riott Interspecies Transmission of Influenza Viruses

Minnesota Center of Excellence for Influenza Research and Surveillance
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INTRODUCTION

Interspecies Transmission of Influenza Viruses

Influenza A viruses are capable of infecting a number of different species. Wild birds, especially wild aquatic birds, are considered to be the natural reservoir of influenza A viruses, but various subtypes have become established in different species, including humans, swine, horses, and dogs. While most influenza viruses are species specific, the transmission of viruses from one species to another can occur. This may or may not result in sustained transmission in the new species; however, influenza viruses can readily mutate, which can lead to adaptation within the new species. This process can result in the formation of novel pandemic or panzootic viruses.

This module reviews the species that are affected by influenza A viruses and discusses how influenza A viruses are transmitted between species. Understanding influenza virus transmission between species is important to understanding the global ecology and migration of these viruses. Such information ultimately can affect influenza virus prevention and control efforts and can aid in early detection of influenza viruses with pandemic or panzootic potential.
LESSON 1: Transmission of Influenza Viruses

In this lesson we will cover

- Influenza A Virus
- Susceptible Species
- Avian Influenza
- Swine Influenza
- Equine Influenza
- Canine Influenza
- Seasonal and Pandemic Influenza
- Evolution of Influenza Viruses

INFLUENZA A VIRUS

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. Influenza A viruses cause illness in a variety of mammals and are the most common cause of influenza in humans.

Influenza A virus subtypes are defined by two of the surface proteins that are part of the structure of the virus, as shown in Figure 2:

- H – Hemagglutinin (HA)
- N – Neuraminidase (NA)

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 (eg H1N1, H3N8, H5N1).
**SUSCEPTIBLE SPECIES**

Various subtypes of influenza A viruses have become endemic in humans and other species of animals, including birds (wild and domestic), pigs, horses, and dogs.

Other species such as whales, seals, mink, camels, ferrets, and cats also have been sporadically infected with influenza A viruses.

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 2015, these two subtypes appear to be unique to the bat population.

**AVIAN INFLUENZA**

**Wild Birds**

Wild birds are considered to be the primary reservoir for influenza A viruses. All HA and NA subtypes of the influenza A virus (except for H17N10 and H18N11, which as of January 2015 had only been identified in bats) have been found in avian species (especially waterfowl and shore birds). Aquatic birds generally do not show any clinical signs of infection, but the viruses replicate in the intestinal tract of the birds and are shed into the environment.

**Domestic Poultry**

Influenza A viruses can infect a variety of domestic bird species, such as chickens, turkeys, ducks, and quail. In poultry, avian influenza (AI) viruses are classified according to the disease severity in domestic chickens, with two recognized forms: highly pathogenic avian influenza (HPAI) and low-pathogenicity avian influenza (LPAI).

HPAI viruses cause severe disease in domestic poultry and can cause mortality rates of up to 100% in affected flocks. Examples of HPAI viruses include H5 and H7 subtypes, such as H5N1, H7N7, and H7N3.

LPAI occurs more frequently than HPAI. LPAI viruses generally cause decreased egg production or mild upper respiratory symptoms in domestic poultry and do not typically cause death. LPAI viruses include a number of different influenza A virus subtypes; examples are H7N7, H9N2, and H7N2.
HPAI H5N1

The HPAI H5N1 virus has demonstrated the ability to infect an unusually broad range of species. While sustained transmission within these species generally has not occurred, the virus can cause severe clinical signs and high mortality in many species, although subclinical infections also can occur.

SWINE INFLUENZA

In swine, influenza A viruses cause outbreaks of respiratory disease in herds. Swine influenza is characterized by rapid onset and spread of disease throughout the herd, with relatively low mortality (approximately 1%-3%). Swine also have receptors for and can become infected with avian and human influenza viruses. For these reasons, swine have been theorized to be “mixing vessels” for reassortment of influenza viruses from humans, birds, and swine.

Swine influenza has been associated with H1N1, H3N2, and H1N2 subtypes.

EQUINE INFLUENZA

Equine influenza is an important respiratory disease of horses and other equines. Although mortality is relatively low, equine influenza spreads rapidly, can result in extended recovery time for infected animals, and can significantly harm equine populations, especially in the racing industry.

