CIDRAP

Center for Infectious Disease Research & Policy

University of Minnesota

MCEIRS AVIAN INFLUENZA TRAINING

Individual Study Guide

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Avian Influenza: The Basics

Minnesota Center of Excellence for Influenza Research and Surveillance

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INTRODUCTION

AVIAN INFLUENZA: THE BASICS

This course will reveal how avian influenza (AI) is making its footprint in the world and will enhance your understanding of how AI viruses evolve, adapt, and spread among animal populations, and from animals to humans. Viral structure, global migration patterns in wild birds, major outbreaks in domestic poultry, and clinical features of AI in birds are among the topics that will be addressed in this module.

LESSON 1: INFLUENZA VIRUSES

In this lesson, we will cover:

- Viral Structure
- Viral Nomenclature
- How Influenza Viruses Evolve

VIRAL STRUCTURE

The overall structure of the virus includes a lipid membrane that has three integral membrane proteins: hemagglutinin (HA), neuraminidase (NA), and the matrix 2 protein (M2). There is also a matrix 1 protein (M1) that serves as a bridge between the lipid membrane and the viral core (not shown in Figure 1 since it is not visible on the surface of the virus).

The HA protein appears as spikes on the lipid membrane and the NA protein forms globular structures that extend outward from the viral surface.

The HA protein is critical for pathogenesis; it contains the receptor for binding to the host cell and allows fusion of the virus membrane to the host cell membrane, which allows the viral contents to enter the host cell. Cleavage of the HA protein is essential for fusion to occur; this happens at the proteolytic cleavage site (PCS). The PCS is the primary virulence factor for AI viruses; alterations at this site affect pathogenesis.

The NA protein also is important in pathogenicity.

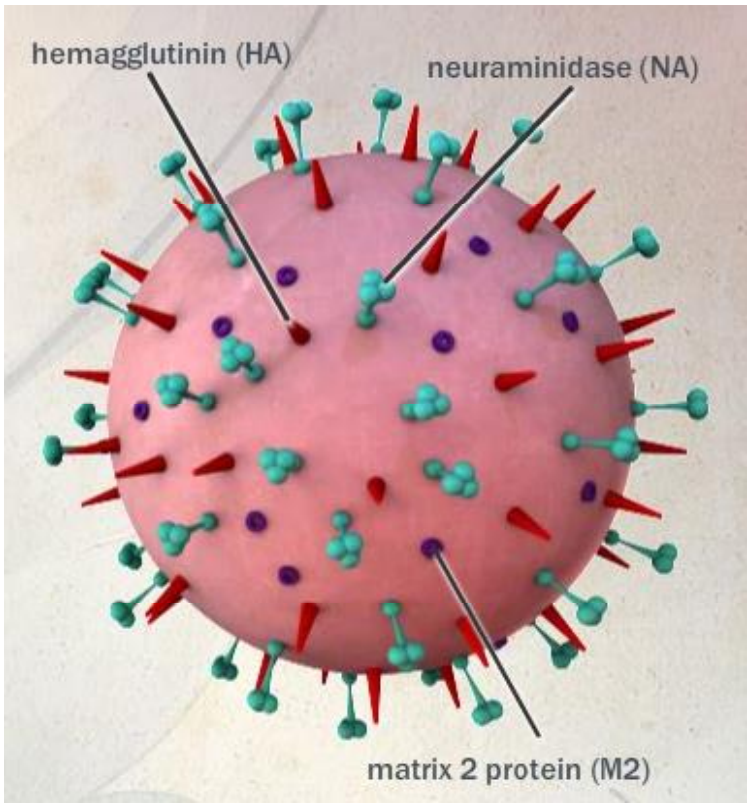


Figure 1: Virus Structure

The lipid membrane surrounds the nucleocapsid, which contains 8 different segments of negative-sense single-stranded RNA. Each segment of RNA is part of a ribonucleoprotein complex that contains the RNA segment, three polymerase proteins, and the nucleoprotein.

The 8 RNA segments code for a total of 10 genes.

The 8 RNA segments are shown in Figure 2 below and include:

- PB1 (codes for basic polymerase 1 protein)
- PB2 (codes for basic polymerase 2 protein)
- PA (codes for acidic polymerase protein)
- HA (codes for the hemagglutinin glycoprotein)
- NA (codes for the neuraminidase glycoprotein)
- NP (codes for the nucleoprotein)
- M (codes for matrix proteins 1 and 2)
- NS (codes for non-structural proteins 1 and 2)

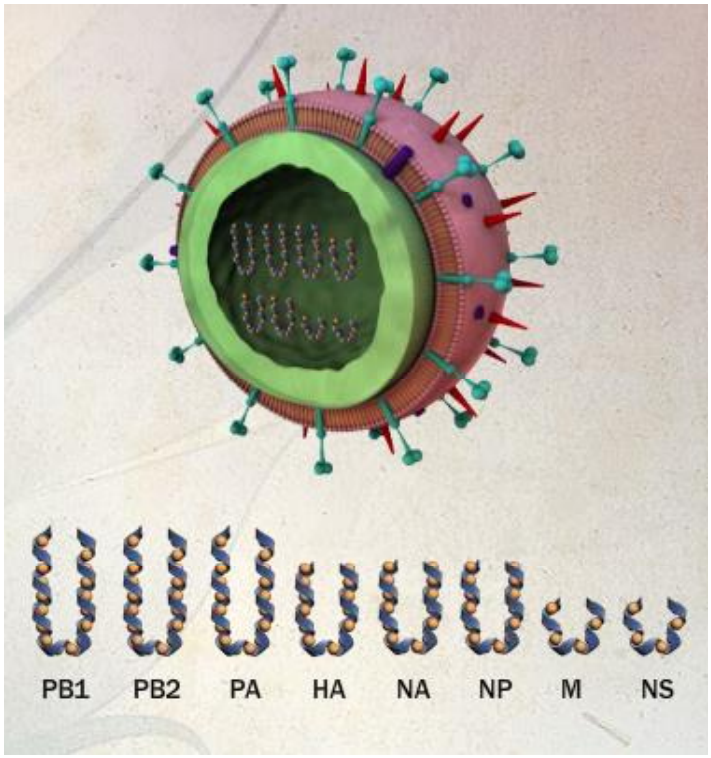


Figure 2: Eight RNA Segments

VIRAL NOMENCLATURE

Influenza viruses belong to the Orthomyxoviridae family of segmented negative-sense RNA viruses.

The genus influenza A consists of a single species: influenza A virus, which is the cause of type A influenza.

