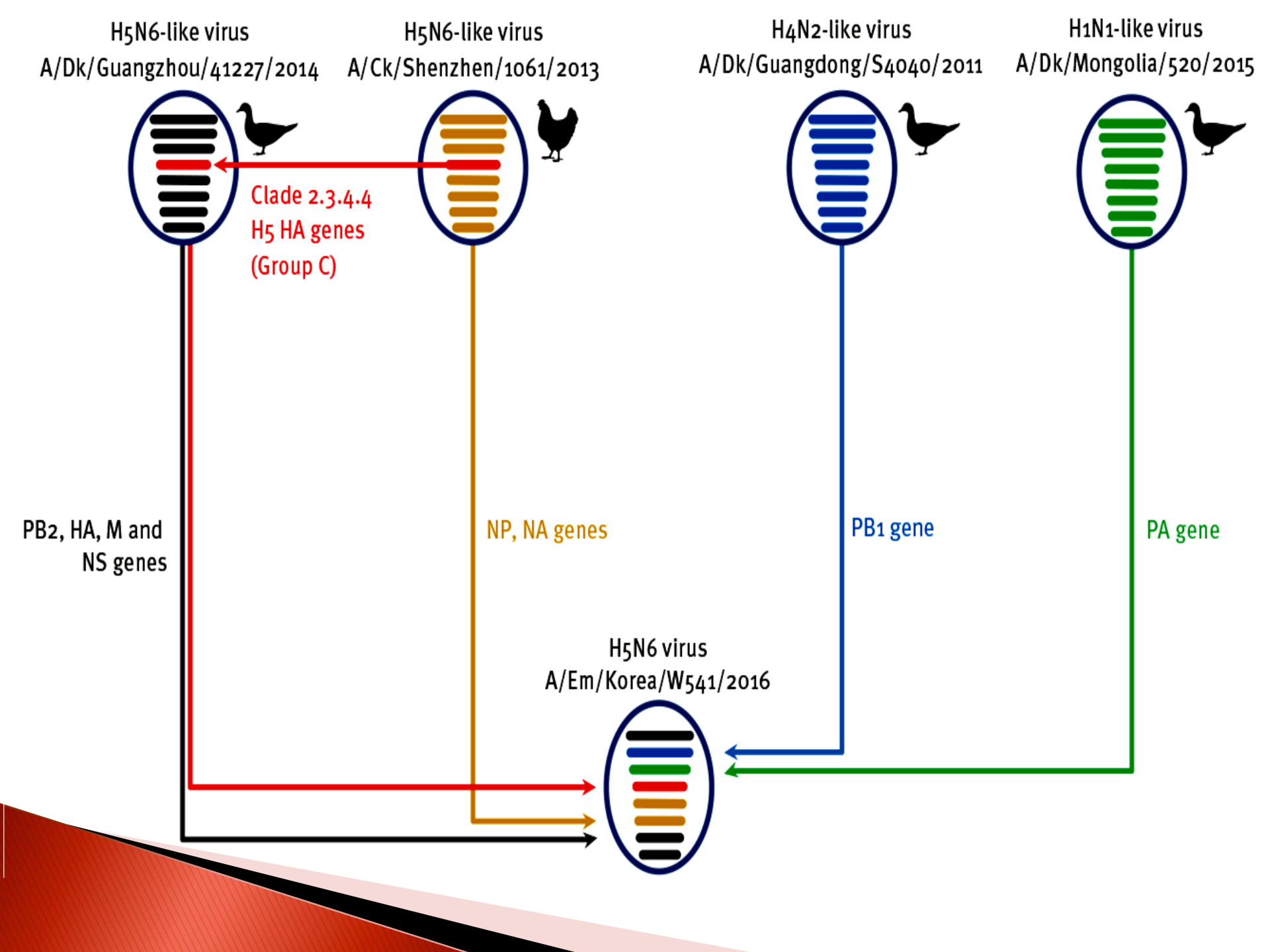
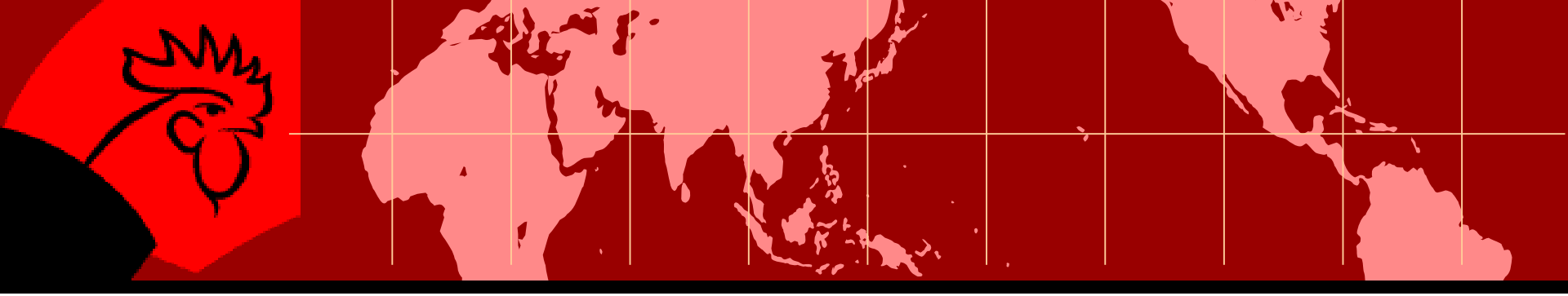
AVIAN INFLUENZA

- **Low Pathogenic or "low path" avian influenza (LPAI)**
  - **LPAI occurs naturally in wild birds and can spread to domestic birds.**
  - **In most cases it causes no signs of infection or only minor symptoms in birds.**
  - **These strains of the disease pose little significant threat to human health.**
  - **These strains are common in the U.S. and around the world.**

www.usda.gov


H5N6


H5N6-like virus
A/Dk/Guangzhou/41227/2014
H5N6-like virus
A/Ck/Shenzhen/1061/2013
H4N2-like virus
A/Dk/Guangdong/S4040/2011
H1N1-like virus
A/Dk/Mongolia/520/2015
Clade 2.3.4.4
H5 HA genes
(Group C)
PB2, HA, M and
NS genes
NP, NA genes
PB1 gene
PA gene
H5N6 virus
A/Em/Korea/W541/2016