H7N7 and H3N8 subtypes have been associated with equine influenza.

CANINE INFLUENZA

Canine influenza is a recently recognized and emerging respiratory disease in dogs. It was initially recognized in racing greyhounds and is now endemic in certain areas of the United States. Another subtype of canine influenza has occurred in South Korea and has the ability to spread from dog to dog.

The subtypes associated with canine influenza have included H3N8 (in the United States) and H3N2 (in South Korea).

SEASONAL AND PANDEMIC INFLUENZA

In temperate climates, influenza in humans tends to occur during the fall and winter and is therefore considered a seasonal illness. In the tropics, however, influenza occurs year round. The circulating strains vary from year to year, as immunity to the viruses develops or the viruses mutate leading to the emergence of new strains.
Pandemic influenza occurs when a new strain of influenza emerges where: (1) there is little or no immunity to the virus in the human population and (2) the virus is able to spread efficiently from person to person. A pandemic virus may cause mild to severe disease.

Currently, seasonal influenza in humans is caused by certain strains of H1N1 or H3N2 influenza A viruses, or by influenza B viruses. Pandemic strains have included H1N1, H2N2, and H3N2 subtypes.

**EVOLUTION OF INFLUENZA VIRUSES**

Influenza viruses are generally species specific, but evolutionary changes in the viral genome can affect virulence and species specificity. These changes occur through small mutations in the genome (genetic drift) or through major changes in the HA or NA (genetic shift). Genetic shift can occur through reassortment of viruses from the same species or, in the case of interspecies transmission, though reassortment of viruses from different species.

Genetic mutations can lead to the interspecies transmission of influenza viruses. The human or animal that becomes infected as the result of interspecies transmission may be a “dead-end host,” or the virus may adapt to the species, resulting in continued intraspecies transmission of that influenza virus.
LESSON 2: TRANSMISSION FACTORS

In this lesson we will cover:

- Molecular Determinants
- Host Factors
- Environmental factors

MOLECULAR DETERMINANTS

Viral Structure

The overall structure of the influenza virus includes a lipid membrane that has three integral surface proteins: HA, NA, and the matrix 2 protein (M2).

The HA protein contains the receptor for binding to the host cell and allows fusion of the virus membrane to the host cell membrane, which results in the viral contents entering the host cell. The receptor binding specificity of the HA surface glycoprotein determines the host range of the virus and its potential for interspecies transmission. Mutations in the HA protein can alter the species specificity of the virus.

The types of linkages present on host epithelial cells are a primary determinant for influenza virus infectivity.

- Avian viruses generally bind to NeuAcα2,3Gal sialic acid (SA) receptors.
- Human viruses generally bind to NeuAcα2,6Gal SA receptors.
- Both NeuAcα2,3Gal and NeuAcα2,6Gal SA receptors are present in the trachea of swine, which allows pigs to be infected by avian and human viruses.

The NA protein plays a smaller role in species specificity. Once the influenza virus has replicated inside of the host cell, the NA protein cleaves specific SA linkages as the new viral particles are released from the host cell. The length of the NA stalk also plays a role in species specificity.

Other elements of the viral structure can affect interspecies transmission. The lipid membrane surrounds the nucleocapsid, which contains eight 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 eight RNA segments code for a total of 10 genes.
The eight RNA segments 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)

The adaptation of the polymerase proteins (that serve as a catalyst for the replication of viruses) to a different host may play an important role in the interspecies transmission of influenza viruses. For example, mutations in the polymerase proteins can cause increased polymerase activity in mammalian versus avian cells. Species adaptations can also result in increased transport of polymerases into the nucleus.

**HOST FACTORS**

Host cell receptors vary between species and in different organs within species. In the bullets below “2,3” refers to the NeuAcα2,3Gal receptor and “2,6” refers to the NeuAcα2,6Gal receptor.