All AI is caused by influenza A virus. Influenza A virus also causes illness in a variety of mammals and is the most common cause of influenza in humans.

Influenza B is also an important cause of influenza in humans, whereas influenza C is a relatively uncommon cause of human disease. Influenza D has recently been found in swine and cattle, but is not known at this time to cause disease in humans.

There are 18 different HA antigens (H1 to H18) and 11 different NA antigens (N1 to N11) for influenza A. These antigens give rise to the subtype designation. Subtypes H1 to H16 and N1 to N9 are found in birds (mostly wild birds) and some of these subtypes have been found in mammals. H17N10 and H18N11 were discovered in bats in Guatemala in 2009 and in Peru in 2013, respectively. The NA genes in these influenza subtypes are highly divergent from other known influenza NAs and researchers propose that the attachment and activation of these viruses occur by a different mechanism than other influenza viruses. As of January 2017, these two subtypes appear to be unique to the bat population but have been shown to infect and replicate in other mammalian cells (such as canine cell lines).

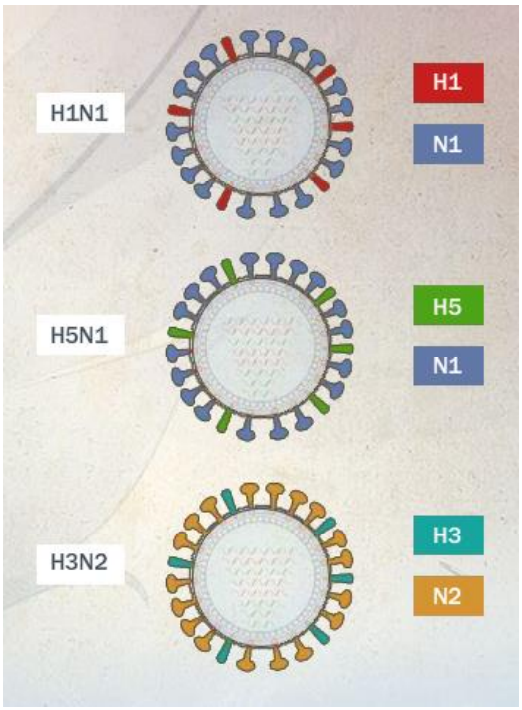


Figure 3: Viral Subtypes

There is only one H and one N in each viral subtype (as shown in Figure 3).

- H1N1 subtype has H1 antigen and N1 antigen.
- H5N1 subtype has H5 antigen and N1 antigen.
- H3N2 subtype has H3 antigen and N2 antigen.

Combinations of the 16 HAs and 9 NAs found in birds can result in up to 144 different unique subtypes.

The vast majority of these subtypes occur only in wild birds.

Human illness historically has been caused by H1, H2, and H3 subtypes.

Several other avian subtypes, including H5 (i.e., H5N1), H7 (i.e., H7N7, H7N9), and H9 (i.e., H9N2) have also caused sporadic illness in humans. In 2013, H6 (H6N1) and H10 (H10N7, H10N8) avian subtypes also caused infections in humans.

Each influenza virus is named on the basis of the following features:

- Type of influenza strain
- Host of origin (if other than human)
- Geographic origin
- Laboratory number
- Year of isolation
- HA and NA subtypes

Examples include the following:

HUMAN STRAIN

A/Brisbane/59/2007/H1N1

This strain was originally isolated from a human in Brisbane, Australia, in 2007 and was used as a source for the 2009-2010 influenza vaccine.

A/Vietnam/1203/2004/H5N1

This strain was isolated in 2004 from a patient in Vietnam with H5N1 influenza.

AVIAN STRAIN

A/bar-headed goose/Qinghai/1A/2005/H5N1

This strain was isolated in 2005 in Qinghai province, China, from a bar-headed goose. A mass die-off of wild migratory birds occurred at Qinghai Lake during that year.

AVIAN STRAIN

A/chicken/Chile/4977/2002/H7N3

This strain caused an outbreak of highly pathogenic avian influenza (HPAI) in Chile in 2002.

SWINE STRAIN

A/Swine/Minnesota/00395/2004/H3N1

This strain was isolated in Minnesota in 2004 and is an example of a triple reassortant swine influenza virus (i.e., a strain that contains genes from viruses of human, avian, and swine origin).

HOW INFLUENZA VIRUSES EVOLVE

Influenza viruses evolve in three ways:

- Antigenic Drift (Mutation)
- Antigenic Shift (Reassortment)
- Gradual Adaptation

ANTIGENIC DRIFT

This process refers to the small genetic mutations that influenza viruses continuously undergo from year to year and is illustrated in Figure 4.

Antigenic drift is an important determinant of influenza epidemiology in humans. Because of antigenic drift, new influenza vaccines for humans are developed each year. Partial immunologic cross-reactivity between new strains and those they are replacing limits morbidity, mortality, and spread in the human population.

Antigenic drift also occurs in influenza viruses in poultry, but the implications for vaccine development are less clear, in part because the pathobiology of highly pathogenic avian influenza (HPAI) in poultry is different than influenza in humans. Also, the antigenic diversity of influenza viruses infecting poultry is much greater than in humans, so the significance of small genetic mutations is different.

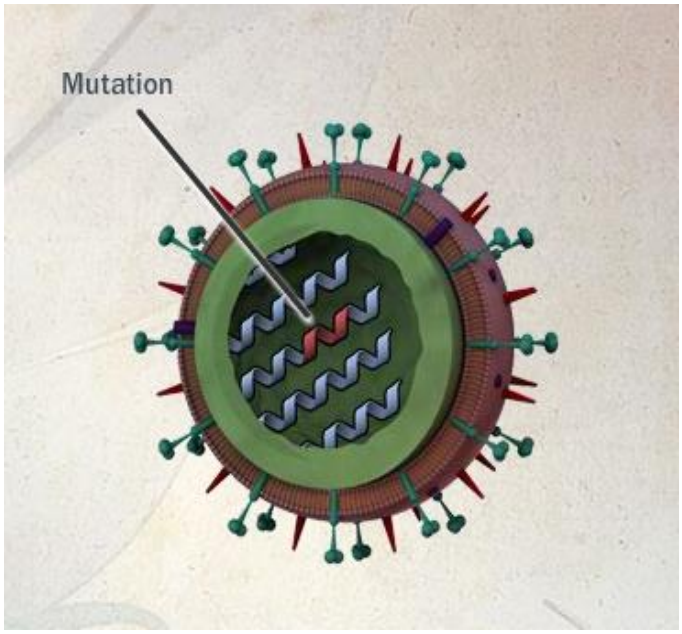


Figure 4: Small Genetic Mutations

ANTIGENIC SHIFT

This process refers to substantial genetic changes in the HA or NA, or a shift from one subtype to another in a given population. Antigenic shift is important for emergence of pandemic strains in humans and also has been seen in swine; however, this process has not been important in poultry.