- **The H5N6 HPAIVs were first reported in China in 2013, which disseminated not only within China but also in Vietnam and Laos.**
- **While the first Chinese H5N6 viruses were novel reassortants of NA from the H6N6 viruses and seven other genes from H5N1 viruses, the Korean H5N6 HPAIVs were novel reassortants of Chinese H5N6 viruses and Eurasian low pathogenicity AI viruses of wild birds**

DEPARTMENT OF HEALTH
RESEARCH INSTITUTE FOR TROPICAL MEDICINE

H5N6

Brief Epidemiological and Clinical Information

Surveillance and Response Unit
Research Institute for Tropical Medicine
August 24, 2017

Highly Pathogenic Avian Influenza

- Consist of H5N1, H5N2, H5N6, and H5N8
- H5N6 was first isolated in mallards in 1975
- In March 2015, an outbreak of influenza A(H5N6) infected 457 birds in Laos, 960 birds in Vietnam, and >20,000 birds in China
- November 2016 – Japan, South Korea
- February 2017 – Taiwan

Source: Shen, H et al. Influenza A(H5N6) Virus Reassortant, Southern China, 2014 Emerg Infect Dis. 21(7):1261-1262.

H5N6 in humans

May 7, 2014

- **First reported case of the H5N6 virus in humans in the world**
- **Death of a man in Sichuan Province, China**
- **Exposure to infected poultry**

Source: http://www.wpro.who.int/china/mediacentre/releases/2014/20140507/en/

H5N6 in humans

- **<20 cases have been confirmed, all from China**
- **Last reported case in December 2016**
- **Severe disease presentation in human cases**
- **75% CFR**
- **Close contacts of patients - none have developed any symptoms of influenza-like illness**

Source: Jiang, H.et al. Preliminary epidemiologic assessment of human infections with highly pathogenic avian influenza A(H5N6) virus, China. Infectious Diseases Society of America 2017

H5N6 in humans

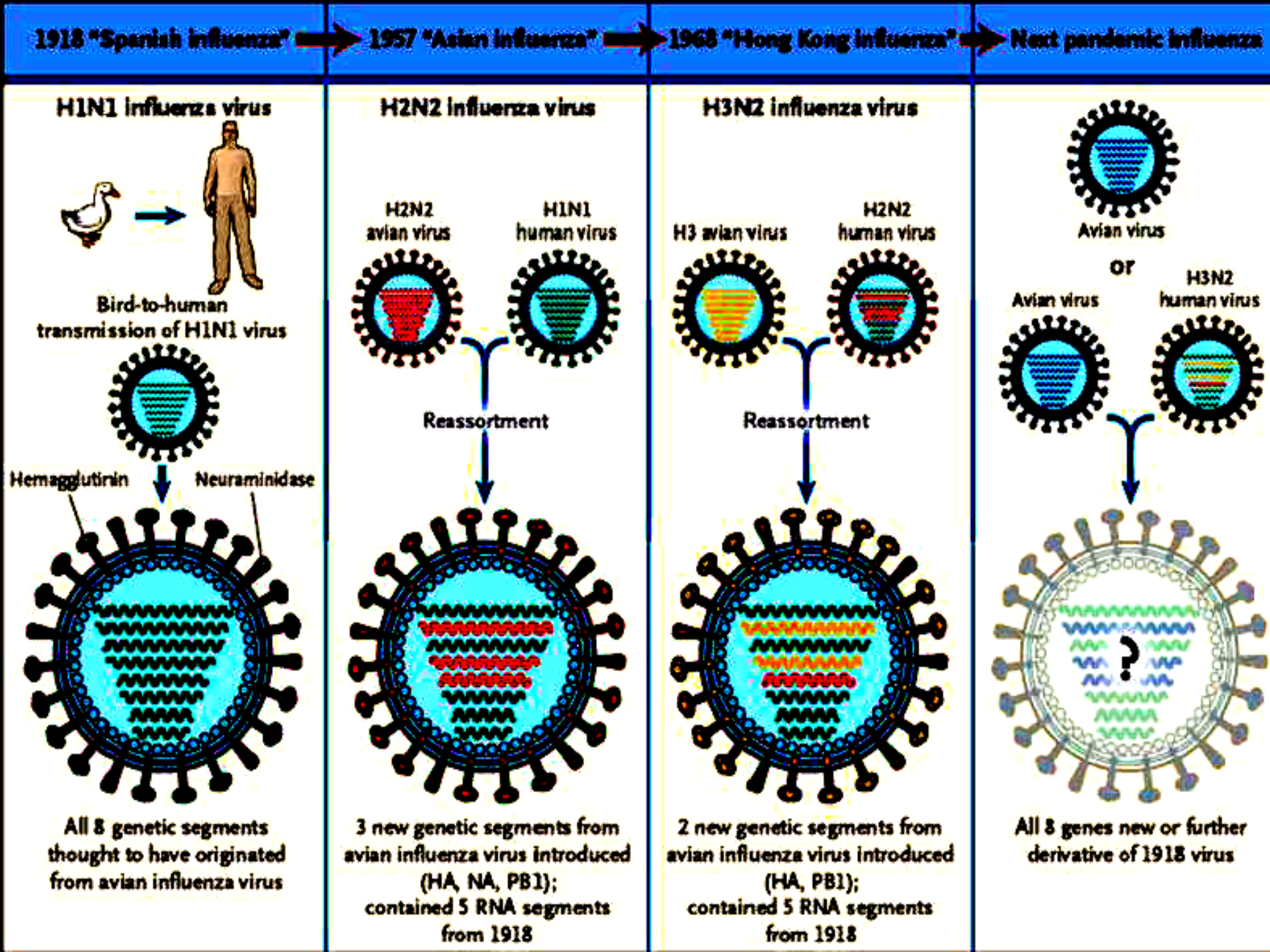
- Sporadic cases of human respiratory illness with high mortality from infections
- Most human infections with HPAI H5N6 viruses have occurred in persons not using appropriate PPE who had exposures consisting of either