- Ducks: 2,3 in the intestine; 2,3 and a few 2,6 in the trachea
- Chickens: 2,3 in the intestine; 2,6 in higher amounts in the trachea
- Turkeys: 2,3 in the intestine; equal amounts of 2,3 and 2,6 in the trachea
- Quail: equal amounts of both in the trachea and the intestine
- Humans: 2,6 in the trachea; 2,3 in ocular and lacrimal ducts and in the lungs
- Pigs: 2,3 and 2,6 in the trachea, although many swine viruses show a preference for the 2,6
- Horses and other equines: bind to 2,3 in the trachea only (similar to avian species)
- Seals: bind to 2,3 in the trachea only (similar to avian species)
- Dogs: 2,3 only in the trachea

Other host factors may influence interspecies transmission of influenza viruses. Physical barriers such as mucins in the respiratory tract may block viral transmission. Immune responses may protect the host against clinical signs of disease but may increase the immune pressure for antigenic shift or drift and result in the shedding of mutated viruses.

**ENVIRONMENTAL FACTORS**

Modes of Transmission and Virus Stability
The mode of transmission can affect the interspecies transmission of influenza viruses. Birds can shed virus in both respiratory secretions and in feces. In mammals, influenza viruses are transmitted primarily by large-droplet spread. Sneezing or coughing can disperse respiratory secretions (large droplets) contaminated with viral particles into the air, which come into direct contact with oral, nasal, or ocular mucosa of nearby people or animals.

Airborne transmission of influenza viruses can occur, at least over short distances, via small droplets expelled by sneezing or coughing. Aerosol spread is affected by temperature and humidity, with cooler and drier conditions increasing infectivity. Higher levels of ultraviolet (UV) radiation also can decrease the survival of influenza viruses in the air.

Respiratory droplets or feces can contaminate surfaces, leading to fomite transmission. The porosity of the surface affects the survival of the virus, with the virus surviving longer on more impermeable surfaces. Other environmental conditions, such as temperature, humidity, and UV radiation, can also influence the survivability of the virus on surfaces. Current information suggests that influenza A viruses generally remain infective on environmental surfaces for 6 days or less.

Virus shed in feces of animals such as ducks, geese, or shore birds can contaminate water. Survival of viruses in water is affected by salinity, pH, and temperature. Lower salinity, pH, and temperature levels increase the persistence of the virus. Influenza viruses can survive in cool, moist, environments for days to months. Because of this, lakes, ponds, or other bodies of water may serve as reservoirs for influenza viruses.

**Host Factors**

Host factors such as the viral load needed to induce infection in a particular species can affect interspecies transmission rates. Species behaviors such as sociability also can affect transmission.

**Other Factors**

Other factors, such as biosecurity measures on farms or the use of personal protective equipment by workers, may influence the transmission of influenza viruses between humans and animals and between animals.
LESSON 3: INTERSPECIES TRANSMISSION BETWEEN BIRDS

In this lesson we will cover:

- Transmission Between Wild Bird Species
- Transmission Between Wild and Domestic Bird Species
- Transmission Between Domestic Bird Species

TRANSMISSION BETWEEN WILD BIRD SPECIES

AI viruses have been isolated from more than 100 wild bird species representing 13 different orders of birds. The most important of these are:

- Anseriformes: ducks, geese and swans (more than 30 species)
- Charadriiformes: gulls, terns and waders (more than 20 species)

These aquatic species are considered to be the primary reservoirs for AI viruses.

More rarely, other bird species have also been infected with AI viruses.

LPAI viruses have been isolated from:

- Psittaciformes (parrots, cockatoos, parakeets)
- Casuariiformes (emu)
- Struthioniformes (ostrich)
- Rheiformes (rhea)

HPAI H5N1 been isolated from many bird species of different orders. Examples include:

- Columbiformes (doves)
- Passeriformes (perching birds)
- Falconiformes (buzzards, falcons)
- Pelecaniformes (cormorants, pelicans)
- Phoenicopteriformes (flamingo)
- Strigiformes (owls)
- Ciconiiformes (storks, herons)

LPAI viruses replicate in the intestines and are shed into the environment by apparently healthy wild birds. The viruses are transmitted from bird to bird via the fecal-oral route,
and contaminated water is likely an important source of virus. LPAI viruses may be transmitted between wetland species that share the same environments. Many such species migrate from breeding areas to overwintering grounds. Because of overlapping flyways and the gregarious behavior of the birds, different species may come into contact with each other, which can amplify transmission of AI viruses between species.