Antigenic shift can occur due to reassortment between human and animal strains, which appears to be what caused the pandemic strains of the 1957 and 1968 pandemics to emerge in the human population; these strains involved genes from viruses of avian and human origin.

Figure 5 illustrates an example of a triple reassortant virus. The blue genes are from the avian reservoir, the red genes are from the swine reservoir, and the green genes are from the human reservoir. The 2009 H1N1 pandemic strain was a triple reassortant virus that contains genes from viruses of avian, human, and swine origin.

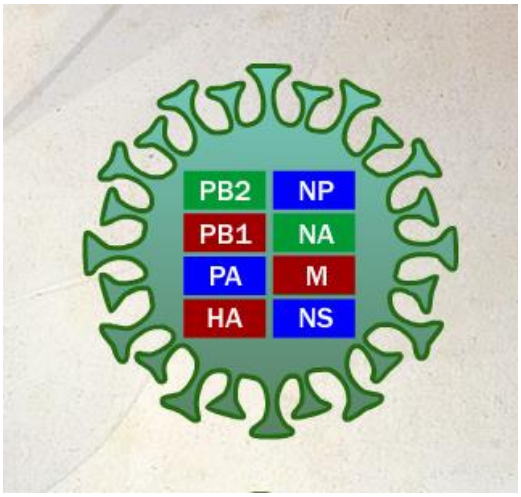


Figure 5: Triple Reassortant Virus

GRADUAL ADAPTATION

Not all pandemic strains arise from genetic reassortment.

For example, the 1918 H1N1 strain may have originated in the avian reservoir and then adapted gradually to the human population over time through a series of genetic mutations to become a global pandemic strain. This process of gradual adaption with multiple small genetic mutations is illustrated in Figure 6.

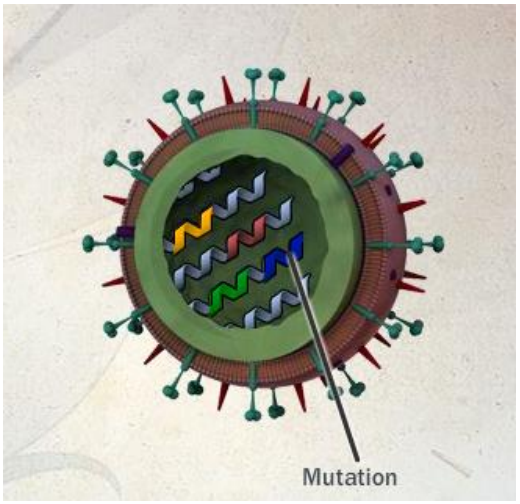


Figure 6: Gradual Adaptation with Small Genetic Mutations

LESSON 2: AVIAN INFLUENZA

In this lesson, we will cover:

- Highly Pathogenic Avian Influenza
- Low Pathogenicity Avian Influenza

AVIAN INFLUENZA CLASSIFICATION

Avian influenza viruses can infect a variety of domestic and wild bird species. Infection can range from asymptomatic to severe, depending on the virulence of the virus, environmental factors, and the susceptibility of the avian host.

Avian influenza viruses in domestic birds are classified according to disease severity, with two recognized forms:

HPAI

Highly pathogenic avian influenza (HPAI) (previously known as fowl plague) is rare.

LPAI

Low pathogenicity avian influenza (LPAI) occurs more frequently than HPAI. LPAI viruses are of much lower virulence than HPAI viruses and typically do not cause high flock mortality.

HIGHLY PATHOGENIC AVIAN INFLUENZA (HPAI)

HPAI viruses are highly virulent and cause systemic infections. HPAI viruses have acquired additional basic amino acids at the HA cleavage site, which allows them to replicate in a wider range of tissues within the host. This property is a key determinant for the increased virulence of HPAI viruses.

Mortality rates in infected flocks often approach 100%.

HPAI viruses are defined as viruses of the H5 or H7 subtype that have "an intravenous pathogenicity index (IVPI) in 6-week-old chickens greater than 1.2 or, as an alternative, cause at least 75% mortality in 4- to 8-week-old chickens infected intravenously." (World Organization for Animal Health [OIE])

An HPAI strain that causes high mortality rates in chickens may not necessarily cause high mortality in other bird species.

Only certain H5 and H7 influenza A subtypes have caused HPAI.

LOW PATHOGENICITY AVIAN INFLUENZA (LPAI)

LPAI viruses are of much lower virulence than HPAI viruses and typically do not cause high flock mortality.

LPAI viruses generally infect tissues of the respiratory and gastrointestinal tracts.

While LPAI viruses generally cause less severe disease, an LPAI strain can sometimes mutate into an HPAI strain; therefore, LPAI in domestic flocks should be controlled.

LPAI viruses, such as H7N9 can also be a source of infection for humans.

LESSON 3: AVIAN INFLUENZA IN WILD BIRDS

In this lesson, we will cover:

- Wild Bird Reservoirs
- AI Viral Subtypes in Wild Birds
- Global Migration Patterns of Wild Birds

WILD BIRD RESOVOIRS

H1 through H16 and N1 to N9 subtypes have been isolated from wild birds and certain groups of wild birds are the primary reservoirs for AI viruses. AI viruses have been isolated from more than 100 wild bird species representing 26 different families of birds.

The most important of these are:

- Anseriformes (ducks, geese, and swans)
- Charadriiformes (terns, shorebirds, and gulls)

Note: Not all species in these groups are important contributors to the AI reservoir. In addition, AI viruses have been found in a number of other bird species, but the contribution of such species to maintaining the AI reservoir is not well understood.

VIRAL ISOLATIONS FROM DUCKS

Most HA and NA subtypes circulate in wild ducks in North America and Northern Europe. In Canadian studies, H3, H4, and H6 are isolated most commonly. Subtype diversity varies over time.

The rates of infection are highest in dabbling ducks (i.e., those ducks that feed primarily near the surface on bodies of water), particularly mallards, the Northern pintail, the blue-winged teal, and the Northern black duck.

In North America, the prevalence is highest in early fall (near Canadian breeding areas); among hatching-year birds, the prevalence of AI may be 30% or higher.

