

Influenza

*Flu, Grippe, Swine Influenza,
Hog Flu, Pig Flu,
Equine Influenza, Avian Influenza*

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Author: Anna Rovid Spickler



**Institute for International
Cooperation in Animal Biologies**
*An OIE Collaborating Center
Iowa State University
College of Veterinary Medicine*



IOWA STATE UNIVERSITY®

**Center for Food
Security and Public Health**
College of Veterinary Medicine
Iowa State University
Ames, Iowa 50011
Phone: (515) 294-7189
FAX: (515) 294-8259
E-mail: cfsph@iastate.edu
Web: <http://www.cfsph.iastate.edu>

Etiology

Viruses in the family Orthomyxoviridae cause influenza. There are three genera of influenza viruses: influenza A, influenza B and influenza C.¹ These viruses are also called type A, type B and type C. Type A viruses include the avian, swine and equine influenza viruses, as well as the human influenza A viruses. The influenza B and C viruses are mainly found in humans, although there is increasing evidence that they can also infect other species.

Influenza A viruses

Influenza A viruses are classified into subtypes based on two surface antigens, hemagglutinin (H) and neuraminidase (N).

There are 15 hemagglutinin antigens (H1 to H15) and 9 neuraminidase antigens (N1 to N9).²⁻⁷ These two proteins are involved in cell attachment and release from cells, and are also major targets for the immune response.⁸⁻¹¹ Only limited subtypes are found in each species of mammal.¹¹

Subtypes of influenza A viruses are classified into strains. Strains of influenza viruses are described by their type, host, place of first isolation, strain number (if any), year of isolation, and antigenic subtype.^{11,12} [e.g., the prototype strain of the H7N7 subtype of equine influenza virus, first isolated in Czechoslovakia in 1956, is A/eq/Prague/56 (H7N7).] For human strains, the host is omitted.

Influenza A viruses change frequently. New strains and subtypes can cause epidemics and pandemics. Strains evolve as they accumulate point mutations during virus replication (antigenic drift).¹¹ Genetic reassortment can occur if two different influenza viruses infect a cell simultaneously.¹⁰ Reassortment between two different strains results in the periodic emergence of novel strains. Reassortment between subtypes can result in the emergence of a new subtype. Reassortment can occur between avian, swine, equine and human influenza A viruses. This type of reassortment can result in a 'hybrid' virus with, for example, both avian and human influenza virus proteins.

An abrupt change in the subtypes found in host species is called an 'antigenic shift.' Antigenic shifts can result from three mechanisms which include the direct transfer of a whole virus from one host species into another - e.g., an avian influenza virus spreading in pigs, reassortment between subtypes, or the re-emergence of a virus that was found previously but is no longer in circulation.^{9,12} For example, human viruses can continue to circulate in pigs and could re-emerge into the human population.⁹

Avian influenza viruses

Avian influenza viruses are found in a wide variety of domestic and wild birds.^{3,12,13} They are also isolated occasionally from mammals including humans.^{3,5,7,9,12,15-17} Waterfowl, which seem to be the natural reservoirs for the type A influenza viruses, carry all of the known subtypes.^{2,7,9,12-20} The predominant subtypes in wild ducks change periodically.¹² Poultry can be infected by a wide variety of subtypes. From 1993 to 2000, subtypes containing H1 to H7 and H9 to H11 were isolated from live bird markets in the northeastern U.S.²¹

Avian influenza viruses are classified as either highly pathogenic avian influenza (HPAI) or low pathogenic avian influenza (LPAI), based on the genetic features of the virus and the severity of disease in poultry.^{2,3} To date, only subtypes that contained H5 or H7 have been highly pathogenic; subtypes that contained other hemagglutinins have been found only in the LPAI form.^{6,20,22} H5 and H7 LPAI viruses also exist, and can evolve into highly pathogenic strains.^{3,19,20} Subtypes found in ratites have included H3N2, H4N2, H4N6, H5N2, H5N9, H7N1, H7N3, H9N2, H10N4 and H10N7.²² All were of low virulence for chickens. Isolates from cage birds usually contain H3 or H4.²²

Swine influenza viruses

Swine influenza viruses are found mainly in pigs, but have also been found in other species including humans.^{7,9,11,12,23,24} There is less antigenic drift in swine influenza A viruses than in human viruses.⁹ The most common subtypes currently found in pigs are H1N1, H1N2 and H3N2.²⁵ Although the swine influenza viruses found in the U.S. and Europe are the same subtypes, they are actually different viruses.

The 'classical' H1N1 swine influenza virus, was initially found in U.S. pigs in 1918.^{9,10,12,18} This virus is also found in Asia.¹⁸

An 'avian-like' H1N1 virus circulates in European and U.S. pigs.^{9,10,18} It seems to be an avian influenza virus that was transmitted whole to pigs and has replaced the classical H1N1 virus.^{10,18,52} A different 'avian-like' H1N1 virus is co-circulating with the classical H1N1 virus in pigs in Asia.¹⁸

The H3N2 viruses that recently entered pigs in the Midwest are triple reassortants.^{10,14,26} They contain hemagglutinin and neuraminidase proteins from a human influenza virus, and internal proteins from the classical swine influenza virus, an avian influenza virus and a human influenza virus.²⁶

The H3N2 viruses in Europe and Asia seem to be the result of reassortment between a human H3N2 virus, circulating there in pigs since the 1970s, and the H1N1 'avian-like' virus.⁹ These H3N2 viruses contain human N3 and N2 proteins, and internal proteins from the avian virus.⁹

The H1N2 virus in the U.S. is a reassortant of the classical H1N1 swine influenza virus and the triple reassortant H3N2 virus circulating in the U.S.⁹

The H1N2 virus in Europe is a reassortant of a human H1N1 virus and the 'human-like' European H3N2 virus.^{9,18}

Equine influenza viruses

Equine influenza viruses mainly infect horses and other Equidae.^{4,12,27} There is less antigenic drift in equine viruses than human viruses.^{4,11} The two subtypes known to cause disease in horses are H7N7 (equine virus 1) and H3N8 (equine virus 2).^{4,11,12} The H7N7 virus is currently extinct or present at only very low levels in some parts of the world.^{4,12}

In 1989, a novel strain of equine influenza [A/eq/Jilin/89 (H3N8)] caused a serious epidemic, with high morbidity and mortality rates, in Chinese horses.⁴ The virus appears to be an avian influenza virus. A related virus caused influenza in a few hundred horses the following year but there were no deaths. The avian-like virus continued to circulate in horses in China for at least 5 years without further fatalities.