HPAI virus infection in wild aquatic birds can result in death, although some infected birds show no clinical signs. In 2005 at Lake Qinghai in China, a breeding area for migrating birds, more than 1,000 birds were found dead. HPAI H5N1 was isolated from multiple species, including geese, gulls, ducks, and swans. Isolates from different species appeared to be closely related, indicating potential transmission between wild bird species. Large mortality events involving multiple bird species have also occurred at congregation sites in Russia and the Middle East.

Scavenger bird species also have died from the HPAI H5N1 virus infection after eating infected birds, demonstrating another route of transmission between bird species.

Terrestrial birds may serve as “bridge” species, transmitting AI viruses between wild and domestic populations of birds. HPAI H5N1 has caused mortality in several species of wild terrestrial birds, including sparrows, pigeons, and crows. In addition, sparrows in China were found to be infected with HPAI H5N1 without showing any clinical signs. It is not known whether the source of AI virus in the sparrows was wild aquatic birds or domestic poultry.

**TRANSMISSION BETWEEN WILD AND DOMESTIC BIRD SPECIES**

Wild aquatic birds are the major reservoir for LPAI viruses, and these viruses can likely be transmitted to domestic poultry through environmental contamination. However, it is not known if the waterfowl viruses adapt to domestic poultry directly or through another avian host. On a molecular level, a deletion in the NA stalk is a component of the adaptation of a wild bird AI virus to a chicken host.

Turkeys appear to be highly susceptible to AI viruses transmitted from waterfowl. An association between LPAI and turkeys raised outdoors on farms that were located along waterfowl migratory flyways resulted in management changes in turkey operations in the US state of Minnesota. The incidence of LPAI was reduced when the turkeys were moved indoors, which reduced the potential for exposure to wild birds. An H7N3 LPAI virus found in turkeys in 2002-03 in Italy was found to be nearly identical to a virus circulating in wild waterfowl in Italy in 2001.

The role of wild birds in the transmission of HPAI viruses is not well understood. Researchers believe that LPAI viruses introduced into domestic poultry from wild bird reservoirs may then mutate into HPAI viruses in domestic populations. Such HPAI
viruses may then be transmitted from domestic populations back to wild birds, thus causing mortality in wild bird species.

Domestic ducks are a likely reservoir for the HPAI H5N1 virus in domestic bird populations. The interaction between wild and domestic ducks, such as ducks being raised in or near rice paddies where wild ducks can be found, may provide an opportunity for virus transmission between wild and domestic species.

TRANSMISSION BETWEEN DOMESTIC BIRD SPECIES

Turkeys are highly susceptible to LPAI viruses originating from other domestic poultry. In addition, the infectious dose for AI viruses from wild or domestic birds is much lower in turkeys than in other poultry. Because of the low infectious dose required to infect turkeys, they have been postulated as a potential bridge species for AI virus incursion into domestic populations.

Live-bird markets are considered to be a potential ongoing source of AI viruses. Live-bird markets mix birds of many different species, ages, and sources, have been a source of outbreaks of both HPAI and LPAI, and are thought to be important in maintaining a nidus of AI viruses in some countries.

In a study of interspecies transmission in live-bird markets in South Korea, the authors found that genetic reassortment events among AI viruses occurred in the live-bird markets. The authors suggested that ducks may serve as mixing vessels for AI viruses to exchange gene segments and generate reassortant viruses in the live-bird markets in South Korea. Quail also were found to be susceptible to multiple AI viruses and could also serve as a mixing vessel in that setting.
LESSON 4: TRANSMISSION BETWEEN BIRDS AND MAMMALS

In this lesson we will cover:

- Transmission Between Birds and Marine Mammals
- Transmission Between Birds and Horses
- Transmission Between Birds and Pigs
- Transmission Between Birds and Dogs
- Transmission Between Birds and Humans
- Transmission of HPAI H5N1 to Other Mammals

TRANSMISSION BETWEEN BIRDS AND MARINE MAMMALS

One of the earliest examples of interspecies transmission of AI viruses to mammals was the occurrence of epizootics of influenza in seals in 1980-81 and 1983-84. The first outbreak was associated with an H7N7 virus of avian origin. An avian H4N5 virus was isolated from the seals during the 1983-84 outbreak. Since that time, influenza viruses of various subtypes thought to be of avian origin have been isolated sporadically from seals, including an avian-origin H3N8 virus that infected and killed more than 160 seals along the New England coast in October 2011. An H10N7 virus was linked to deaths of over 2,200 seals in Sweden, Denmark, and Germany in 2014.