The prevalence in migrating ducks decreases to 2% or less in wintering grounds in the southern United States although native ducks in the wintering grounds may have a higher prevalence. The prevalence is usually <1% in ducks returning to their breeding

grounds in the spring. Similar patterns have been observed in Northern Europe, although detection during spring migration may be higher (up to 6.5%).

There is little information about the prevalence of AI viruses in ducks in the Southern Hemisphere.

VIRAL ISOLATIONS FROM SHOREBIRDS & GULLS

Influenza viruses can be detected in a small proportion of gulls, with prevalence rates generally <2%. The highest prevalence is reported in late summer and early fall.

The most frequently detected AI virus subtype in gulls is H13; this subtype is rarely found in other birds. H16 also is associated with gulls.

HPAI H5 VIRUSES IN WILD BIRDS

Historically, wild birds have remained relatively asymptomatic when infected with avian influenza viruses. Before 2002, only one outbreak of HPAI in wild birds had been reported.

Since 2002, however, HPAI H5 viruses have emerged as an important pathogens in wild birds. Outbreaks of HPAI H5N1 in wild birds initially were recognized in Asia; subsequently, wild bird deaths from additional HPAI H5 viruses have been noted in other regions of the world, including Europe. Wild bird migration is considered to be an important factor in the global spread of HPAI H5 viruses.

HPAI H5N1 IN WILD BIRDS

Since 2002, H5N1 HPAI viruses have been isolated from more than 50 species of wild birds. Most species are either: 1) aquatic birds or 2) raptors and other species that feed on wild or domestic birds.

Several outbreaks of H5N1 have occurred in wild birds. Examples include the following:

HONG KONG

An outbreak of H5N1 occurred in 2002 in two Hong Kong parks causing the death of captive and wild birds, including a variety of ducks, geese, swans, flamingos, and other species.

CHINA

In May 2005, an outbreak of H5N1 was identified among migratory geese and other wild birds in Qinghai Province, China.

AZERBAIJAN

In February 2006, an outbreak in wild swans occurred in Azerbaijan.

BANGLADESH

In February 2016, 40 dead crows tested positive for the H5N1 virus in Bangladesh.

HPAI H5 VIRUSES IN WILD BIRDS

Other HPAI H5 viruses have emerged in wild birds since 2014. HPAI H5N8 was first seen in wild birds in Asia and Europe in 2014. Since then, HPAI H5N8 and other HPAI H5 viruses have caused wild bird die-offs throughout Asia, Africa, and Europe.

GLOBAL MIGRATION PATTERNS OF WILD BIRDS

Migration patterns for different bird species may range from short movements to extended inter-continental distances.

AI viruses generally lead to minimal symptoms in wild birds, thus allowing birds to travel while infected. Therefore, wild birds potentially can distribute AI viruses between countries, continents, and even hemispheres.

The major global flyways (shown in Figure 7) overlap and thus bird populations have opportunities to interface with each other, which can lead to further dispersion of AI viruses.

The flyways provide only a rough idea of migration patterns and it is important to note that the flyways are fluid and overlap.

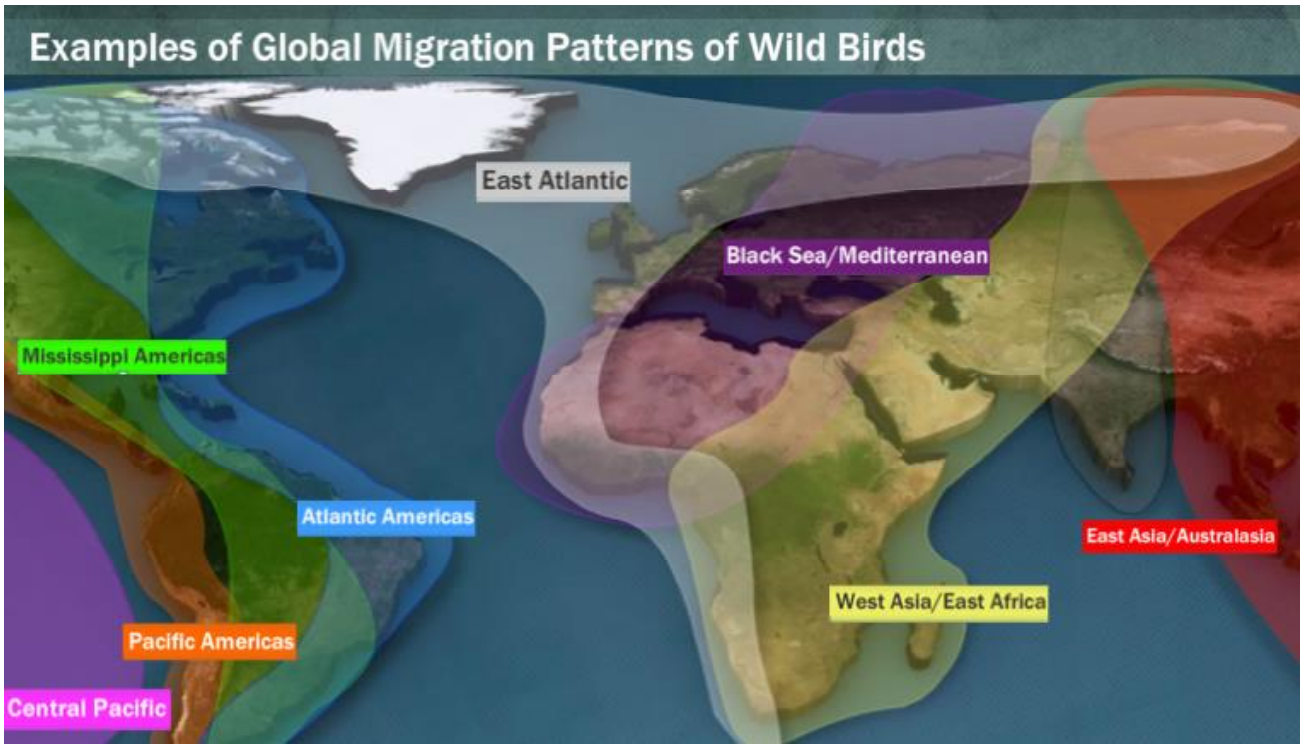


Figure 7: Global Wild Bird Migration Pattern Examples

LESSON 4: HISTORIC OUTBREAKS OF HPAI IN DOMESTIC BIRDS

In this lesson, we will cover:

•Examples of Major HPAI outbreaks

- H5N1 in Asia, Europe, Africa
- HPAI in Birds 2014-16
- H5N2 Outbreak in the US 2015
- Spread of H5N8 2014-17

The table below illustrates examples of HPAI outbreaks that have occurred since 1980 in domestic poultry.