Human influenza viruses

Human influenza viruses are mainly found in humans, but also infect ferrets and sometimes swine.^{11,12,18,28-32} H1N1, H1N2 and H3N2 viruses are currently in general circulation in humans.^{3,33} The H1N2 viruses appeared in 2001, probably as a result of genetic reassortment between the H3N2 and H1N1 viruses.^{33,34} H2N2 viruses circulated in the human population between 1957 and 1968.¹²

Human influenza viruses change frequently as the result of antigenic drift, and occasionally as the result of antigenic shift. Epidemics occur every few years, as a result of small changes in the influenza viruses.^{9,35} Human pandemics, resulting from antigenic shift, were most recently reported in 1918, 1957 and 1968.

Influenza viruses in other species

H7N7 and H4N5 viruses, closely related to avian viruses, have been isolated from seals.¹² In 1984, a H10N4 virus was isolated from mink during an epidemic in Sweden.¹² This virus is thought to have been of avian origin. A H5N1 avian influenza virus was recently isolated from sick domestic and zoo cats in Asia.^{15,17}

Influenza B viruses

Influenza B viruses are not categorized into subtypes, but are classified into strains.³ Influenza B viruses undergo antigenic drift but not antigenic shift.³ Antigenic drift is slower in influenza B than in influenza A viruses.^{12,33} Influenza B viruses can cause epidemics in humans, but have not, to date, been responsible for pandemics.¹² They have also been found in animals.^{9,12,23,29,36}

Influenza C viruses

Influenza C viruses are not classified into subtypes, but are classified into strains.³ Each strain is antigenically stable, and accumulates few changes over time.³⁷ However, recent evidence suggests that reassortment does occur frequently between different strains of influenza C viruses.^{37,38} Type C viruses can cause mild disease in humans, but have never been associated with large scale epidemics.^{8,12,35,39} They have also been found in animals.^{9,11,12,23,29,39,40-42}

Geographic Distribution

Human and avian influenza viruses are found worldwide.^{2,11-13} Avian HPAI viruses have been eradicated from domestic poultry in most developed nations, but are found worldwide in waterfowl.² In North America, H3, H4 and H6 viruses are found most often in wild ducks, but H5, H7 and H9 viruses are also found at low levels.⁴³

In early 2004, widespread outbreaks of an avian influenza H5N1 (HPAI) virus occurred in poultry in Cambodia, China, Indonesia, Japan, Laos, South Korea, Thailand and Vietnam.³ Beginning in June 2004, new outbreaks of a H5N1 (HPAI) virus were reported in poultry in China, Indonesia, Thailand and Vietnam. Human, feline and possibly porcine infections and deaths have been associated with these outbreaks.

Swine influenza is common in North and South America, Europe and Asia and has been reported from Africa.^{18, 23} Although the subtypes of the swine influenza viruses found in the U.S. and Europe are the same, they are actually different viruses (see 'Etiology').

Only Australia, New Zealand and Iceland are known to be free from equine influenza.²⁷ The H3N8 subtype is widespread in horse populations.⁴ The H7N7 subtype may be either extinct or present at only very low levels in some parts of the world, including the North America and Europe.^{4,12,27} It can still be found at low levels in Central Asia.¹²

Transmission

In mammals, the influenza viruses are transmitted in aerosols created by coughing and sneezing, and by contact with nasal discharges, either directly or on fomites.^{4,11,12,18,25,33,35} Close contact and closed environments favor transmission. Influenza viruses are relatively labile, but can persist for several hours in dried mucus.³⁵ In ferrets, *in utero* transmission can occur with high viremia after experimental infection.³²

In birds, avian influenza viruses are shed in the feces as well as in saliva and nasal secretions; fecal-oral transmission is the most common means of spread.^{2,3,11,12} Waterfowl can carry the avian influenza viruses asymptotically and transmit them to poultry.^{2,11} Viruses have also been found in the yolk and albumen of eggs from infected hens.² Although these eggs are unlikely to hatch, broken shells could transmit the virus to other chicks in the incubator. Fomites can be important in transmission and flies may act as mechanical vectors.^{2,19,20}

Recently, avian influenza H5N1 was reported in domestic and zoo cats during an outbreak in Asia.^{15,17} The cats were all thought to have been infected by eating raw infected poultry. Experimental infections were established in cats by intratracheal inoculation with H5N1 viruses and by feeding H5N1-infected chicks.¹⁷

Avian influenza viruses (H7N2, LPAI) can persist for up to 2 weeks in feces and on cages.⁴⁴ They can also survive for up to 32 days at 15–20°C, and at least 20 days at 28–30°C, but are inactivated more quickly when mixed with chicken manure.⁴⁴ HPAI viruses can survive indefinitely when frozen.¹⁹ The avian viruses have also been isolated from the water in ponds where ducks swim.^{9,12}

Transmission between species

Ordinarily, swine influenza viruses circulate only among pigs, equine influenza viruses among the Equidae, avian influenza viruses among birds, and human influenza viruses among humans. Occasionally, these viruses cross species barriers. Generally, the virus is not well adapted to the new host species and does not undergo sustained transmission.^{3,10,12,23}

Transmission of the avian influenza viruses to people is rare, and has been reported only with the H5, H7 and H9 viruses.^{3,7} Most infections have been the result of direct contact with infected poultry or fomites; however, during a 2003 outbreak in the Netherlands, three human infections occurred in family members of infected poultry workers.^{3,5} The virus subtype was H7N7. No cases of sustained person-to-person transmission with the avian viruses have been reported, to date.

The H5N1 avian influenza viruses may be likely to undergo cross-species transmission. These viruses have been isolated at least 56 times in humans, after contact with infected poultry.^{3,9,14,19,20,45} They have also been isolated recently from cats that ate infected poultry.^{15,17} Cats, pigs and mice have been experimentally infected.^{14,17} In addition, preliminary evidence of natural infections with the H5N1

viruses has been reported for the first time in pigs, in Fujian province, China.¹⁴

Infections with swine influenza viruses have been reported sporadically in humans in the U.S., Europe and New Zealand.^{7,9,12,24,46} One college student transmitted the virus to his roommate, who remained asymptomatic.²⁴ Limited person-to-person transmission was also reported in 1976, when approximately 500 military recruits in Fort Dix, New Jersey were infected with a swine influenza virus.^{9,12,24} This virus spread to a limited extent on the base, which contained approximately 12,000 people, but did not spread to the surrounding community. Recent serologic evidence suggests that swine influenza infections may occur regularly in people who have contact with pigs.^{7,9,12} If these infections resemble human influenza, they may not be recognized or reported as caused by a swine influenza virus.