Influenza viruses also have been isolated from whales. The source of exposure is presumed to be wild birds or wild bird habitat.

TRANSMISSION BETWEEN BIRDS AND HORSES

Both subtypes of the equine influenza virus (H7N7, H3N8) are thought to have been originally transmitted from birds to horses. An outbreak of equine influenza in China in 1989-90 was caused by an H3N8 virus that was genetically distinct from any other circulating equine influenza virus. Genetic analysis revealed that the virus was of recent avian origin. The virus continued to circulate for several more years in China but has not been detected outside of China.

The discovery of equine influenza–like genes in a virus isolated from a wild duck also suggests interspecies transmission of influenza between horses and birds.

TRANSMISSION BETWEEN BIRDS AND PIGS

AI viruses can be transmitted to pigs.

- AI viruses have been found in pigs in Europe and Asia.
• In 1999, a wholly AI virus (H4N6) was found in pigs in Canada. In this case the farm used water from a nearby pond that was also used by migrating ducks.
• Other AI viruses (H3N3, H1N1) have recently been found in pigs in North America.

Because pigs are susceptible to infection with avian, human, and swine influenza viruses, this species has been proposed to be a vehicle for the reassortment of influenza viruses. Since 1998, strains of triple reassortant H1N1, H3N2, and H1N2 have become endemic in swine in North America. Reassortant influenza viruses also have been found in pigs in Europe and Asia.

Pigs can also transmit influenza viruses to birds. Both H1N1 and H3N2 influenza viruses of swine origin have been found in turkeys. Swine influenza viruses also have been found in ducks.

TRANSMISSION BETWEEN BIRDS AND DOGS

An H3N2 influenza virus was isolated from dogs in South Korea in 2007. This virus appears to have originated from an entirely AI virus. This virus has been shown to spread from dog to dog, but has not been found outside the country. The virus is thought to be a reassortant strain originating from viruses found in wild aquatic birds and those found in live-bird markets in South Korea.

TRANSMISSION BETWEEN BIRDS AND HUMANS

Wholly AI strains have shown limited ability to replicate in humans in experimentally induced infections and were rarely reported as causing clinical cases of illness (mainly conjunctivitis) before 1997.

In 1997, 18 people became infected with an HPAI H5N1 strain during a poultry outbreak in Hong Kong; 6 people died. Since 2003, more than 700 people in Asia, Europe, and Africa have become ill with HPAI H5N1, and more than 400 have died. Human-to-human transmission of the H5N1 HPAI virus has been rare and has not been sustained.

Since 1997, HPAI infections other than H5N1 have been reported in humans. Examples of outbreaks include the following:

• HPAI H7N7 in the Netherlands: 89 cases of conjunctivitis in poultry workers, 1 death (2003)
• HPAI H7N3 in Canada: 2 confirmed cases, 55 suspected cases; conjunctivitis and other flu-like symptoms were reported (2004)
• HPAI H7N3 in Mexico: 2 confirmed cases of conjunctivitis associated with an outbreak in poultry (2012)
LPAI viruses also can infect humans and generally have caused conjunctivitis or mild respiratory symptoms. Examples of involved subtypes include H7N7, H9N2, and H7N2. In the spring of 2013, a novel H7N9 virus was recognized in humans in China. Since then a seasonal pattern has emerged with the majority of cases occurring in winter months or early spring. As of January 2015, 526 cases and more than 185 deaths were recognized had been reported. An LPAI H7N9 virus similar to the virus that caused disease in humans was isolated from chickens, pigeons, and environmental samples in the outbreak area.