Location	Year	Subtype	Impact	Comments
Pennsylvania	1983-84	H5N2	Caused severe disease and high mortality rates in chickens, turkeys, and guinea fowl; 17 million birds were culled.	A serologically identical but apparently mild virus had been circulating in poultry in the area for 6 months. No human cases were identified. This was the first documentation of an HPAI virus emerging from an LPAI virus outbreak.
Mexico	1994-2003	H5N2	Nearly a billion birds were affected.	An LPAI virus mutated to an HPAI virus and caused an outbreak in 1994-1995. The H5N2 strain has continued to circulate in Mexico since that time. No human cases have been identified.
Pakistan	1994-95, 2001, 2004	H7N3	About 3.2 million birds died from HPAI during the initial outbreak in 1995; 2.52 million layers died in 1995.	Surveillance, quarantine, vaccination, and controlled marketing were used as control strategies. No human cases were identified.
Hong Kong	1996-97	H5N1	Virus was isolated from chickens; avian mortality rates were high. Over 220 million birds died or were culled.	18 human cases with 6 deaths were recognized. Prior to this outbreak, the H5 subtype was not known to infect humans.

Location	Year	Subtype	Impact	Comments
Italy	1999-2000	H7N1	Between 13 and 14 million birds died; chickens, turkeys, guinea fowl, quail, ducks, pheasants, and ostriches were involved. Here again an HPAI virus emerged from an LPA virus outbreak.	No human cases were identified.
Chile	2002	H7N3	About 800,000 birds died or were culled.	No human cases were identified.
The Netherlands	2003	H7N7	30 million birds out of 100 million birds in the country were killed; 255 flocks were infected. Disease spread to Belgium but was rapidly contained.	Over 80 human cases were reported, and one veterinarian died. Most of the human cases involved conjunctivitis.
Texas	2004	H5N2	One noncommercial farm and five poultry markets were depopulated. This virus was not pathogenic for poultry, but molecular markers were consistent with an HPAI virus.	No human cases were identified.
British Columbia	2004	H7N3	Approximately 16 million birds were killed.	Two human cases were identified; both patients had conjunctivitis.
North Korea	2005	H7	About 200,000 birds were culled.	No human cases were identified.
Jalisco, Mexico	2012-13	H7N3	In 2012, over 22 million birds were slaughtered to control the spread of the disease. 140 million birds were immunized. In 2013, 64 new outbreaks were reported in Jalisco and surrounding states, causing the death or destruction of over 7 million birds.	Two poultry workers developed conjunctivitis caused by H7N3 in association with the outbreak.
US	2015	H5N2	Over 48 million birds were affected especially in the	No human disease has been associated with this outbreak.

			Midwestern states of Minnesota and Iowa. The first case was detected on 12/19/14 and the last case was detected on 6/17/15. No further cases have been reported as of January 2017.	
Europe, Africa, Asia	2014-17	H5N8	HPAI H5N8 has caused disease outbreaks in over 35 countries in Europe, Asia, the Middle East, and Africa, resulting in the death or culling of millions of birds.	No human disease has been associated with this outbreak.

H5N1 in Asia, Europe and Africa

A panzootic of H5N1 avian influenza has been occurring since 2003, with mortality in affected flocks of nearly 100%. Outbreaks in domestic poultry and wild birds have been recognized in East Asia, Southeast Asia, Siberia, Central Asia, the Middle East, Europe, and Africa. The strain of highly pathogenic H5N1 circulating in Asia has not entered the Western Hemisphere; however, other reassortant Eurasian H5 viruses have been found in wild birds and poultry in North America.

In addition to disease in birds, more than 850 human cases have been recognized (through January 2017) with more than half of them fatal. Cases have occurred in a number of countries, including the following:

- Azerbaijan
- Bangladesh
- Cambodia
- Canada
- China
- Djibouti
- Egypt
- Indonesia
- Iraq
- Lao People's Democratic Republic
- Myanmar
- Nigeria
- Pakistan
- Thailand
- Turkey

- Vietnam

HPAI in Birds 2014-16

From January 2014 through January 2017, OIE received multiple reports of HPAI in both wild birds and poultry:

H5N8

Austria
Canada
China
Chinese Taipei
Croatia
Czech Republic
Denmark
Egypt
Finland
France
Germany
Greece
Hungary
India
Iran
Ireland
Israel
Italy
Japan
Kazakhstan
Korea
Macedonia
Netherlands
Nigeria
Poland
Romania
Russia
Serbia
Slovakia
Slovenia
Spain
South Korea
Sweden
Switzerland
Tunisia
Ukraine
United Kingdom

United States

H5N2

Canada
China
Chinese Taipei
France
United States

H5N3

China
Chinese Taipei

H5N6

China
Hong Kong
Japan
Laos
South Korea
Vietnam

H5N1

Bangladesh
Bhutan
Bulgaria
Burkina Faso
Cambodia
Cameroon
Canada
China
Cote d'Ivoire
France
Ghana
India
Iran
Iraq
Israel
Korea
Laos
Lebanon
Libya
Myanmar
Nepal

Niger
Nigeria
Palestine
Romania
Russia
Togo
Turkey
United States
Vietnam

H5N9

France

H5N5

Netherlands
Montenegro

H5

Bulgaria
Kazakhstan
Palestine
Russia
Slovakia
Ukraine
Palestine
Vietnam

H7N1

Algeria

H7N7

Italy
Germany
United Kingdom

H7N3

Mexico

H7N8

United States

HPAI H5N2 Outbreak in US 2015

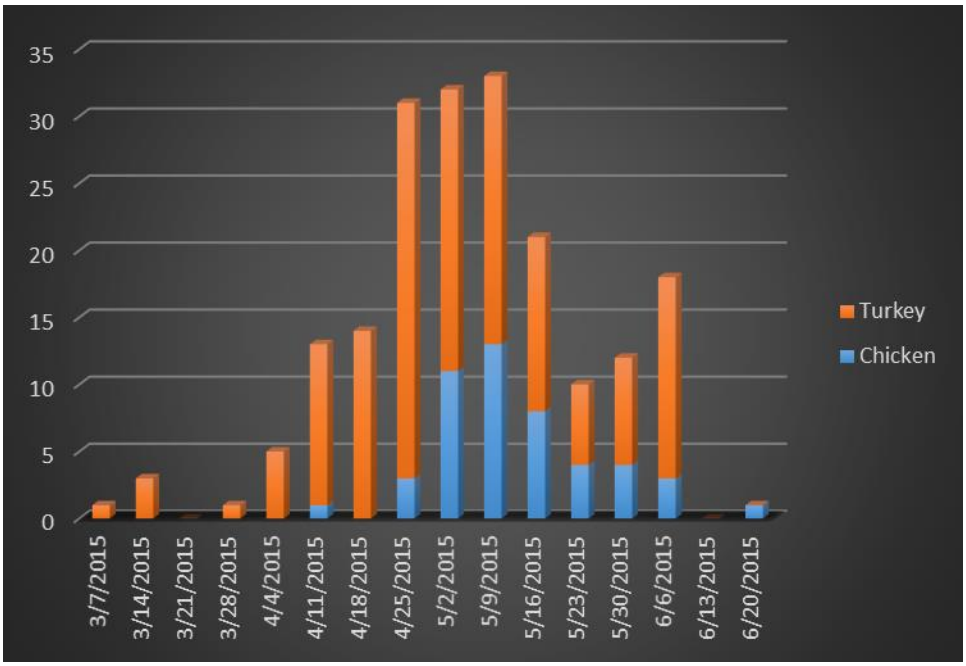
HPAI H5 Occurrence in the Western Hemisphere