Pigs are readily infected with human influenza A viruses, but most strains do not spread widely.¹² Pigs can also be infected with human influenza B viruses; serologic studies from the U.K. suggest that these infections are sporadic and do not spread to other pigs.²⁹

Rarely, transmission between species results in an epidemic in the new host. Generally, this requires a novel hemagglutinin and/or neuraminidase protein to evade the immune response, together with viral proteins that are well adapted to the new host's cells.¹⁰ Occasionally, a virus is transferred whole to the new host and can spread. This has occurred a few times when avian viruses infected mink, horses, seals and pigs.^{4,10,12,16,18} However, dissemination is more likely if the novel virus reassorts with a virus that is already adapted to the host species.³ Reassortment can occur in the new host's own cells.^{3,10,20} It could also occur in an intermediate host, particularly a pig.^{3,9,10,20} Pigs have receptors that can bind swine, human, and avian influenza viruses.^{7,9,18,25} For this reason, they have been called 'mixing vessels' for the formation of new viruses.

Although reassortment can occur anywhere, many of the new viruses originate in Asia. In rural China and other regions, a variety of species including ducks are kept in close proximity to each other and to humans.^{9,12,14} This results in an increased opportunity for virus reassortment. The last three human pandemics appear to have been the result of reassortments.¹⁰

The 1957 H2N2 ('Asian flu') virus contained avian hemagglutinin, neuraminidase and an internal protein, and 5 other proteins from a human H1N1 strain.^{9,10} The H3N2 'Hong Kong flu' virus of 1968 had two new proteins from an avian virus – the new hemagglutinin and an internal protein – but kept the neuraminidase and remaining proteins from the H2N2 virus.^{9,10} The origin of the strain that caused the 1918 human pandemic ('Spanish flu') is uncertain. Although the hemagglutinin protein is more closely related to avian influenza viruses than to human influenza viruses, there is some evidence that this virus may have evolved in an intermedi-

ate host before causing an epidemic in humans.¹⁰ Repeated reassortments of human, avian and swine influenza viruses have also resulted in novel swine viruses (see ‘etiology’ for a description of these viruses).

Reassortant highly pathogenic avian influenza viruses may become progressively more virulent for mammals. From 1999 to 2002, H5N1 avian influenza viruses isolated from healthy ducks in southern China acquired the ability to replicate and cause lethal disease in mice.¹⁴ Most of these viruses appear to be reassortants that contained a hemagglutinin gene related to the A/Goose/Guangdong/1/96 (H5N1) HPAI avian influenza virus and other genes from unknown Eurasian avian influenza viruses.

Disinfection

The influenza viruses are susceptible to a variety of disinfectants including 1% sodium hypochlorite, 70% ethanol, glutaraldehyde, formaldehyde and lipid solvents.^{1,11,23,35} They can also be inactivated by heat of 56°C for a minimum of 30 min, radiation or pH 2.^{1,11,35,44}

Infections in Humans

Incubation Period

The incubation period is usually short; most infections appear after 1 to 4 days.^{12,33-35}

Clinical Signs

Uncomplicated infections with the human influenza A or B viruses are usually characterized by upper respiratory symptoms, which may include fever, chills, anorexia, headache, myalgia, weakness, sneezing, rhinitis, sore throat or a nonproductive cough.^{8,12,32-35} Diarrhea, abdominal pain and photophobia have also been reported.^{8,32} Nausea, vomiting and otitis media are common in children, and febrile seizures have been reported in severe cases.^{33,34} In young children, the initial signs may mimic bacterial sepsis.³³ Most people recover in 1 to 5 days but, in some cases, the symptoms may last up to 2 weeks or longer.^{8,33,35}

More severe symptoms, including pneumonia, can be seen in individuals with chronic respiratory or heart disease.^{8,33-35} Secondary bacterial or viral infections may also occur.^{8,12,33,34} In addition, influenza A has been associated with encephalopathy, transverse myelitis, Reye syndrome, myocarditis, pericarditis and myositis.^{33,34}

Influenza C viruses are thought to mainly cause a mild upper respiratory disease in children and young adults, but more severe cases similar to influenza A or B have also been reported.^{12,37-39} Some infections have resulted in bronchitis or pneumonia.³⁷ Infections may also be asymptomatic.

Avian influenza infections in humans

Rare infections with avian influenza viruses have been reported in humans. Healthy children and adults, as well as

those with chronic medical conditions, have been affected.²⁰ While some infections have been limited to conjunctivitis and/or typical influenza symptoms, others were serious or fatal.^{3,5,9,14,19,20,45,49} Viral pneumonia, acute respiratory distress syndrome, severe bronchointerstitial pneumonia, multiple organ dysfunction and other severe or fatal complications have been reported.^{5,20} In one fatal case, the initial symptoms were limited to a persistent high fever and headache, and respiratory disease was not seen until later.⁵ The HPAI viruses appear to cause more severe infections than the LPAI viruses.³

The following human infections have been reported recently:

- In 1997, eighteen human infections were reported in association with a H5N1 avian influenza virus outbreak in poultry in Hong Kong.^{3,9,14,19,20} The symptoms included fever, sore throat and cough and, in some cases, severe respiratory distress and viral pneumonia.²⁰ Eighteen people were hospitalized and six died.
- In 1999, avian influenza (H9N2) was confirmed in two children in Hong Kong.^{3,14,20} The illnesses were mild and both children recovered. No other cases were found. Six unrelated H9N2 infections were also reported from mainland China in 1998-99; all six people recovered.^{3,14}
- In 2002, antibodies to an avian H7N2 virus were found in one person after an outbreak in poultry in Virginia.³
- In 2003, two avian influenza H5N1 infections were reported in a Hong Kong family that had traveled to China.^{3,14,20} One of the two people died. Another family member died of a respiratory illness while in China, but no testing was done.
- In 2003, 347 total and 89 confirmed human infections were associated with an outbreak of avian H7N7 influenza virus in poultry in the Netherlands.^{3,5,14,49} Most cases occurred in poultry workers, but three family members also became ill.^{3,5} In 78 of the confirmed cases, conjunctivitis was the only sign of infection.⁵ Two people had influenza symptoms such as fever, coughing and muscle aches. Five had both conjunctivitis and influenza-like illnesses. (Four cases were classified as “other.”) The single death occurred in an otherwise healthy veterinarian who developed acute respiratory distress syndrome and other complications.⁵ His initial symptoms included a persistent high fever and headache but no signs of respiratory disease. The virus isolated from the fatal case had accumulated a significant number of mutations, while viruses from most of the other individuals had not.⁵
- Cases of conjunctivitis have been reported after contact with H7N7 avian viruses in infected seals.^{5,16}

