

# Influenza

*Flu, Grippe, Avian Influenza,  
Grippe Aviaire, Fowl Plague,  
Swine Influenza, Hog Flu, Pig Flu,  
Equine Influenza, Canine Influenza*

**Last Updated:** January 19, 2009

**Author:**

Anna Rovid Spickler, DVM, PhD



IOWA STATE UNIVERSITY®

College of Veterinary Medicine  
Iowa State University  
Ames, Iowa 50011  
Phone: 515.294.7189  
Fax: 515.294.8259  
cfsph@iastate.edu  
www.cfsph.iastate.edu



INSTITUTE FOR  
INTERNATIONAL  
COOPERATION IN  
ANIMAL BIOLOGICS

*an OIE Collaborating Center*

Iowa State University  
College of Veterinary Medicine  
www.cfsph.iastate.edu/IICAB/



## Importance

Influenza viruses are found in a number of species including birds, humans, swine, horses and dogs. In the mammalian species to which they are adapted, these viruses cause respiratory disease with high morbidity and low mortality rates. More severe cases can occur in conjunction with other diseases or debilitation, as well as in infancy or old age. In wild birds, avian influenza viruses are typically, though not always, carried asymptomatically.<sup>1-7</sup> In poultry, there are two forms of disease. Low pathogenicity avian influenza (LPAI) viruses generally cause asymptomatic infections, mild respiratory disease or decreased egg production.<sup>4,8-10</sup> In contrast, high pathogenicity avian influenza (HPAI) viruses cause severe disease that can kill up to 90-100% of a poultry flock.<sup>2,4</sup> Some avian influenza viruses can also infect mammals including humans. The severity of zoonotic avian influenza varies with the virus. Although many human infections are limited to conjunctivitis or mild respiratory disease, some viral strains cause severe disease and death.<sup>4,7,11-15</sup> Generally, avian influenza viruses do not spread efficiently in mammals, and infections remain limited to individual animals or small groups.<sup>1,4,16</sup> However, some viruses can become adapted to a new species and cause outbreaks, epidemics or pandemics.<sup>1,16-20</sup>

Currently, the world is experiencing an extensive HPAI outbreak, with no immediate prospects for complete, worldwide eradication. In 2003, HPAI viruses of the H5N1 subtype appeared in poultry in several nations in Southeast Asia.<sup>7</sup> Although at times this epidemic appeared to be under control, eradication was never complete. The outbreaks continued to smolder and spread, and eventually avian H5N1 viruses reached other parts of Asia, as well as parts of Europe, the Pacific, Africa and the Middle East.<sup>4</sup> The H5N1 strains responsible for this epidemic appear to be unusually virulent. As of January 2009, they have been responsible for approximately 390 human infections, generally as the result of close contact with poultry; about two thirds of these cases were fatal.<sup>21</sup> Avian H5N1 viruses have also infected and killed mammals of other species, including tigers, leopards, housecats, palm civets, a dog and a stone marten.<sup>4,22-31</sup> In addition, numerous deaths have been reported in wild birds, which usually carry avian influenza viruses asymptomatically.<sup>4,7,29,32-34</sup> There are fears that an avian H5N1 strain could eventually become adapted to humans, resulting in a human pandemic.

Other avian influenza viruses can also undergo cross-species transmission. LPAI H9N2 viruses, which have become endemic in poultry in parts of Asia and the Middle East, may be of particular concern.<sup>35-37</sup> These viruses have caused disease outbreaks in poultry in many countries.<sup>37-39</sup> Recently, they were found in pigs with respiratory disease and fatal paralysis in China.<sup>36</sup> In addition, H9N2 viruses have infected humans.<sup>35,36</sup> As of January 2009, human H9N2 infections have been significantly less severe than those caused by avian HPAI H5N1 viruses.<sup>35,36</sup>

## Etiology

Viruses in the family Orthomyxoviridae cause influenza. There are three genera of influenza viruses: *influenzavirus A*, *influenzavirus B* and *influenzavirus C*.<sup>40</sup> These viruses are also called type A, type B and type C influenza viruses.