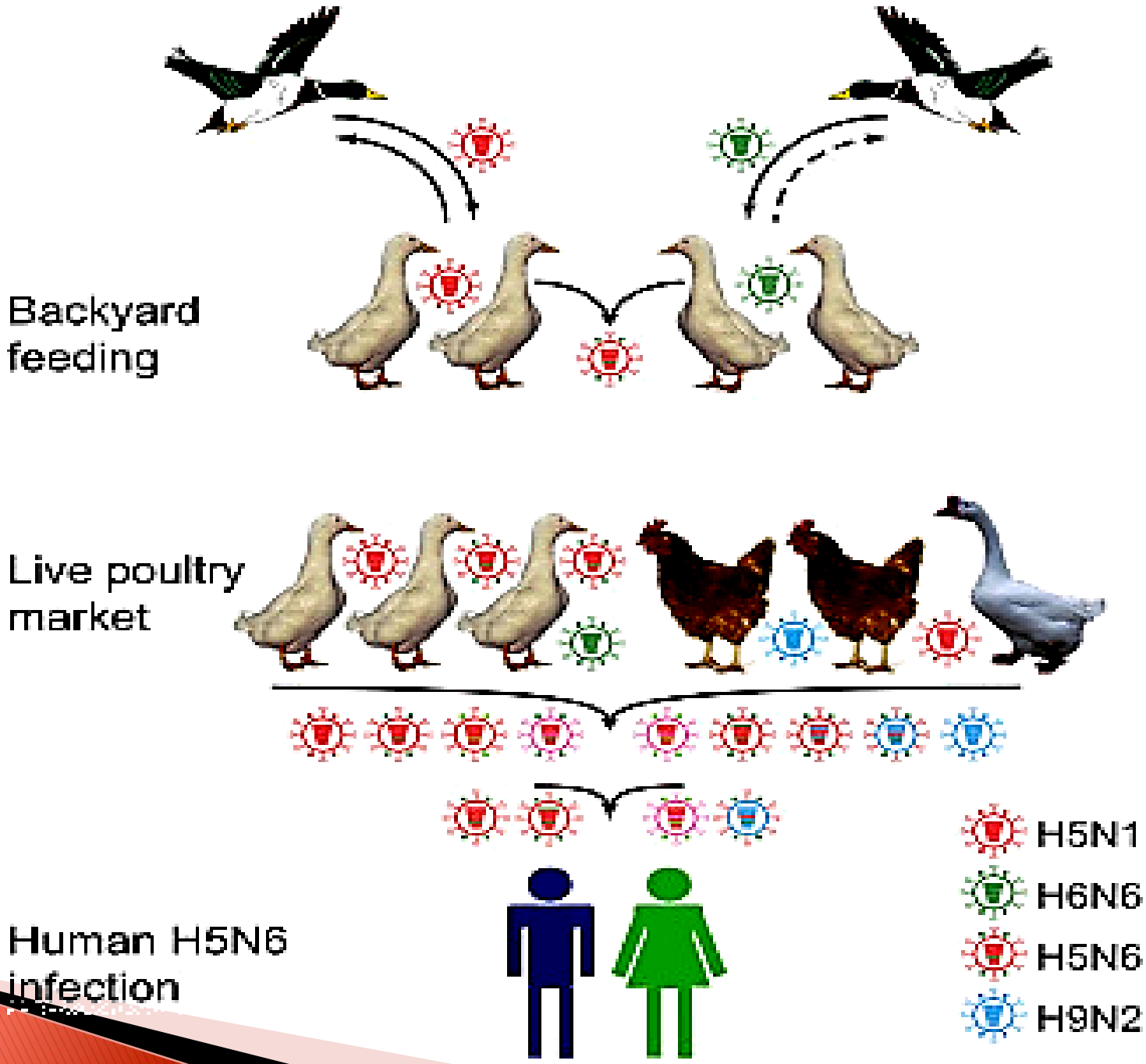
  1) direct physical contact with infected birds or surfaces contaminated by the viruses;

  2) being in close proximity (e.g., within about 6 feet) to infected birds; or

  3) visiting a live poultry market

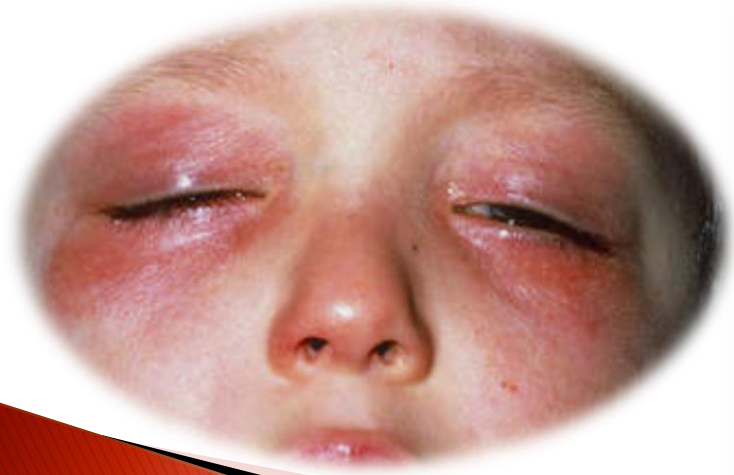
Source: https://www.cdc.gov/flu/avianflu/hpai/hpai-background-clinical-illness.htm

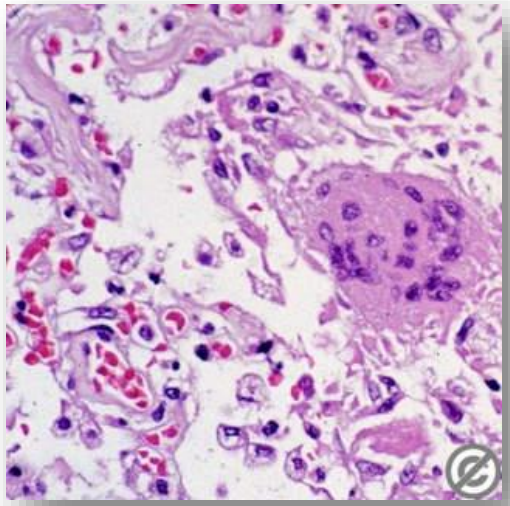

1918 "Spanish influenza"
1957 "Asian influenza"
1968 "Hong Kong influenza"
Next pandemic influenza
H1N1 influenza virus
Bird-to-human transmission of H1N1 virus
Hemagglutinin
Neuraminidase
All 8 genetic segments thought to have originated from avian influenza virus
H2N2 influenza virus
H2N2 avian virus
H1N1 human virus
Reassortment
3 new genetic segments from avian influenza virus introduced (HA, NA, PB1); contained 5 RNA segments from 1918
H3N2 influenza virus
H3 avian virus
H2N2 human virus
Reassortment
2 new genetic segments from avian influenza virus introduced (HA, PB1); contained 5 RNA segments from 1918
Avian virus
or
Avian virus
H3N2 human virus
?
All 8 genes new or further derivative of 1918 virus