- In 2003, a H9N2 avian influenza virus infection was confirmed in a child in Hong Kong.^{3,20} The child was hospitalized but recovered.
- In 2003, a H7N2 infection with respiratory signs was reported in a patient in New York.³ The person, who had serious underlying medical conditions, was hospitalized but recovered.
- In 2004, two cases of conjunctivitis and flu-like symptoms were confirmed in poultry workers in Canada.⁴⁵ Both people recovered after treatment with an antiviral drug. Ten other infections were suspected but not confirmed; these cases included both conjunctivitis and upper respiratory symptoms. All of the infections were associated with a H7N3 virus outbreak in poultry.
- In 2004 and early 2005, human illness and deaths have been associated with widespread outbreaks of avian influenza (H5N1) among poultry in Asia. Seventy six cases with 37 deaths were confirmed in Vietnam, 17 cases with 12 deaths in Thailand, and 4 cases with 4 deaths in Cambodia.⁵¹ Deaths were not reported in other countries.

Swine influenza virus infections in humans

Although serologic evidence suggests that zoonotic infections with swine influenza viruses may be common, relatively few infections have been documented.⁷ It is unknown whether infections with swine influenza viruses differ significantly from infections with human influenza viruses.⁷

Reported cases of influenza caused by swine influenza viruses include the following:

- A self-limiting illness with flu symptoms was reported in a college student.²⁴ There was evidence that his roommate had been infected but remained asymptomatic.
- An infection with flu symptoms including diarrhea was reported in a young boy, who recovered.²⁴ There was no evidence of spread to his family.
- Swine influenza virus was isolated from an immunocompromised child with pneumonia who died.⁴⁶ Serologic evidence of possible infection was found in five contacts, but the infection did not spread further.
- A localized outbreak was reported at Fort Dix, New Jersey. A swine influenza virus was isolated from 5 recruits with respiratory disease, including one who died of pneumonia.^{9,12,24} Serologic evidence suggested that approximately 500 people on the fort had also been infected by person-to-person spread.

Equine influenza virus infections in humans

Antibodies to the equine H3N8 viruses have been reported in humans.¹² Human volunteers inoculated with an equine virus became ill, and virus could be isolated for up to 10 days.¹²

Communicability

The human influenza viruses are readily transmitted from person to person. Infected adults usually begin to shed influenza A viruses the day before the symptoms appear, and are infectious for 3 to 5 days after the initial signs.^{33,35} Young children can shed virus for up to 6 days before, and more than 10 days after they become ill.^{33,34} Severely immunocompromised individuals may remain infectious for weeks to months.^{33,34} Humans can transmit influenza viruses to ferrets and, occasionally, to swine.^{11,12,28,31}

Rare cases of person-to-person spread, including a localized outbreak among recruits at a military base, have been reported in humans infected with swine influenza viruses.^{9,12,24} Rare cases of probable person-to-person transmission, and no cases of sustained transmission, have been reported in humans infected with the avian influenza viruses.^{3,5}

Diagnostic Tests

In humans, influenza A and B can be diagnosed by virus isolation, detection of antigens or nucleic acids, or retrospectively by serology. The viruses can be isolated in cell lines or chicken embryos, and are identified by hemagglutination inhibition tests.^{8,12} Antigens can be detected in respiratory secretions by immunofluorescence or ELISAs.^{8,34} Commercial rapid diagnostic test kits (Directigen® Flu A test) can provide a diagnosis within 30 minutes.³⁴ PCR techniques are also available.^{33,34} Serologic tests include complement fixation, hemagglutination inhibition, and immunodiffusion.^{8,12,34} A rising titer is necessary to diagnose influenza by serology.

Avian influenza viruses can be identified by PCR, antigen detection or virus isolation.³ In the U.S., samples that test positive by PCR or antigen tests are confirmed by the Centers for Disease Control and Prevention (CDC). PCR and antigen testing of avian influenza viruses must be carried out in Biosafety Level (BSL) 2 laboratory conditions.³ BSL 3+ laboratory conditions are needed for isolation of the HPAI viruses.³

Treatment

Four antiviral drugs are available for influenza treatment in the U.S. Amantadine and rimantadine are active against influenza A viruses, if treatment is begun within the first 48 hours.^{8,33,35,50} Zanamivir and oseltamivir are effective for both influenza A and influenza B.^{33,50} Treatment usually results in milder symptoms and recovery, on average, one day sooner.^{8,33,50}

Drug resistance develops rapidly in viruses exposed to amantadine or rimantadine, and may emerge during treatment.^{8,12,33} Some of the H5N1 viruses isolated in 2004 in Asia have been resistant to amantadine and rimantadine. Laboratory studies have shown that influenza viruses can also become resistant to zanamivir and oseltamivir.^{33,50}

Prevention

An annual vaccine is available for influenza A and B.^{8,12} Both inactivated (injected) and live (intranasal) vaccines may be available.³³ The vaccine is given in the fall before the flu season.⁸ It contains the strains of viruses thought most likely to produce epidemics during the following winter, and is updated annually. Details on vaccine efficacy, vaccine types, and recommendations for vaccination in specific population groups are available from the CDC.³⁴

Three antiviral drugs - amantadine, rimantadine and oseltamivir - can be used for prophylaxis in high risk populations such as the elderly or immunocompromised.^{33,34,50}

Other preventative measures include avoidance of contact with people with symptomatic disease, as well as hand washing and other hygiene measures. People with influenza should avoid contact with ferrets.³¹ If contact is unavoidable, they should wear gloves and face masks to prevent transmitting the virus to the animal.²⁸

Preventative measures for the avian influenza viruses

The control of epidemics in poultry decrease the risk of exposure for humans.²⁰ People working with infected birds should follow good hygiene practices and wear protective clothing, including boots, coveralls, gloves, face masks and headgear.^{19,20} In addition, the World Health Organization (WHO) recommends prophylaxis with antiviral drugs in people who cull birds infected with H5N1 HPAI viruses.²⁰

To prevent reassortment between human and avian influenza viruses, people in contact with infected birds should be vaccinated against human influenza.^{10,20} They are also discouraged from having contact with sick birds while suffering flu symptoms.¹⁰