The following events mark the first detections of Eurasian H5 viruses in North America.

- In 2014, Eurasian H5N8 viruses spread from wild bird breeding areas in northern Asia and parts of Alaska into the North American Pacific Flyway.
- In the United States, HPAI H5N8 was first confirmed in a captive gyrfalcon in Washington State on December 14, 2014.

- On December 15, 2014, a novel reassortant HPAI H5N2 containing Eurasian and North American genes was confirmed in a wild northern pintail duck that had been found dead, also in Washington State. This virus had also been detected in poultry in British Columbia Canada in November 2014.
- Additional cases of H5N8, H5N2 and H5N1 viruses were seen in the Pacific flyway in wild birds, captive wild birds, backyard poultry, and in 2 commercial poultry operations through mid-February 2015.

The first case of HPAI H5N2 in the Mississippi flyway was confirmed on a commercial turkey farm in Pope County, Minnesota on March 4, 2015. Between then and June 17, 2015, more than 195 commercial operations were affected in states in the upper Midwest and over 48 million turkeys and egg-laying chickens died, or were destroyed to stop the spread of the virus. No new cases of HPAI H5N2 in commercial poultry had been identified as of January 2017.



Overall, all of the H5N2 viruses detected in commercial poultry were highly similar (>99% similar to the index virus: A/Northern pintail/WA/40964/2014/H5N2), but more genetic diversity was noted in the turkey viruses.

Molecular epidemiologic studies determined that cases in turkeys were likely independent introductions (earlier cases) or common source introductions (later cases), whereas most cases in chickens were common source introductions. The virus currently

lacks genes associated with virulence and transmission in humans; therefore, it is not thought to be a risk to human health.

HPAI H5N8 OUTBREAK 2014-16

- A novel Eurasian HPAI H5N8 virus caused outbreaks of disease in poultry in Japan and Korea in the spring of 2014.
- During of the winter of 2014-15, the H5N8 virus spread to China, Taiwan, Russia, and several European countries including Germany, Italy, the Netherlands, Hungary, Sweden, and the United Kingdom. This virus also spread to North America.
- In June 2016, a variant of the HPAI H5N8 virus was detected in wild birds in Tyva Republic, Russia, and the FAO warned of the potential for spread across Europe in the late fall and winter of 2016-17.
- As of January 2017, over 35 countries in Europe, Asia, the Middle East, and Africa have detected outbreaks of HPAI H5N8 in domestic poultry or in wild or captive wild birds.

LESSON 5: CLINICAL FEATURES OF AI IN DOMESTIC POULTRY

In this lesson, we will cover:

- LPAI
- HPAI

LPAI

Generally associated with low mortality (<5%).

Birds most commonly exhibit profound depression, listlessness, reluctance to move, and respiratory signs (such as coughing, sneezing, rattles, and excessive lacrimation).

Decreased egg production may be seen.

Ruffled feathers and decreased feeding also may be seen.

Mortality rates may be higher if co-morbid conditions are present, such as secondary pathogens.

HPAI

HPAI viruses are highly lethal, with flock mortality usually near 100% in susceptible species.

Birds may be found dead without any prior appearance of clinical signs or symptoms.

Common clinical features of HPAI include the following:

- Listlessness or coma
- Decreased feed and water intake leading to dehydration
- Decreased egg production
- Diarrhea
- Necrosis and hemorrhage of the comb and wattles
- Subcutaneous hemorrhage and edema of feet and leg shanks
- Nervous disorders (if birds survive for 3 to 7 days)

NECROPSY LESIONS FOR HPAI

Characteristic necropsy lesions for HPAI, listed below, also can help make the diagnosis.

These include:

- Lesions may be absent in young birds and birds that die from peracute disease
- Severe congestion of musculature
- Severe congestion of conjunctivae, sometimes with petechiae
- Excessive mucous exudates in lumen of trachea
- Severe hemorrhagic tracheitis
- Petechiae on inside of sternum
- Petechiae on serosal and abdominal fat and in body cavity
- Severe kidney congestion, sometimes with urate deposits in tubules
- Hemorrhages on mucosal surface of proventriculus, especially at juncture with gizzard
- Hemorrhages and erosions of gizzard lining
- Hemorrhagic foci on lymphoid tissues in intestinal mucosa
- Ovary may be hemorrhagic or degenerated with darkened areas of necrosis
- Peritoneal cavity often filled with yolk from ruptured ova

LESSON 6: INTERSPECIES TRANSMISSION OF AVIAN INFLUENZA VIRUSES

In this lesson, we will cover:

- Animal species shown to be infected with Influenza A viruses

The following animal species have been shown to be infected with avian influenza viruses:

MARINE MAMMALS

Symptomatic influenza A has been identified in seals and serologic evidence of influenza A virus infection has been found in whales and seals. A variety of subtypes have been identified and the source of exposure is assumed to be wild birds or wild bird habitat.

CATS (DOMESTIC AND WILD)

Several domestic cats in Europe have acquired H5N1 infection, presumably through contact with infected wild birds. Domestic cats have also become infected with the human pH1N1 2009 virus.

Leopards, tigers, lions, and domestic cats have become infected with H5N1 through feeding on infected bird carcasses.

In 2003, a large outbreak of H5N1 influenza occurred in a Thailand zoo among tigers fed H5N1-infected poultry carcasses; tiger-to-tiger transmission also appeared to have occurred. Other outbreaks among captive wild cats have been reported.

In 2016, 45 cats in a shelter in New York became infected with an LPAI H7N2 virus; one cat died. (A veterinarian at the shelter became infected and suffered mild illness.)