Serological surveys have demonstrated the development of antibodies to AI viruses in persons who have been exposed to wild birds or domestic poultry, including hunters, wildlife professionals, veterinarians, and poultry workers. In addition, the pH1N1 2009 virus was transmitted from infected humans to turkeys in several facilities in the US, Canada, and Chile.

TRANSMISSION OF HPAI H5N1 TO OTHER MAMMALS

Since 2003, the HPAI H5N1 virus has been shown to infect a variety of other mammalian species, predominantly through consumption of infected bird carcasses. Examples include the following:

- Tigers and leopards in captivity in Thailand: were fed infected chicken carcasses.
- Domestic cats in Thailand, Germany, and Austria: primarily infected through consumption of infected bird carcasses in areas of outbreaks in domestic or wild birds, although cat-to-cat transmission may have occurred.
- Domestic cats in Iran: presumably infected through consumption of infected bird carcasses, although the route of infection remains unclear.
- Stone marten in Germany: presumably infected through consumption of infected carcasses.
- Dog in Thailand: infected through consumption of an infected carcass.
- Civets in Vietnam: mode of infection is not known.
- Species that have been experimentally infected include mice, ferrets, non-human primates, rats, mink, fox, cattle (calves), and hamsters.
- Pigs appear to have a low susceptibility to infection with H5N1, although infection in pigs has been reported in China and Indonesia.
LESSON 5: INTERSPECIES TRANSMISSION BETWEEN MAMMALS

In this lesson we will cover:

- Transmission Between Horses and Dogs
- Transmission Between Dogs and Cats
- Transmission Between Swine and Humans
- Transmission Between Humans and Other Mammals

TRANSMISSION BETWEEN HORSES AND DOGS

Transmission of an influenza virus from one mammalian species to another occurs but rarely results in sustained transmission within the new species. In 2004, an outbreak of respiratory disease occurred in racing greyhounds in Florida. The virus was very closely related to an H3N8 equine influenza virus.

Evidence suggests that the virus was transferred from horses to dogs in a single event and then gradually adapted to dogs, becoming endemic in racing greyhounds and pet dogs in some areas of the United States.

In 2002 and 2003, a different equine H3N8 virus was found in a kennel in the United Kingdom; however, sustained dog-to-dog transmission of the virus did not occur. During an equine influenza outbreak in Australia in 2007, several dogs became infected with the equine virus, but the virus did not become established in dogs.

TRANSMISSION BETWEEN DOGS AND CATS

A 2010 study demonstrated the probable transmission of the South Korean H3N2 canine influenza virus to cats. During an outbreak of respiratory disease in an animal shelter, both dogs and cats were affected. The cats suffered 100% morbidity and 40% mortality during the outbreak, and a virus nearly identical to the canine H3N2 virus was isolated from one of the dead cats. Experimental inoculation of cats with the canine virus resulted in the development of clinical signs and shedding of virus.

TRANSMISSION BETWEEN SWINE AND HUMANS

Swine can become infected with human influenza strains, and people can become infected with swine influenza strains.

Transmission of swine influenza viruses to humans has been relatively uncommon.

- An outbreak of swine-origin H1N1 influenza was recognized in early 1976 among military personnel atFort Dix, New Jersey. Thirteen clinical cases occurred with 1
death; the cause of the outbreak remains unknown, and no exposure to pigs was identified.

- A subsequent report identified 37 civilian cases of swine influenza in the medical literature from 1958 to 2005. Of these, 19 occurred in the United States, 6 in Czechoslovakia, 4 in the Netherlands, 3 in Russia, 3 in Switzerland, 1 in Canada, and 1 in Hong Kong. Twenty-two of the 36 for whom data were available (61%) reported recent exposure to pigs.
- From December 2005 to February 2009, 11 human cases of swine influenza caused by triple-reassortant swine influenza A H1 viruses were reported to the Centers for Disease Control and Prevention (CDC). Seven cases involved either direct exposure to pigs or close proximity to pigs (ie, within 6 feet) shortly before illness onset. Of the remaining 4 cases, 2 were in the general vicinity of pigs before illness onset, 1 was epidemiologically linked to a possible case, and 1 had no pig exposure.
- In 2011, an H3N2 swine influenza virus containing the M gene from the pH1N1 virus was detected in people and associated with exposure to pigs at agricultural fairs in the United States. As of January 2015, 343 cases of H3N2 (H3N2v) variant virus have been reported in 13 states. Most cases had very close contact with swine, but human-to-human spread of the virus also has been recognized.