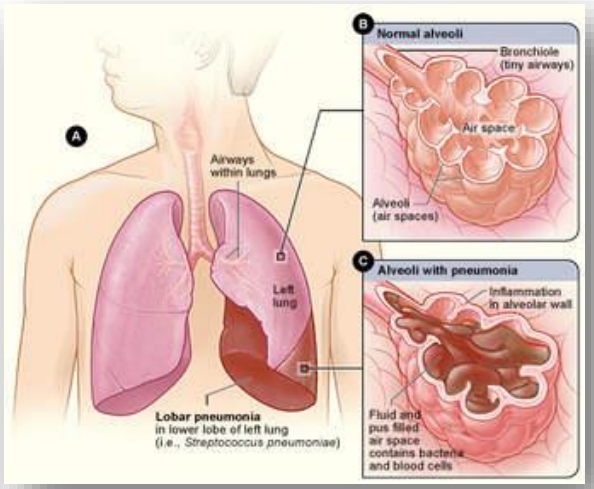

Backyard feeding
Live poultry market
Human H5N6 infection
H5N1
H6N6
H5N6
H9N2

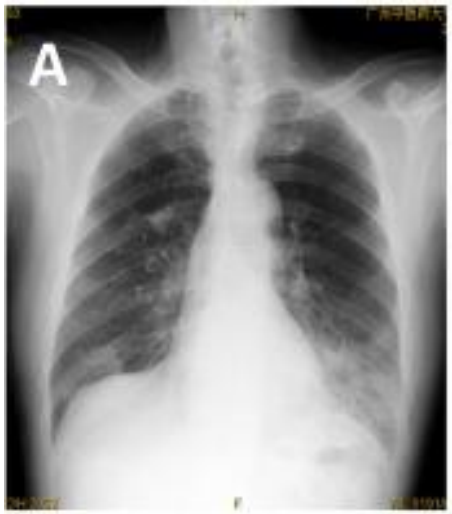
AVIAN FLU

- **Avian and other zoonotic influenza infections in humans may cause disease ranging from <u>mild conjunctivitis to severe pneumonia and even death</u>.**









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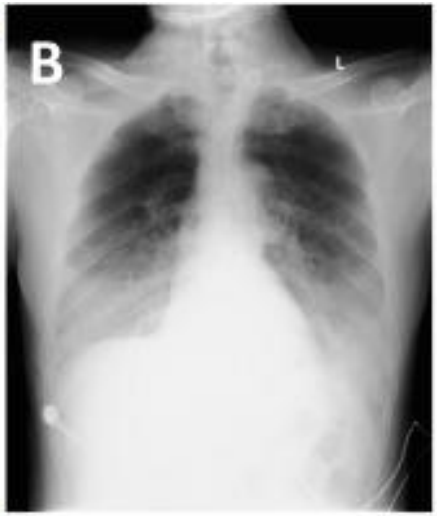

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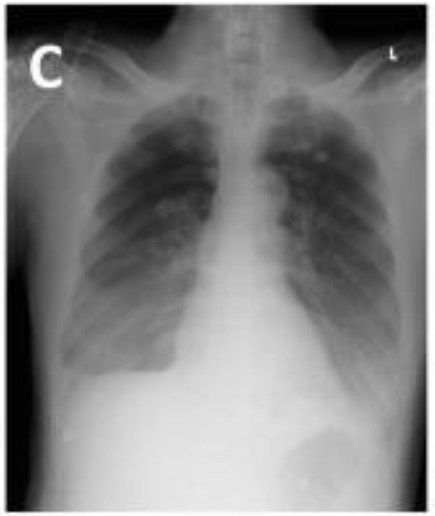

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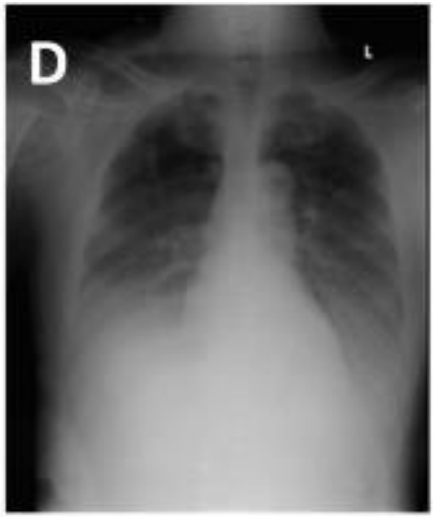

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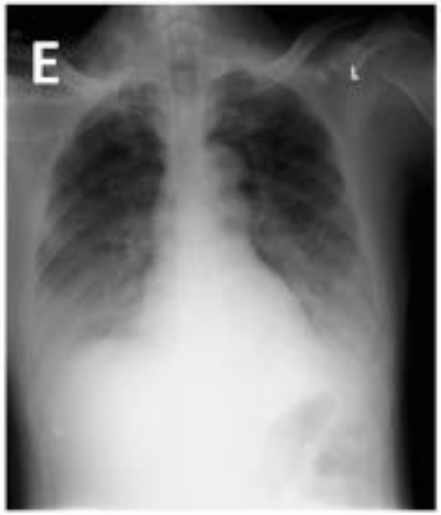

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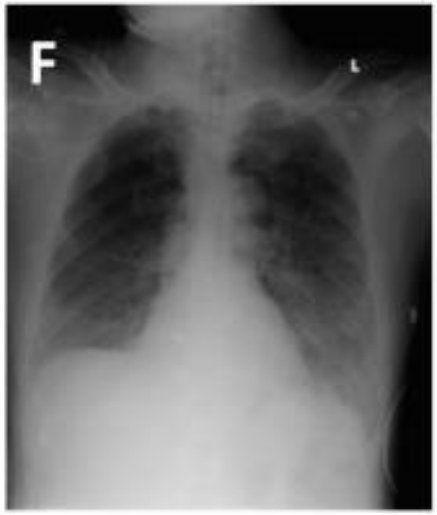