DOGS

An outbreak of H3N8 was identified in racing greyhounds in the U.S. in 2004; the strain was closely related to equine H3N8 viruses, suggesting that transmission occurred from horses to dogs. Since then, H3N8 has been identified in other dog breeds across the United States.

An H3N2 virus was isolated from dogs in Korea in 2007. This virus seems to have originated from an entirely avian influenza virus.

Dogs can become infected with H5N1, through contact with wild or domestic birds.

Dogs have also become infected with the human pH1N1 2009 virus.

HORSES

Influenza A has long been recognized as an illness in horses. The main subtype is H3N8. The avian reservoir is assumed to be the original source of influenza in horses, although this has not been definitively demonstrated.

SWINE

Influenza A has been recognized in swine since 1918. H1N1 is the most common serotype, but H1N2, H3N1, and H3N2 have also been recognized. Outbreaks in swine herds are common; the illness is relatively mild and most animals recover. H5N1 has been recognized in swine in Asia. Domestic birds can be a source of influenza A in swine, and transmission from humans to swine has occurred. This triad (poultry, swine, and people) appears to be important for the emergence of new influenza virus strains.

PEOPLE

Currently, H1N1 and H3N2 cause seasonal influenza in humans each year. H2N2 caused the 1957-1958 pandemic and circulated for a few years after that pandemic. Humans also have been infected with other influenza A subtypes from domestic poultry (H5N1, H5N6, H9N2, H7 viruses, H6N1, H10N7, and H10N8) and pigs (eg, H1N1 and H3 viruses. Humans also can acquire influenza from wild birds. A new strain of novel H1N1 entered the human population in the spring of 2009; this strain led to a global pandemic in 2009-2010.

OTHER MAMMALS

H5N1 infection has been identified in several other mammalian species, such as stone martin and mink in Europe, civets in Southeast Asia, and camels in Mongolia. Several other species, including fox, have been experimentally infected with H5N1. Serologic evidence of influenza A infection has been found in wild raccoons in North America.

WILD BIRDS

Wild aquatic birds are the main reservoir for avian influenza A viruses. Historically, wild birds have usually harbored these viruses without becoming ill; however, recently H5N1, H5N8, and H5N6 viruses have been shown to cause severe disease and death in wild birds.

POULTRY

Domestic poultry can become infected with a variety of AI strains, some of which cause mild disease (LPAI strains) and some of which cause severe disease (HPAI strains). H5 or H7 LPAI strains can mutate into HPAI strains. Domestic poultry primarily transmit influenza A viruses to swine and to people; this triad appears to be important for the emergence of new influenza strains.

LESSON 7: ROUTES OF TRANSMISSION FOR AVIAN INFLUENZA VIRUSES

In this lesson, we will cover:

- AI Transmission Between Birds
- Spread of AI Between Poultry Flocks
- AI Transmission from Infected Birds to other Animals
- AI Transmission From Infected Birds to Humans

GENERAL MODES OF TRANSMISSION BETWEEN BIRDS

- Airborne transmission if birds are in close proximity
- Contact with contaminated respiratory secretions or fecal material
- Vertical transmission (i.e., from a hen to the chick) has not been demonstrated

FACTORS THAT CONTRIBUTE TO TRANSMISSION BETWEEN WILD BIRDS AND DOMESTIC POULTRY

- Contamination of drinking water with feces or respiratory secretions
- Fecal contamination of the general environment
- Direct contact between wild birds and poultry

FACTORS THAT CONTRIBUTE TO TRANSMISSION BETWEEN POULTRY FLOCKS

- Movement of infected birds between flocks
- Movement of infected birds to and from live poultry markets
- Movement of contaminated equipment (such as crates, bird-moving trucks, manure-moving equipment, rendering trucks, and egg flats)
- Contamination of clothing and shoes of employees and service crews
- Fecal contamination of the general environment

AI TRANSMISSION FROM INFECTED BIRDS TO OTHER ANIMALS

- Feeding on dead carcasses of infected birds (associated with HPAI H5N1)
- Fecal contamination of the environment

AI TRANSMISSION FROM INFECTED BIRDS TO HUMANS

- Slaughtering, defeathering, butchering, and preparing diseased birds
- Handling infected birds that appear to be well (such as fighting cocks or ducks)
- Playing with or holding diseased or dead poultry
- Consumption of raw or undercooked poultry or poultry products, such as raw duck blood soup (associated only with HPAI H5N1)

LESSON 8: AVIAN INFLUENZA IN THE ENVIRONMENT

In this lesson, we will cover:

- Persistence in Natural Environments

Current evidence suggests that the maintenance cycle of AI in nature is based on the combined effects of continual bird-to-bird transmission and environmental persistence. AI viruses are excreted from birds into the environment (through respiratory secretions and feces).

The pH, temperature, and salinity in natural aquatic habitats can influence the ability of AI viruses to remain infective within such environments.

The viruses appear to be able to survive in water or moist environments for extended periods at cool temperatures. This is an important feature in the ecology of AI viruses. Examples of data on environmental persistence include the following:

- Data from studies of H5N1 in domestic ducks have shown that H5N1 can survive in the environment for 6 days at 37°C.
- At 17°C, H5N1 can persist in water for up to 158 days.
- HPAI H5N2 can persist in liquid poultry manure for 105 days under winter conditions.
- LPAI viruses from waterfowl can persist for up to 207 days at 17°C and 102 days at 28°C in water.

Even though AI viruses can survive in water and organic material for up to several months (and perhaps longer), recent research suggests that influenza viruses generally persist on inanimate environmental surfaces for no more than 6 days.

GLOSSARY

Anseriformes - An order of birds that are highly adapted to aquatic environments; anseriformes are characterized by webbed feet. There are approximately 150 species of birds in the order, including ducks, geese, swans, and screamers.

Antigenic Drift - One of two ways that influenza viruses can change (the other is antigenic shift, see below). Antigenic drift refers to small, gradual changes that occur through point mutations in the two genes that contain the genetic material to produce the main surface proteins, hemagglutinin and neuraminidase. These point mutations occur unpredictably and result in minor changes to these surface proteins. Antigenic drift produces new virus strains that may not be recognized by antibodies to earlier influenza strains. This process works as follows: a person infected with a particular influenza virus strain develops antibodies against that strain. As newer virus strains appear, the antibodies against the older strains might not recognize the "newer" virus, and infection with a new strain can occur. This is one of the main reasons why people can become infected with influenza viruses more than one time and why global surveillance is critical in order to monitor the evolution of human influenza virus strains for selection of which strains should be included in the annual production of influenza vaccine. In most years, one or two of the three virus strains in the influenza vaccine are updated to keep up with the changes in the circulating influenza viruses. For this reason, people who want to be immunized against influenza need to be vaccinated every year.