Morbidity and Mortality

Although the morbidity rates for influenza are high, uncomplicated infections with the human viruses are rarely fatal in healthy individuals.^{8,10,12,32,35} Infections are more severe in the elderly, young children (particularly infants), people with respiratory or cardiac disease, and those who are immunosuppressed.^{8,33-35} Influenza-related deaths are usually the result of pneumonia or the exacerbation of a cardiopulmonary condition or other chronic disease.³⁴ Over 90% of these deaths occur in the elderly.³³ The estimated mortality rate from influenza is 0.0004-0.0006% in persons from 0-49 years old, 0.0075% between the ages of 50 and 64, and 0.1% in those over 65.^{33,34} Deaths are rare in children, but can occur.^{33,34} Immunity to the viral surface antigens reduces the risk of infection and severity of disease. Antibodies offer limited or no protection against other virus types or subtypes.³³

Human influenza can occur as a localized outbreak, an epidemic, a pandemic, or as sporadic cases.¹⁰ Although a new virus may spread among a population before the "flu season," epidemics in temperate regions usually do not begin

until after school starts in the fall.⁸ During a typical epidemic, influenza appears first among school-aged children, then spreads to preschool children and adults.^{8,12} During epidemics, 15- 40% of the population may be infected.^{10,12} The outbreak usually lasts for 3 to 6 weeks.^{8,12} Epidemics in tropical regions are not usually seasonal.¹²

Antigenic drift is usually responsible for small scale epidemics and localized outbreaks.⁹ In North America, an epidemic of influenza A usually occurs every 1 to 3 years, and an epidemic of influenza B every 3 to 4 years.³⁵ Since 1968, the type A (H3N2) viruses have caused the most serious outbreaks with the highest mortality rates.^{33,34} Influenza C viruses cause sporadic cases of influenza and minor localized outbreaks, but have not, to date, been associated with epidemics.^{8,12,35,39}

Severe pandemics, which last occurred in 1918, 1957 and 1968, are caused by antigenic shifts in influenza A viruses.^{8,10} During influenza pandemics, the morbidity and mortality rates can increase dramatically in all age groups.^{3,8,9,12,18,34} In the most severe pandemic, in 1918, the morbidity rate was 25-40% and the case fatality rate 2-5%.¹⁰ Approximately 500,000 deaths were reported in the U.S. and an estimated 20-50 million deaths worldwide.^{3,8-10,12,18} After a pandemic, an influenza virus usually becomes established in the population and circulates for years.³

Zoonotic influenza

Human infections with avian influenza viruses are rarely reported. The severity of the disease seems to depend on the virus subtype and strain. More severe infections have been reported with the HPAI viruses, particularly H5N1. From 1997 to 2005, there were at least 119 confirmed H5N1 virus infections, and 60 of these cases were fatal.^{3,9,14,19,20,45,51} Human disease has also been reported after infections with H7N2, H7N3, H7N7 and H9N2 viruses.^{3,5,14,16,45,49} Most infections with the H7 viruses have been limited to conjunctivitis, but influenza symptoms have also been seen. A single death was seen in an otherwise healthy veterinarian who became infected with a H7N7 virus.⁵

Most humans infected with the swine influenza viruses have had mild disease or been asymptomatic, but three deaths were reported: one in a young boy who was immunosuppressed, one in a military recruit and one in a pregnant woman who developed pneumonia.^{9,12,24,46} During the only known outbreak, on a military base in New Jersey, the swine influenza virus was isolated from 5 people with respiratory disease, including one who died of pneumonia, and serologic evidence of infection was found in approximately 500 of 12,000 people on the base.^{9,12,24} Serologic evidence also suggests that people who work with pigs are occasionally infected with swine influenza viruses, but these infections may not be reported if they resemble human influenza.^{7,9,12}

Infections in Animals

Species Affected

Influenza A Viruses

Influenza A viruses can cause disease in birds, swine, horses, ferrets, mink, seals, whales, humans and other species.

Avian influenza viruses mainly infect birds, but can also cause disease in horses, swine, mink, cats, marine mammals and humans.^{3,4,9,10,12,15-18} Waterfowl appear to be the natural reservoirs for the influenza A viruses.^{2,9,12,18,20} Most, but not all, infections in wild birds are asymptomatic.^{2,3,9,12} Poultry can develop serious or mild disease, depending on the subtype and strain of virus.^{2,22} In cage birds, most infections have been recorded in passerine birds.²² Psittacine birds are rarely affected.

Swine influenza viruses mainly affect pigs but can also cause disease in turkeys and humans.^{7,11,12,23}

Equine influenza viruses mainly affect horses, donkeys and other Equidae.^{4,27} Antibodies to the equine H3N8 viruses have been reported in humans.¹²

Human influenza viruses mainly cause disease in humans and ferrets.^{28,30-32} They can also infect pigs and have been reported in dogs, cattle and birds.^{11,12,29} Experimental infections have been reported in horses.¹²

Influenza B viruses

Influenza B viruses can cause disease in humans, ferrets and seals, however these viruses have also been isolated from pigs and a horse.^{9,12,23,36} Serologic evidence of infection has been found in pigs, dogs and horses.^{12,29}

Influenza C viruses

Influenza C viruses have been isolated from humans and swine.^{9,11,12,23,39,40} These viruses can cause disease in experimentally infected dogs.¹² Serologic evidence of infection has been found in pigs, dogs and horses.^{12,29,41,42}

Incubation Period

The incubation period is generally short. The clinical signs usually appear within 1 to 3 days in horses, pigs or seals.^{4,11,12,23,25,27,47} Rarely, incubation periods up to 7 days have been reported in some horses.²⁷ In poultry, the incubation period can be a few hours to a week.^{2,11,13}

Clinical Signs

Avian influenza

The highly pathogenic avian influenza (HPAI) viruses cause severe disease in poultry. These viruses can cause serious infections in some species of birds on a farm while leaving others unaffected.^{2,12} The clinical signs are variable.^{2,6,11,22} The typical symptoms are those of a respiratory disease with sinusitis, lacrimation, edema of the head, cyanosis of the

head, comb and wattle, and green to white diarrhea.^{2,6,11,13,19} Hemorrhagic lesions may be found on the comb and wattles of turkeys.^{2,11} Other signs may include anorexia, coughing, sneezing, blood-tinged oral and nasal discharges, ecchymoses on the shanks and feet, neurologic disease, decreased egg production, loss of egg pigmentation and deformed or shell-less eggs.^{2,11-13, 19} Sudden death may occur with few other signs.⁶ Most of the flock usually dies.² In ducks, the most common symptoms are sinusitis, diarrhea and increased mortality.^{2,11}