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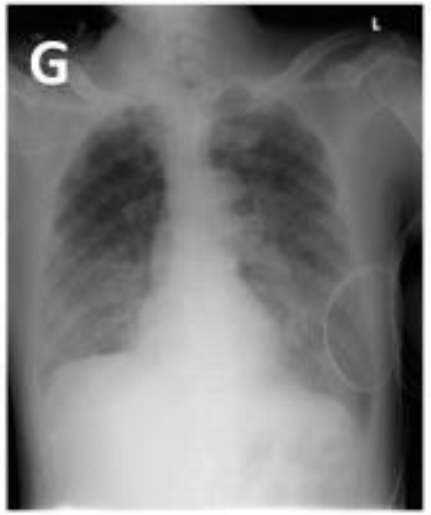

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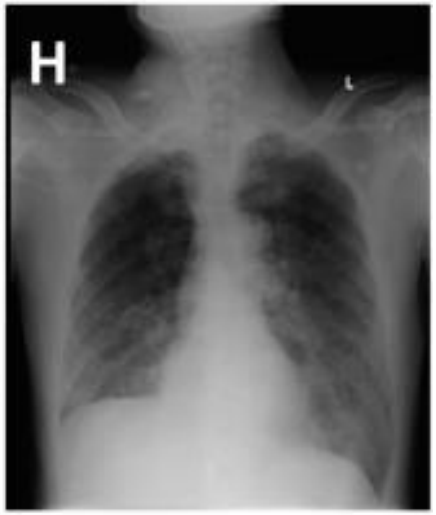

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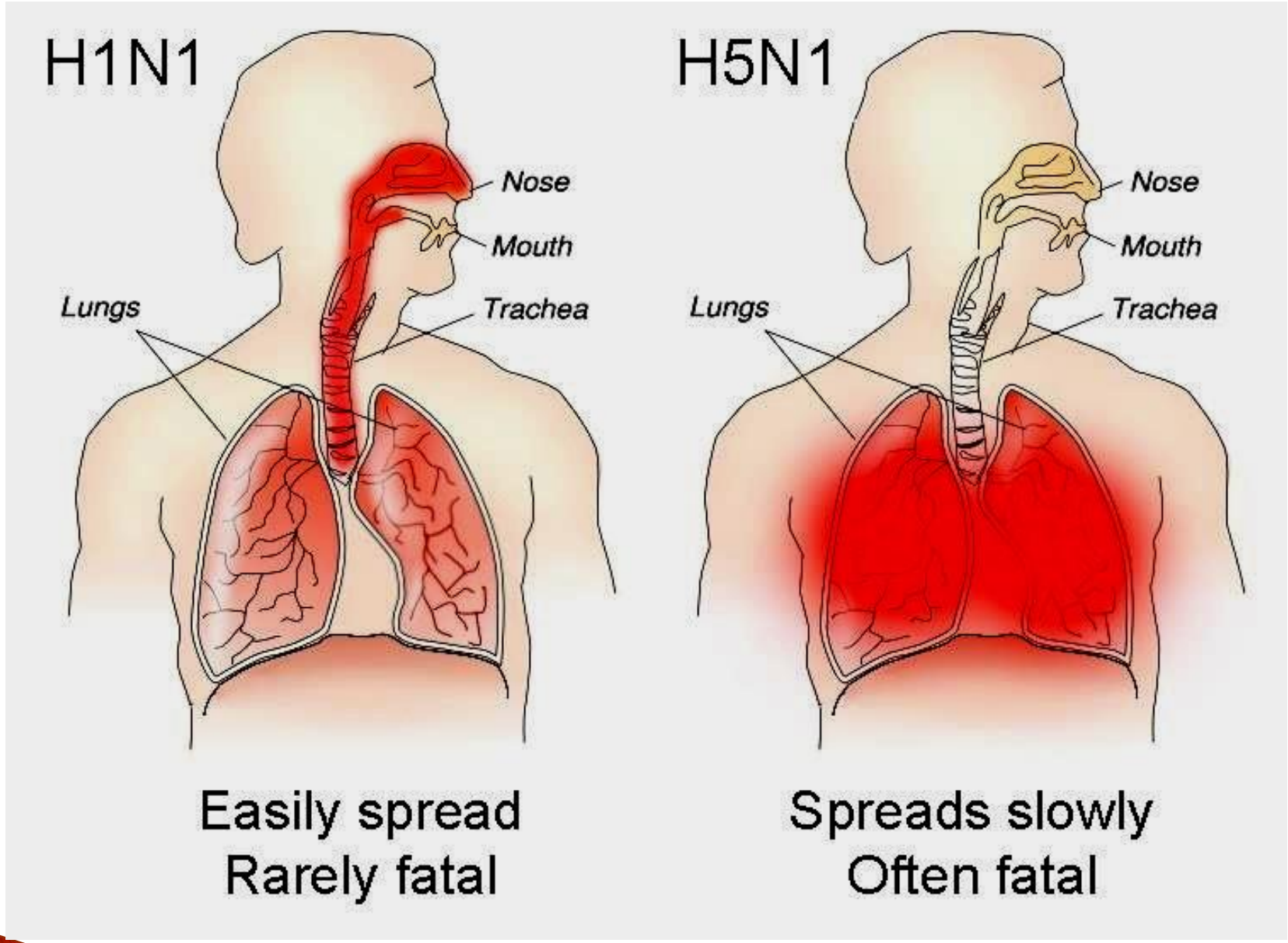

H1N1
Nose
Mouth
Lungs
Trachea
H5N1
Nose
Mouth
Lungs
Trachea
Easily spread
Rarely fatal
Spreads slowly
Often fatal

How to recognize a sick bird?