Antigenic Shift - Antigenic shift is one of two ways that influenza viruses can change (the other is antigenic drift, see above). Antigenic shift refers to an abrupt, major change to produce a novel influenza A virus subtype in humans (i.e., one that has not circulated previously among people). Antigenic shift can occur either through direct animal (poultry)-to-human transmission or through mixing of human influenza A and animal influenza A virus genes to create a new human influenza A subtype virus through a process called genetic reassortment. Antigenic shift results in a new human influenza A subtype.

Antigens - Any foreign substance, usually a protein, that stimulates the body's immune system to produce antibodies.

Charadriiformes - A large diverse order of aquatic birds found along sea coasts and inland waters; includes shorebirds and coastal diving birds. This order includes approximately 350 species.

Chicken Pathogenicity Test - This test involves the inoculation of 4 to 8 week old disease-free chickens and observation for signs of avian influenza for 10 days. According to the World Organization for Animal Health, highly pathogenic avian influenza is defined as any avian influenza virus that is lethal for 6 or more of 8 chickens (75% mortality).

Epidemic - A disease occurring suddenly in humans in a community, region or country in numbers clearly in excess of normal.

Epizootic - A disease occurring suddenly in animals in a community, region or country in numbers clearly in excess of normal.

Flyway - A major route of travel for migratory birds; a flyway may cover thousands of miles.

Genetic Drift - See Antigenic Drift

Gradual Adaptation - A process of small genetic changes in the viral genome that allows an influenza virus to adapt over time to become an efficient pathogen in the human host; this process does not involve reassortment events. Researchers believe that the 1918 H1N1 pandemic strain was initially of avian origin and that the virus evolved into a severe pandemic strain in humans through the process of gradual adaption.

Hemagglutinin (HA) - An important surface structure protein of the influenza virus that is an essential gene for the spread of the virus throughout the respiratory tract. This protein enables the virus to attach itself to a cell in the respiratory system and penetrate it. It is used to name influenza A subtypes and is referred to as the "H" in the influenza virus subtype (e.g., H5N1).

Host - An organism on or in which a parasite lives.

HPAI (Highly Pathogenic form of Avian Influenza) - Often fatal in chickens and turkeys. HPAI spreads more rapidly than LPAI and has a high mortality rate in domestic birds.

Infection - Invasion of the body or a part of the body with a pathogenic organism, which multiplies in the host. A person or animal with an infection may or may not exhibit symptoms. An infection without symptoms is called asymptomatic.

LPAI (Low-pathogenic form of Avian Influenza) - Naturally occurs in wild birds and can spread to domestic birds. In wild birds, LPAI strains generally do not cause signs of infection. In domestic birds, the illness is not severe and mortality rates are low. LPAI H5 and H7 strains have the potential to mutate into HPAI and are therefore closely monitored.

Morbidity - Disease; morbidity rate is the incidence or prevalence of disease in a specific population during a specified interval of time or a specific point in time.

Mortality - Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutation - Any alteration in a gene from its natural state. Specific mutations and evolution in influenza viruses cannot be predicted, making it difficult if not impossible to know if or when a virus such as H5N1 might acquire the properties needed to spread easily among humans.

Necrosis - The death of living cells or tissues.

Neuraminidase (NA) - An important surface structure protein of the influenza virus that is an essential enzyme for the spread of the virus throughout the respiratory tract. This protein enables the virus to escape the host cell and infect new cells. It is used to name influenza A subtypes and is referred to as the "N" in the influenza virus subtype (e.g., H5N1).

Nucleocapsid - The genome (i.e., the RNA or DNA) and the protein coat (or capsid) of a virus.

Outbreak - Presence of disease in numbers in excess of normal in a specific geographic area or population.

Pandemic - A worldwide outbreak of a disease in humans in numbers clearly in excess of normal. A global influenza pandemic may occur if two conditions are met:

- A new subtype of influenza A virus emerges for which there is little or no immunity in the human population.
- The virus can spread easily from person to person in a sustained manner.

Panzootic - A worldwide outbreak of a disease in animals in numbers clearly in excess of normal.

Pathogenic - Causing disease or capable of doing so.

Petechiae - Numerous tiny purple or red spots appearing on the skin or mucosal surfaces as a result of tiny hemorrhages within the dermal or submucosal layers.

Prevalence - The proportion of individuals (humans or animals) in a population having a disease or specific characteristic (such as a positive antibody test to a particular pathogen).

Reservoir - A person or animal that serves as a host to a pathogenic agent, generally without visible symptoms of the disease or injury.

Quarantine - The period of isolation decreed to control the spread of disease. Before the era of antibiotics, quarantine was one of the few available means of halting the spread of infectious disease. It is still employed today as needed. The list of quarantinable diseases in the U.S. is established by Executive Order of the President, on recommendation of the Secretary of the Department of Health and Human Services, and includes cholera, diphtheria, infectious tuberculosis, plague, smallpox, yellow fever, and viral hemorrhagic fevers (such as Marburg, Ebola, and Congo-Crimean disease). In 2003, SARS (severe acute respiratory syndrome) was added as a quarantinable disease. In 2005 another disease was added to the list: influenza caused by novel or reemergent influenza viruses that are causing, or have the potential to cause, a pandemic.

Seasonal Flu ("Common Flu", "Winter Flu") - Influenza caused by one of the common influenza subtypes known to be circulating in the human population; seasonal influenza peaks in the winter months in the Northern and Southern Hemispheres and tends to be year-round in tropical regions.

Strain - Influenza virus subtypes are further characterized into strains. New strains of influenza viruses replace older strains through the process of antigenic drift (i.e., small mutations in the genetic material of the virus).

Swine Flu - A respiratory disease in pigs caused by influenza A virus. Outbreaks in swine herds are common; the illness is relatively mild, and most animals recover. Domestic birds can be a source of influenza A in swine, and transmission from humans to swine and from swine to humans has occurred.

Virulence - A pathogen's ability to invade host tissues and the severity of disease produced.

Virulent - Highly lethal; causing severe illness or death.

Virus - Any of various simple submicroscopic parasites of plants, animals, and bacteria that often cause disease and that consist essentially of a core of RNA or DNA surrounded by a protein coat. Unable to replicate without a host cell, viruses are typically not considered living organisms.

Zoonoses - Diseases that transfer from animals to humans.

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