The low pathogenic (LPAI) viruses usually cause subclinical or mild illness.²² The symptoms may include decreased egg production or increased mortality rates.^{3,13} More severe disease, mimicking highly pathogenic avian influenza, can be seen if the birds are concurrently infected with other viruses or there are other exacerbating factors.^{6,22}

Turkeys infected with swine influenza viruses may develop respiratory disease, have decreased egg production, or produce abnormal eggs.¹¹

Avian influenza is often subclinical in wild birds, but some strains can cause illness and death.^{2,3,9,12}

Swine influenza

Swine influenza is an acute upper respiratory disease characterized by fever, lethargy, anorexia, weight loss and labored breathing.^{9,11,12,23,25} Coughing may be seen in the later stages of the disease.⁹ Sneezing, nasal discharge and conjunctivitis are less common symptoms.⁹ Abortions may also occur.^{23,25} Some virus strains can circulate in pigs with few or no clinical signs.^{9,12,18}

Complications may include secondary bacterial or viral infections.^{9,25} Severe, potentially fatal bronchopneumonia is occasionally seen.¹¹

Equine influenza

Equine influenza usually spreads rapidly in a group of animals. In naïve horses, the first sign is usually a fever, followed by a deep, dry cough.⁴ Other symptoms may include a serous to mucopurulent nasal discharge, myalgia, inappetence and enlarged submandibular lymph nodes.^{4,11,12,27} There may be edema of the legs and scrotum, and spasmodic impaction colic has been reported.^{4,27} Animals with partial immunity can have milder, atypical infections with little or no coughing or fever.⁴

Healthy adult horses usually recover within 1-2 weeks, but the cough may persist longer.^{4,12,27} Secondary bacterial infections prolong recovery.^{4,11,27} Death in adult horses usually results from bacterial pneumonia, pleuritis or purpura hemorrhagica.⁴ Sequelae may include chronic pharyngitis, chronic bronchiolitis and emphysema.^{4,27} Interstitial myocarditis can occur during or after the infection.¹² Young foals without maternal antibodies can develop a rapidly fatal viral pneumonia.^{4,12}

Horses experimentally infected with human influenza virus (H3N2 ‘Hong Kong’) developed a mild febrile illness.¹² The virus could be isolated for up to 5 days.

Influenza in ferrets

Ferrets are susceptible to the human influenza viruses. The symptoms may include fever, anorexia, depression, listlessness, sneezing, purulent nasal discharge and coughing.^{28,30,32} The infection is not usually fatal in adult animals, which generally recover in 5 days to 2 weeks.^{28,31,32} More severe or fatal disease can be seen in neonates.³²

Influenza in mink

In 1984, a H10N4 avian influenza virus caused an epidemic on 33 mink farms in Sweden.¹² The symptoms included anorexia, sneezing, coughing, nasal and ocular discharges, and numerous deaths.

H5N1 influenza in cats

Influenza A was recently reported in cats. During an epidemic of H5N1 avian influenza in Asian poultry, there were anecdotal reports of fatal influenza in domestic cats, a white tiger and a clouded leopard.¹⁵ H5N1 avian influenza virus was isolated from these animals, which were all thought to have been infected by eating raw, infected poultry.

Clinical signs in cats experimentally infected with the H5N1 virus included fever, lethargy, conjunctivitis, protrusion of the third eyelid and dyspnea.¹⁷ One cat died on the 6th day after inoculation; the remaining animals were euthanized and necropsied the following day. There was no evidence of infection after inoculation with a human H3N2 virus.¹⁷

Influenza in marine mammals

Influenza A viruses have been associated with outbreaks of pneumonia in seals and disease in a pilot whale.^{12,16,47} The viruses appear to be of avian origin.¹⁶ Clinical signs in seals have included weakness, incoordination, dyspnea and swelling of the neck.⁴⁷ A white or bloody nasal discharge was seen in some animals. In the single known case in a whale, the symptoms included extreme emaciation, difficulty maneuvering and sloughing skin.⁴⁷

Influenza in dogs

The clinical signs in dogs experimentally infected with influenza C virus included nasal discharge and conjunctivitis, which persisted for 10 days.¹²

Communicability

Influenza viruses are readily transmitted between animals in the same species. More rarely, they can be transmitted to other species. Pigs may begin excreting influenza viruses within 24 hours of infection and typically shed the viruses for 7 to 10 days.^{18,25} Shedding up to 4 months has been documented in one pig.¹⁸ Horses begin excreting the virus during the incubation period and usually excrete the virus for 4 to 5 days or less after the onset of clinical signs.^{4,11}

Most chickens shed LPAI influenza viruses for only a week, but a minority of the flock can excrete the virus in the feces for up to 2 weeks.⁴⁴ Ducks can shed avian influenza viruses for up to 30 days.⁹

Cats experimentally infected with the avian influenza H5N1 virus shed the virus by the third day post-inoculation, and were able to infect two sentinel cats in close contact.¹⁷

Diagnostic Tests

Avian influenza

Avian influenza is usually diagnosed by virus isolation in embryonated eggs.^{6,13} The virus can be isolated from tracheal, oronasal or cloacal swabs in live birds, and pooled or individual organ samples (trachea, lungs, air sacs, intestine, spleen, kidney, brain, liver and heart) from dead birds.^{2,6} Feces can be substituted in small birds if cloacal samples are not practical. The virus is subtyped with immunodiffusion tests, or hemagglutination and neuraminidase inhibition tests.⁶ Virus inoculation into susceptible birds, together with genetic tests, is used to differentiate LPAI from HPAI viruses.⁶

Viral antigens can be detected with ELISAs, including a rapid test (Directigen® Flu A kit, Becton Dickinson Microbiology Systems).⁶ Reverse transcription polymerase chain reaction (RT-PCR) tests may be used to identify nucleic acids.⁶ Serological tests, including agar gel immunodiffusion, hemagglutination inhibition and ELISAs, may be used as supplemental tests.⁶

Swine influenza

Swine influenza can be diagnosed by virus isolation, detection of viral antigens or nucleic acids, and serology. Mammalian influenza viruses can be isolated in embryonated chicken eggs or cell cultures.^{9,25} The swine influenza viruses can be recovered from lung tissues at necropsy, or nasal or pharyngeal swabs from acutely ill pigs.^{11,23,25} Recovery is best from an animal with a fever, 24–48 hours after the onset of disease.²⁵ Isolated viruses are subtyped with hemagglutination inhibition and neuraminidase inhibition tests.^{9,25}