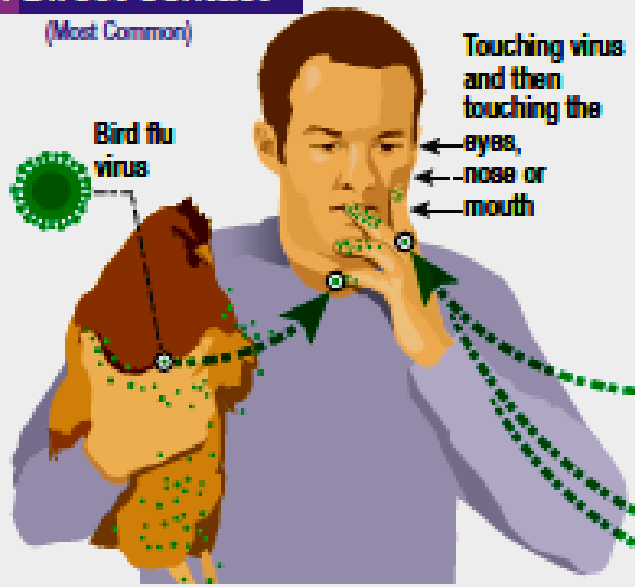

Signs of a Sick Bird
Legs swell
Sneezing, cough, nasal discharge, fever, weakness, diarrhoea, lost of appetite, swelling, excessive thirst
Crown and wattle turn purple
Ruffled feathers
Sudden death

How Infected Backyard Poultry Could Spread Bird Flu to People

Human Infections with Bird Flu Viruses Rare But Possible

1 Direct Contact

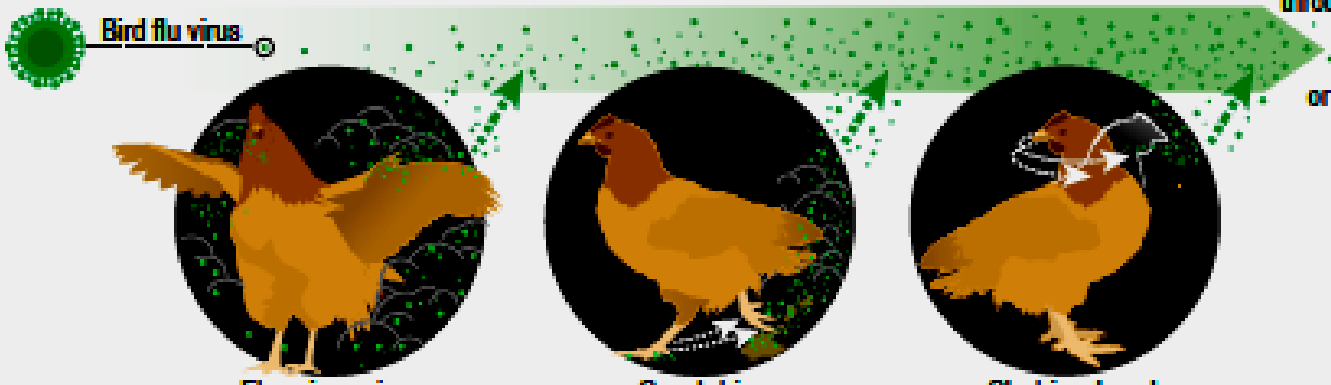
(Most Common)

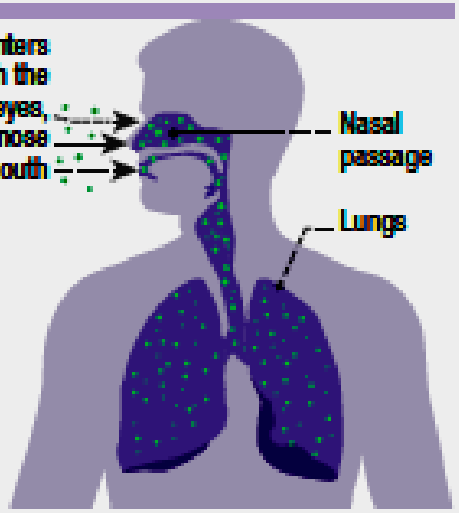


Infection can occur without touching poultry.

2 Contaminated Surfaces

3 Bird Flu Virus in the Air (in Droplets or Dust)





U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

www.cdc.gov/flu/avianflu/avian-in-humans.htm

Clinical Manifestations of Avian Influenza (HPAI) in Human

Exposure

Recovery In 30-50% of cases

Incubation Period	Prodromal Stage	Lower Respiratory Stage
3 days, range 2-4 days	0-1 days High fever (above 38°C), cough and shortness of breath	1-7 days dyspnea, crackles Rapid progress to respiratory distress -> Respiratory failure

Death inspite of ventilator Support after about 10 days

Clinical Manifestation of Human Avian Flu infection

- You may have an AI infection if you experience typical flu-like symptoms such as:
  - cough
  - diarrhea
  - respiratory difficulties
  - fever (over 100.4°F or 38°C)
  - headache
  - muscle aches
  - malaise
  - runny nose
  - sore throat

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Incubation Period of Human Avian Influenza (AI) Infections

- After exposure to infected poultry, the incubation period generally appears to be 7 days or less, and in many cases this period is 2 to 5 days.
- In clusters in which limited, human-to-human transmission has probably occurred, the incubation period appears to be approximately 3 to 5 days, although in one cluster it was estimated to be 8 to 9 days.

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Epidemiology of Human Avian Influenza (AI) Infections

- median age of patients = 18 years
- The overall case fatality proportion is 61%
  - highest among persons 10 to 19 years of age
  - Lowest among persons 50 years of age or older
- Most patients with influenza A (H5N1) virus infection were previously healthy
- Increases cases of influenza A (H5N1) have been observed during cooler months in association with increases in outbreaks among poultry

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Pathological Findings

Limited Autopsy Findings:

- **diffuse alveolar damage with hyaline membrane formation, patchy interstitial lymphoplasmacytic infiltrates, bronchiolitis with squamous metaplasia, and pulmonary congestion with varying degrees of hemorrhage**
- **Acute exudative, diffuse alveolar damage with macrophages, neutrophils, and activated lymphocytes**
- **Apoptosis in alveolar cells and infiltrating leukocytes are prominent findings.**

Pathological Findings

Limited Autopsy Findings:

- **Lymphocyte depletion occurs in the spleen, lymph nodes, and tonsils**
- **histiocytic hyperplasia and reactive hemophagocytosis presumably result from host cytokine responses and viral infection**
- **Edema and degeneration of myocytes in the heart and extensive acute tubular necrosis in the kidney**

Update on Avian Influenza A (H5N1) Virus Infection in Humans

Table 1. Case Fatality Proportion According to Clade or Subclade and Median Time from Onset of Illness to Hospitalization or Death in Patients with Confirmed Influenza A (H5N1) Illness.