While human illness with swine influenza is not common, studies have shown that persons exposed to pigs (swine workers, swine veterinarians, etc) are more likely to have antibodies to swine influenza viruses than persons with no exposure to pigs, suggesting that some people may develop subclinical infections.

The 2009-10 H1N1 influenza pandemic (pH1N1 2009) was caused by an influenza strain that was genetically related to viruses that had been circulating in swine over recent years. Public health officials generally believe that the virus originated in the swine reservoir and at some point was transmitted to humans.

Similarly, human influenza viruses can be transmitted to swine.

- Human H3N2 and H1N1 viruses have been isolated from swine.
- The double and triple reassortant viruses that emerged in pigs in the US in 1998 contained genes of human influenza origin and demonstrate transmission between the two species.
- The pH1N1 2009 influenza virus was found in swine facilities in a number of countries, including the United States, Canada, Argentina, Russia, and several other European and Asian countries. Evidence suggests that the pigs were exposed to the virus by persons who were sick. In one case, the virus was transmitted from the pigs back to swine workers in the facility.
TRANSMISSION BETWEEN HUMANS AND OTHER MAMMALS

During the 1980 H7N7 outbreak of influenza in seals, several field workers in contact with the infected seals developed severe cases of conjunctivitis. The virus was not isolated from the infected workers, but interspecies transmission was suspected. Near that same time, an experimentally infected seal sneezed into the face of an investigator who subsequently developed a similar case of conjunctivitis. A conjunctival swab obtained from the investigator two days after exposure demonstrated high titers of influenza virus; the virus was the same as the virus isolated from the seals.

The H3N8 virus that caused mortality in seals in New England in 2011 has been shown to have affinity for mammalian receptors, can be transmitted by the respiratory droplets in ferrets, and can replicates in human lung cells suggesting that transmission to humans could occur; however, no human infections were recognized at the time of the outbreak.

The pH1N1 2009 virus was isolated from household pets, including cats, dogs, and ferrets. These companion animals were diagnosed as having pH1N1 influenza after family members had experienced influenza symptoms, indicating likely interspecies transmission of the pandemic virus.
LESSON 6: PREVENTING INTERSPECIES TRANSMISSION OF INFLUENZA VIRUSES

In this lesson we will cover:

- Importance of Preventing Interspecies Transmission of Influenza Viruses
- Biosecurity Measures in Agricultural Settings
- Personal Hygiene and Personal Protective Equipment
- Vaccination

IMPORTANCE OF PREVENTING INTERSPECIES TRANSMISSION OF INFLUENZA VIRUSES

Interspecies transmission of influenza viruses should be reduced for several reasons:

- Influenza viruses that are transmitted to people from other animals could adapt, or mutate, and become easily transmissible in the human population.
- Disease spread from humans to domestic agricultural species, or from wild bird species to domestic species, can seriously harm the agricultural industry.
- Interspecies transmission increases the risk of further reassortment of influenza viruses, which could lead to emergence of new pandemic strains.

BIOSECURITY MEASURES IN AGRICULTURAL SETTINGS

Biosecurity measures in agricultural settings are important to reduce the risk of interspecies transmission of influenza viruses. Biosecurity is the development of specific management practices and behaviors to prevent the introduction of disease. Biosecurity measures can also contain a disease within the facility, preventing its spread to other operations or other species.

Biosecurity Measures in Poultry Operations

Biosecurity measures in poultry operations involve preventing exposure to potential disease reservoirs, such as wild aquatic birds, infected poultry from other sources, or live-bird markets.