Immunofluorescent techniques can detect antigens in fresh lung tissue, nasal epithelial cells or bronchoalveolar lavage.^{9,25} Other antigen tests include immunohistochemistry on fixed tissue samples, and ELISAs including the Directigen® Flu A test.^{9,25} RT-PCR assays are also available.^{9,25}

Serology on paired samples can diagnose swine influenza retrospectively.²³ The hemagglutination inhibition test, which is subtype specific, is most often used.^{9,23,25} It may not detect new viruses.⁹ ELISA tests are also used. Rarely used serological tests in swine include agar gel immunodiffusion, the indirect fluorescent antibody test and virus neutralization.²⁵

Equine influenza

Equine influenza may tentatively be diagnosed based on the clinical signs.²⁷ As in swine, the disease is confirmed by virus isolation, the detection of viral antigens or nucleic

acids, or retrospectively by serology.^{4,27} In horses, peak virus shedding is thought to occur during the first 24 to 48 hours of fever.⁴

As in swine, a serological diagnosis requires paired acute and convalescent samples.⁴ The most commonly used tests in horses are the hemagglutination inhibition test and a single-radial hemolysis (SRH) test.⁴ An ELISA that can distinguish natural from vaccine-induced antibodies is in development.⁴

Treatment

Animals with influenza are usually treated with supportive care and rest.^{4,13,23,27} Antibiotics may be used to control secondary infections.^{4,13,27} Antiviral drugs are not generally given to animals, but could be of use in valuable horses.²

Poultry flocks with highly pathogenic avian influenza are depopulated and are not treated.^{3,11}

Prevention

Inactivated influenza vaccines are available for pigs, horses and, in some countries, birds.^{4,11,12,23,25,27} The vaccines do not always prevent infection, but the disease is usually milder if it occurs. In the U.S., avian influenza vaccines are used most often in turkeys and are intended only to prevent infection by LPAI viruses.⁶ HPAI vaccines are not used routinely in the U.S. or most other countries.⁶ A “DIVA” (differentiating infected from vaccinated animals) strategy has been successfully used to control a low pathogenicity avian influenza outbreak in Italy.⁴⁸ This strategy depends on using an inactivated vaccine containing the homologous H type and a heterologous N type. Vaccinated birds that subsequently become infected can be detected by testing for antibodies to the N type of the field strain.

Influenza vaccines change periodically to reflect the current subtypes and strains in a geographic area. In general, swine and equine viruses display less antigenic drift than human viruses and these vaccines are changed less often.^{4,9,11} Avian vaccines are usually autogenous or from viruses of the same subtype or hemagglutinin type.⁶

Poultry can be infected by contact with newly introduced birds or wild birds, particularly waterfowl.^{9,11,19,20} The risk of infection can be decreased by all-in/ all-out flock management, and by preventing any contact with wild birds or their water sources.^{2,19} Biosecurity measures can prevent the entry of the virus on fomites.^{2,19,20} Birds should not be returned to the farm from live bird markets or other slaughter channels.¹⁹

In pigs and horses, influenza is usually introduced into a facility in a new animal.^{9,11,18,23,27} Isolation of newly acquired animals can decrease the risk of transmission to the rest of the herd.²⁷ The virus usually persists in an infected swine herd and causes periodic outbreaks, but good management can decrease the severity of disease.^{9,12,18,23} Infected swine herds can be cleared of influenza viruses by depopulation.¹⁸

Ferrets can be infected by the human influenza viruses; people with influenza should avoid contact with ferrets.³¹ If contact is unavoidable, a face mask and gloves should be worn.²⁸

Cats should not be fed poultry infected with the avian influenza viruses.¹⁵

Prevention of virus transmission during outbreaks

During an outbreak of influenza among mammals, quarantines and isolation of infected animals help prevent virus dissemination.^{4,11} Good hygiene can keep the virus from spreading on fomites. Rest decreases virus shedding in horses.⁴ Infected facilities should be cleaned and disinfected after the outbreak.

In poultry, outbreaks of highly pathogenic avian influenza are controlled by eradication.^{3,11} The outbreak is managed by quarantine, depopulation, cleaning and disinfection, and surveillance around the affected flocks. Strict hygiene is necessary to prevent virus transmission on fomites.

Morbidity and Mortality

The severity of an influenza virus infection varies with the dose and strain of virus and the host's immunity. In mammals, uncomplicated infections are usually associated with high morbidity rates, low mortality rates and rapid recovery.^{4,9,11,12,23,25,27} Secondary bacterial infections can exacerbate the symptoms, prolong recovery and result in complications such as pneumonia.

Swine influenza

Influenza is a major cause of acute respiratory disease in finishing pigs. Approximately 25-33% of 6-7 month old finishing pigs and 45% of breeding pigs have antibodies to the classical swine H1N1 virus in the U.S.^{12,18} High seroprevalence rates to swine influenza viruses have also been reported in other countries.^{9,12,18,29} In addition, pigs can be infected with the human influenza A, B and C viruses.^{9,11,12,23,29,39,40,42} In the U.K., a study found antibodies to both swine and human influenza viruses in 14% of all pigs.¹⁸ Approximately 10% of the pigs were seropositive for influenza C viruses, but only sporadic infections with the human influenza B viruses were found.²⁹ In Japan, a similar study found antibodies to the type C viruses in 19% of pigs.⁴²

Swine influenza viruses are usually introduced into a herd in an infected animal, and can survive in carrier animals for up to 3 months.^{11,18,23} In a newly infected herd, up to 100% of the animals may become ill but most animals recover within 5 to 7 days if there are no secondary bacterial infections or other complications.^{9,11,23,25} In uncomplicated cases, the case fatality rate has ranged from less than 1-3%.^{11,12}

Once the virus has been introduced, it usually persists in the herd.^{9,12,18} Annual outbreaks are often seen, and occur mainly during the colder months.^{9,12,18,23} Many of the infec-

tions in endemically infected herds are subclinical; typical signs of influenza may occur in only 25% to 30% of the pigs.^{9,18} Maternal antibodies decrease the severity of disease in young pigs.⁹ Some viruses can infect the herd with few or no clinical signs.^{9,12,18}