Country	Predominant Clade or Subclade*	Case Fatality Proportion	Onset of Illness to Hospitalization		Onset of Illness to Death	
		no. of patients/ total no. (%)	*days*	*no. of patients*	*days*	*no. of patients*
Cambodia, Thailand, Vietnam†	1	66/123 (54)	4	109	9	65
Indonesia	2.1	76/96 (79)	5	64	9	72
Azerbaijan, Djibouti, Egypt, Iraq, Nigeria, Turkey	2.2	26/59 (44)	3	36	9	24
China, Laos	2.3	17/26 (65)	5	16	10	17

* The presumed clade or subclade assignment is based on the known geographic distribution of the viruses and is not verified by individual patient data. Few sequences are available for human isolates in the public database for some countries. Multiple clades and subclades have circulated in China in poultry. The numbers of patients for whom data were available are listed. The analysis was provided by Dr. Christoph Steffen and Dr. Julia Fitzner, WHO, Geneva.

† Among 61 patients with documented clade 1 infection, the case fatality proportion was 75%; the median time from the onset of illness to hospitalization was 5 days in 48 patients, and the median time from the onset of illness to death was 9 days in 46 patients.

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Table 2. Clinical and Common Laboratory Features of Influenza A (H5N1) Disease at Hospital Admission.*

Variable	Vietnam, Thailand, Cambodia, 2004–2005, Clade 1†	Indonesia, 2005–2006, Clade 2.1‡	China, 2005–2006, Clade 2.3§	Egypt, 2006–2007, Clade 2.2¶	Turkey, Azerbaijan, 2006, Clade 2.2‖
Age — yr					
Median	14–22	18.5	30	12.5	16.5–10.0
Range	2–58	1.5–45.0	12–41	1–75	5–20
Male sex — no./total no. (%)	19/41 (46)	33/54 (61)	3/8 (38)	12/38 (32)	9/16 (56)
Contact with poultry within previous 2 weeks — no./total no. (%)	31/36 (86)	41/54 (76)	8/8 (100)**	31/38 (82)	8/8 (100)††
Time from onset of symptoms to hospitalization — days					
Median	6–8	5	6	3	5–6
Range	3–8	1–14	3–11	0–14	1–12

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358 (3): 261, Figure 1 January 17, 2008

Clinical presentation — no./ total no. (%)					
Fever	41/41 (100)	54/54 (100)	8/8 (100)	34/38 (89)	15/16 (94)
Dyspnea	33/37 (89)	51/54 (94)	4/8 (50)	14/38 (37)	7/16 (44)
Cough	40/41 (98)	50/54 (93)	7/8 (88)	27/38 (71)	12/15 (80)
Pneumonia	41/41 (100)	54/54 (100)	8/8 (100)	23/38 (61)‡‡	14/16 (88)
Coryza	9/27 (33)	NR	NR	NR	2/14 (14)
Sore throat	13/41 (32)	NR	NR	26/38 (68)	14/16 (88)
Vomiting	5/31 (16)	6/54 (11)	NR	3/37 (8)	0/7 (0)
Diarrhea	16/31 (52)	6/54 (11)	NR	2/37 (5)	4/14 (29)
Depressed consciousness	NR	NR	NR	3/38 (8)	4/8 (50)
Seizures	NR	1/54 (2)	NR	NR	2/7 (29)
Headache	5/14 (36)	7/54 (13)	NR	19/38 (50)	7/15 (47)
Conjunctivitis	0/22 (0)	NR	NR	14/38 (37)	1/8 (12)
Myalgia	11/37(30)	7/54 (13)	NR	17/38 (45)	4/15 (27)
Leukopenia	17/22 (77)	41/49 (84)	NR	10/37 (27)	11/15 (73)
Lymphopenia	16/24 (67)	16/29 (55)	NR	4/25 (16)	7/13 (54)
Thrombocytopenia	13/24 (54)	29/45 (64)	NR	8/26 (31)	9/13 (69)
Increased aminotransferase levels	20/28 (71)	NR	NR	15/27 (56)	6/8 (75)
Deaths — no./ total no. (%)	32/41 (78)	41/54 (76)	7/8 (88)	15/38 (39)	9/16 (56)
Time from onset of symptoms to death — days					
Median	8–12	9	9	11.5	10–13
Range	4–30	5–19	8–19	6–32	9–17

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Update on Avian Influenza A (H5N1) Virus Infection in Humans

Table 3. Initial Diagnosis in Patients with Confirmed Influenza A (H5N1) Virus Infection.*

Diagnosis	Indonesia (N=52)	Thailand (N=25)
	number (percent)	
Pneumonia	24 (46)	11 (44)
Dengue virus infection	6 (12)	4 (16)
Typhoid fever	2 (4)	0 (0)
Upper respiratory illness	14 (27)	4 (16)
Avian influenza	6 (12)	2 (8)
Other	0 (0)	4 (16)†

* Data are from Chotpitayasunondh T and Soeroso S (unpublished data).
† Tuberculosis was diagnosed in one patient, diarrhea in one patient, dizziness in one patient, and leptospirosis in one patient.

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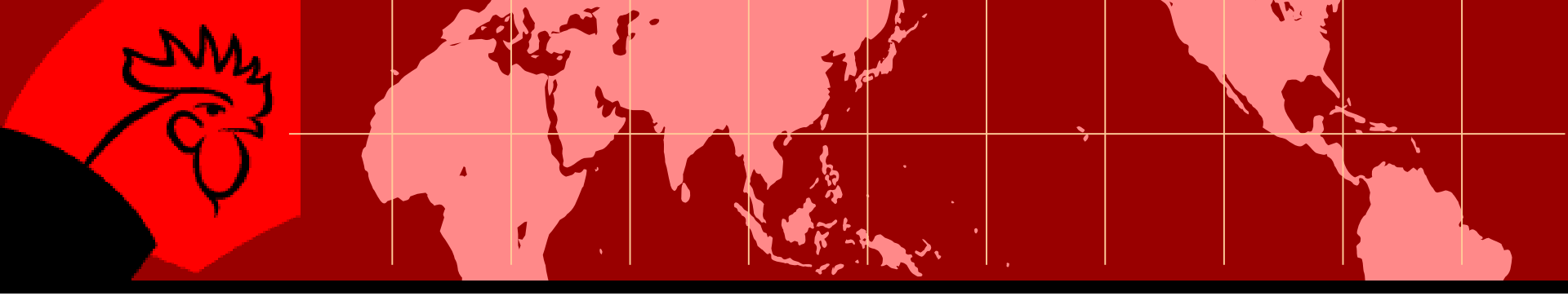