This is done through:

- Implementing isolation practices, such as raising birds indoors and quarantining new arrivals to the flock
- Ensuring adequate traffic control, such as managing who and what comes into and out of the operation, including visitors, equipment, and vehicles
• Practicing adequate sanitation, including cleaning and disinfection, carcass and manure management, and pest control

Biosecurity Measures in Swine Operations

Basic biosecurity measures in swine operations:

• Separating pigs and isolating them from other herds, including management practices such as “all-in, all-out” and quarantine and isolation practices
• Controlling the number of people, vehicles, and equipment coming onto the operation; ensuring that people have not been in contact with other pigs; using “shower in, shower out” practices; and ensuring that anyone or anything coming onto the farm is cleaned and disinfected
• Preventing humans with respiratory symptoms from entering swine facilities
• Practicing robust sanitation and pest management procedures
• Implementing steps that prevent exposure of pigs to wild birds

Biosecurity Measures in Other Settings

Biosecurity principles also can be applied to infection control practices in veterinary hospitals, clinics, kennels, and wildlife rehabilitation centers.

PERSONAL HYGIENE AND PERSONAL PROTECTIVE EQUIPMENT

Hand washing is one of the most important infection control methods that can be used to prevent the spread of influenza viruses. Hand washing can help prevent the spread of influenza from animals to people and can also help prevent people from spreading influenza from infected to uninfected animals.

Hands should be washed after handling any animal, whether wild or domestic.

The use of personal protective equipment when working with animals also can reduce the risk of interspecies transmission of influenza viruses. Protective clothing and gloves are often used, and eye and respiratory protection can be worn in higher-risk situations.

VACCINATION

Vaccination may reduce the risk of co-infection and development of novel viruses. Influenza vaccinations are available for humans, swine, poultry, horses, and dogs. Vaccination does not eliminate viral replication or shedding of virus but may reduce clinical signs and the amount of virus shed.
**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 (ie, 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** - A substance that elicits a specific (as opposed to nonspecific) immunological response. Foreign antigens typically stimulate a response from the body’s adaptive immune system resulting in the production of antibodies and effector T-cells; antigens that produce an immune response can also be called “immunogens.”

**Antibody** – serum proteins produced by B lymphocytes in response to exposure to antigens. Antibodies produces by a particular antigen bind to that antigen only.
**Biosecurity** - Security from transmission of infectious diseases, parasites and pests.

**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.

**Fomite** – Inanimate objects or materials on which disease producing agents may be conveyed.

**Genetic Drift** - See Antigenic Drift

**Genetic Shift** – See Antigenic Shift

**Glycoprotein** - Any of a group of conjugated proteins having a carbohydrate as the non-protein component.

**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 (eg, 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.

**Interspecies transmission** – Transmission of microorganisms between animals of different species (including humans).

**Intraspecies transmission** – Transmission of microorganisms between animals of the same species (including humans).

**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.

**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 (eg, H5N1).

**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 these 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.

**Polymerase** - Any of various enzymes, such as DNA polymerase, RNA polymerase, or reverse transcriptase, that catalyze the formation of polynucleotides of DNA or RNA using an existing strand of DNA or RNA as a template.

**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.

**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.

**Sialic acid (SA)** - Any of a group of amino carbohydrates that are components of mucoproteins and glycoproteins, especially in animal tissue and blood cells.

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

**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.
RESOURCES


CDC. Case Count: Detected U.S. Human Infections with H3N2v by State since August 2011 http://www.cdc.gov/flu/swineflu/h3n2v-case-count.htm


Lipatov AS, Kwon YK, Sarmento LV, et al. Domestic pigs have low susceptibility to H5N1 highly pathogenic avian influenza viruses. PLOS Pathogens 2008;4(7):31000102


Morens DM, Taubenberger. Historical thoughts on influenza viral ecosystems, or behold a pale horse, dead dogs, failing fowls, and sick swine. Influenza Other Respi Viruses 2010 Nov;4(6):327-37


Pillai SP, Pantin-Jackwood M, Yassine HM. The high susceptibility of turkeys to influenza viruses of different origins implies their importance as potential intermediate hosts. Avian Dis Mar 2010;54 (1 Suppl):522-6


All glossary definitions are found at one or more of the following sources (or are adapted from those sources):

Centers for Disease Control and Prevention Avian Influenza (Bird Flu). [Website: http://www.cdc.gov/flu/avian/]

Flu.gov Glossary. [Website: www.pandemicflu.gov/glossary/index.html]