Influenza epidemics can occur if a virus infects a population without immunity to the virus, or if the infection is exacerbated by factors such as poor husbandry, stress, secondary infections or cold weather.^{12,18} In the epidemic form, the virus spreads rapidly in pigs of all ages.²⁵ In a 1918 epizootic, millions of pigs developed influenza, and thousands of the infections were fatal.¹² Recently, a novel H3N2 entered pigs in the Midwest and has caused serious illness and reproductive losses in sows.⁹

Equine influenza

In horses, influenza outbreaks are not as seasonal as they are in pigs or humans.⁴ Most outbreaks are associated with sales, races and other events where horses congregate.^{4,11} Widespread epidemics can be seen, with morbidity rates up to 60-90%, in naïve populations.^{4,12} In 1987, an equine influenza epidemic in India affected more than 27,000 animals and killed several hundred.⁴ In populations that have been previously exposed, cases are seen mainly in young and newly introduced animals.^{4,12}

Unless there are complications, healthy adult horses usually recover within 1 to 2 weeks, although coughing can persist.^{4,12,27} The H3N8 viruses usually cause more severe disease than the H7N7 viruses.^{4,12} Deaths are rare in adult horses, and are usually the result of secondary bacterial infections.^{4,12,27} Higher mortality rates have been reported in foals, animals in poor condition and donkeys.^{4,27} A rapidly fatal viral pneumonia may be seen in young foals with no maternal antibodies.^{4,12} In horses, tracheal clearance rates can be depressed for up to a month after infection.⁴

Avian influenza viruses have rarely been reported in horses. In 1989, a novel strain of equine influenza [A/eq/Jilin/89 (H3N8)] caused a serious epidemic in Chinese horses.⁴ The morbidity rate was 80% and the mortality rate was 20%. The virus appeared to be an avian influenza virus. A related virus caused influenza in a few hundred horses the following year but there were no deaths. The avian-like virus continued to circulate in horses for at least 5 years without further fatalities.

Influenza in other mammals

In 1984, an outbreak with an avian H10N4 virus was reported on Swedish mink farms. The outbreak affected 33 farms and killed 3,000 mink.¹² The morbidity rate was nearly 100%.

Fatal infections with an avian H5N1 virus were recently reported in 3 domestic cats, a white tiger and a clouded leopard.¹⁵ Experimental infections were also reported in 8 cats.¹⁷ The morbidity and mortality rates are unknown. Cats

inoculated with a human H3N2 virus had no evidence of virus replication or disease.¹⁷

In seals, the case fatality rate was estimated to be 20% in one outbreak with a H7N7 virus, and 4% in an outbreak with a H4N5 virus.¹² Explosive epidemics in seals are thought to be exacerbated by high population densities and unseasonably warm temperatures.⁴⁷

Avian influenza

Avian influenza outbreaks occur in most countries including the U.S. Low pathogenic forms are seen most often, but outbreaks with the highly pathogenic H5 and H7 viruses are also reported periodically.^{2,3} In poultry, HPAI viruses are associated with very high morbidity and mortality rates, up to 90-100%.^{2,3} Any surviving birds are usually in poor condition. LPAI viruses usually result in mild or asymptomatic infections, but may also mimic HPAI viruses.^{6,22}

Symptomatic infections and outbreaks have been reported in wild birds, but are unusual.^{2,3,9,12}

Post-Mortem Lesions

Avian influenza

The lesions in poultry are highly variable and can resemble other avian diseases.² There may be subcutaneous edema of the head and neck, fluid in the nares and oral cavity, and severe congestion of the conjunctivae. Hemorrhagic tracheitis can be seen in some birds; in others, the tracheal lesions may be limited to excess mucoid exudate. Petechiae may be found throughout the abdominal fat, serosal surfaces and peritoneum. Hemorrhages may also be seen on the mucosa of the proventriculus, beneath the lining of the gizzard, and in the intestinal mucosa. The kidneys can be severely congested and are sometimes plugged with urate deposits. The ovaries may be hemorrhagic or degenerated, with areas of necrosis. The peritoneal cavity often contains yolk from ruptured ova. Severe airsacculitis and peritonitis may be seen in some birds. In birds that die peracutely and in young birds, the only lesions may be severe congestion of the musculature and dehydration.

Swine influenza

In uncomplicated infections, the gross lesions are mainly those of a viral pneumonia.⁹ Affected parts of the lungs are depressed and consolidated, dark red to purple-red, and sharply demarcated.^{9,23} The lesions may be found throughout the lungs but are usually more extensive in the ventral regions.⁹ Other parts of the lungs may be pale and emphysematous.²³ The airways are often dilated and filled with mucopurulent or blood-tinged, fibrinous exudate.²³ The bronchial and mediastinal lymph nodes are typically enlarged.^{9,23} Severe pulmonary edema, or serous or serofibrinous pleuritis may also be seen.²³ Some strains of swine influenza viruses produce more marked lesions than others.⁹ Generalized lymphadenopathy, hepatic congestion and

pulmonary consolidation were reported in one outbreak of severe disease in swine.¹²

Equine influenza

Interstitial pneumonia, pleuropneumonia, bronchitis, perivascularitis and interstitial myocarditis have been reported in fatal cases in horses.²⁷

Influenza in cats

The lesions reported in experimentally infected cats were multiple to coalescing foci of pulmonary consolidation.¹⁷ The lesions were similar whether the cats were infected intratracheally or by the ingestion of infected chicks.

Influenza in marine mammals

In seals, pneumonia with necrotizing bronchitis, bronchiolitis and hemorrhagic alveolitis have been reported.^{16,47} In a single case in a whale, the lungs were hemorrhagic and a hilar lymph node was greatly enlarged.⁴⁷

Internet Resources

Animal Health Australia. The National Animal Health Information System (NAHIS)

<http://www.aahc.com.au/nahis/disease/dislist.asp>

Centers for Disease Control and Prevention (CDC)

<http://www.cdc.gov/flu/>

Material Safety Data Sheets – Canadian Laboratory Center for Disease Control

<http://www.hc-sc.gc.ca/pphb-dgspssp/msds-ftss/index.html#menu>

Medical Microbiology

<http://www.gsbs.utmb.edu/microbook>

OIE Manual of diagnostic tests and vaccines for terrestrial animals

http://www.oie.int/eng/normes/mmanual/a_summry.htm

Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP)

<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5306a1.htm>

The Merck Manual

<http://www.merck.com/pubs/mmanual/>

The Merck Veterinary Manual

<http://www.merckvetmanual.com/mvm/index.jsp>

USAHA Foreign Animal Diseases book

http://www.vet.uga.edu/vpp/gray_book/FAD/

World Organization for Animal Health (OIE)

<http://www.oie.int/>

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