Current Treatment Against Avian Influenza A (H5N1) in Humans

Treatment of AI

M2 Inhibitors

- **Clade 1 viruses and most clade 2 viruses from Indonesia are fully resistant to M2 inhibitors**

- **Clade 2 viruses from the lineages in other parts of Eurasia and Africa are usually susceptible**

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Treatment of AI

Neuraminidase Inhibitors

- **Clade 1 viruses - enhanced susceptibility to oseltamivir carboxylate, but the high-level replication of some oseltamivir-susceptible strains requires higher doses or more prolonged administration, or both, in animal models**

- **Clade 1 viruses - 15 to 30 times more sensitive to oseltamivir than clade 2 isolates from Indonesia and Turkey**

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All persons exposed to infected chickens or to farms under suspicion:

- **It is recommended that oseltamivir be readily available for the treatment of suspected H5N1 respiratory infections in cullers & farm workers involved in the mass culling.**

  – **Oseltamivir phosphate (Tamiflu®) 75 mg capsule BID, for 5 days)**

WHO interim recommendations for the protection of persons involved in the mass slaughter of animals potentially infected with highly pathogenic avian influenza virus (January 26, 2004)

ANTIVIRAL AGENTS

- **ADULT: Oseltamivir 75 mg BID for 5 days**
- **CHILDREN : weight-adjusted BID doses for 5 days in children > 1 year of age**
  - **15kg or less = 30mg BID**
  - **15-23kg = 45mg BID**
  - **23-40kg = 60mg BID**
  - **>40kg = 75mg BID**

Avian Influenza A (H5N1) Infection in Humans. Influenza. N Engl J Med 2005; 353:1374-1385

ANTIVIRAL AGENTS

Table 1. Dosing Schedule of Neuraminidase Inhibitors for the Treatment and Prevention of Influenza, According to Patient's Age and Coexisting Illnesses.*

Antiviral Drug	Recommended Dose According to Age				Coexisting Illness	
	1–6 yr	7–12 yr	13–64 yr	≥65 yr	Renal Disease	Hepatic Disease
Treatment						
Zanamivir	NA	10 mg (equivalent to 2 inhalations) twice daily for 5 days	10 mg (equivalent to 2 inhalations) twice daily for 5 days	10 mg (equivalent to 2 inhalations) twice daily for 5 days	10 mg (equivalent to 2 inhalations) twice daily for 5 days	—
Oseltamivir	Weight <15 kg: 30 mg twice daily for 5 days; 15–23 kg: 45 mg twice daily for 5 days; >23–40 kg: 60 mg twice daily for 5 days; >40 kg: 75 mg twice daily for 5 days	Weight <15 kg: 30 mg twice daily for 5 days; 15–23 kg: 45 mg twice daily for 5 days; >23–40 kg: 60 mg twice daily for 5 days; >40 kg: 75 mg twice daily for 5 days	75 mg twice daily for 5 days	75 mg twice daily for 5 days	For adults, reduce dose if creatinine clearance is ≤30 ml/min; if creatinine clearance is 10–30 ml/min, 75 mg once daily†	Not evaluated
Prevention						
Oseltamivir	NA	NA	75 mg once daily for >7 days (up to 6 wk)	75 mg once daily for >7 days (up to 6 wk)	If creatinine clearance is 10–30 ml/min, 75 mg every other day†	Not evaluated

* The doses listed are those currently approved in the United States. NA denotes not applicable.
† No regimen is available for patients with end-stage renal disease.

Moscona A. Neuraminidase Inhibitors for Influenza. N Engl J Med 2005; 353:1363-1373

Treatment of AI

- A higher dose of oseltamivir

150 mg twice daily in adults and an increased duration of therapy, for a total of 10 days

- ***may be reasonable, given the high levels of replication of the influenza A (H5N1) virus, observations of progressive disease despite early administration of standard-dose oseltamivir (75 mg twice daily for 5 days in adults) within 1 to 3 days after the onset of the illness, and the proven safety of higher doses in adults with seasonal influenza, especially if there is pneumonic disease at presentation or evidence of clinical progression***

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Treatment of AI

- **Combination therapy among mouse models of amantadine-sensitive influenza A (H5N1) virus infection, significantly increased survival rates and inhibited viral replication in the internal organs.**
- **No adverse pharmacologic interactions have been shown in humans.**
- **In areas where influenza A (H5N1) viruses are likely to be susceptible to amantadine, combination treatment with oseltamivir would be reasonable, especially in seriously ill patients.**

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Other Treatment

- Supportive care
- correction of hypoxemia
- treatment of nosocomial complications remains fundamental in the management of influenza A (H5N1) disease
- immunomodulators – values remain to be determined.

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Other Treatment

- **Corticosteroids should not be used routinely.**
  - not been shown to be effective in patients with influenza A (H5N1) virus infection
  - can result in serious adverse events, including opportunistic infections such as central nervous system toxoplasmosis *(Soeroso S: unpublished data).*
- **In northern Vietnam, mortality was 59% among 29 recipients of corticosteroids, as compared with 24% among 38 persons who did not receive corticosteroids (P=0.004)** *(Cao T, Thanh Liem N: personal communication).*

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SUMMARY

- **Ongoing circulation of some avian influenza subtypes in poultry, such as A(H5) or A(H7N9) viruses, are of public health concern as these viruses commonly cause severe disease in humans and the viruses have the potential to mutate to become more transmissible between humans. .**

SUMMARY

- **To date, although human-to-human transmission of these viruses is thought to have occurred in some rare instances when there had been very close and prolonged contact between a very sick patient and caregivers such as family members, there has been no sustained human-to-human transmission.**

SUMMARY

- **If these viruses adapt or acquire certain genes from human viruses, they could trigger a pandemic.**

SUMMARY

- **Whether currently-circulating avian and other zoonotic influenza viruses will result in a future pandemic is UNKNOWN.**

- **However, the diversity of avian and other zoonotic influenza viruses that have caused human infections necessitates ongoing surveillance in both animal and human populations, detailed investigation of every human infection and risk-based pandemic planning.**


...Thank you for Listening