### *Influenza A viruses*

Influenza A viruses include the avian, swine, equine and canine influenza viruses, as well as the human influenza A viruses. Influenza A viruses are classified into subtypes based on two surface antigens, the hemagglutinin (H) and neuraminidase (N) proteins. There are 16 hemagglutinin antigens (H1 to H16) and nine neuraminidase antigens (N1 to N9).<sup>2,4,10,41</sup> These two proteins are involved in cell attachment and release from cells, and are also major targets for the immune response.<sup>14,16,42</sup> Only limited subtypes are found in each species of mammal.<sup>43</sup> Influenza A viruses are also 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.<sup>1,43</sup> [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.

## Antigenic shift and drift in influenza A viruses

Influenza A viruses change frequently. Strains evolve as they accumulate point mutations during virus replication; this process is sometimes called ‘antigenic drift’.<sup>43</sup> A more abrupt change can occur during genetic reassortment. Reassortment is possible whenever two different influenza viruses infect a cell simultaneously; when the new viruses (the ‘progeny’) are assembled, they may contain some genes from one parent virus and some genes from the other.<sup>16</sup> Reassortment between different strains results in the periodic emergence of novel strains. Reassortment between subtypes can result in the emergence of a new subtype. Reassortment can also occur between avian, swine, equine, canine 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 a host species is called an ‘antigenic shift.’ Antigenic shifts can result from three mechanisms: 1) genetic reassortment between subtypes, 2) the direct transfer of a whole virus from one host species into another, or 3) the re-emergence of a virus that was found previously in a species but is no longer in circulation.<sup>1,14</sup> For example, human viruses can continue to circulate in pigs and could re-emerge into the human population.<sup>14</sup> Antigenic drift and antigenic shifts result in the periodic emergence of novel influenza viruses. By evading the immune response, these viruses can cause influenza epidemics and pandemics.

## Avian influenza viruses

Avian influenza viruses are found in a wide variety of domesticated and wild birds.<sup>1,4,9,12</sup> They are also isolated occasionally from mammals including humans.<sup>1,4,13,18,19,22-31,44,45</sup> Waterfowl (order Anseriformes) and shorebirds (order Charadriiformes) seem to be the natural reservoirs for the type A influenza viruses, and carry all of the known subtypes.<sup>1,2,7,9,15,17,41</sup> The predominant subtypes in wild ducks change periodically.<sup>1</sup> Most, though not all, infections in wild waterfowl and shorebirds are asymptomatic.<sup>1-5,7,14</sup>

Poultry can be infected by a wide variety of subtypes; some of these viruses cause avian influenza. Avian influenza viruses are classified as either high pathogenicity avian influenza (HPAI) viruses or low pathogenicity avian influenza (LPAI) viruses, based on the genetic features of the virus and the severity of disease in poultry.<sup>2,4</sup> To date, only subtypes that contained H5 or H7 have caused HPAI; subtypes that contained other hemagglutinins have been found only in the LPAI form.<sup>7,8,10</sup> H5 and H7 LPAI viruses also exist, and can evolve into high pathogenicity strains.<sup>4,7,15</sup> From 1993 to 2000, LPAI subtypes containing H1 to H7 and H9 to H11 were isolated from live bird markets in the northeastern U.S.<sup>46</sup>

Limited information is available on the subtypes found in other species of birds. Subtypes that have been found in ratites include H3N2, H4N2, H4N6, H5N1,

H5N2, H5N9, H7N1, H7N3, H9N2, H10N4 and H10N7.<sup>8,29,47,48</sup> Isolates from cage birds usually contain H3 or H4; however, infections with high pathogenicity subtypes containing H7 or H5 can also occur.<sup>8,29,32,49-51</sup>

## Swine influenza viruses

Swine influenza viruses are found mainly in pigs, but they have also been found in other species including humans.<sup>1,14,41,43,52-54</sup> There is less antigenic drift in swine influenza viruses than in human influenza A viruses.<sup>14</sup> The most common subtypes currently found in pigs are H1N1, H1N2 and H3N2; however, the situation is complex, as two or more viruses of each subtype are circulating in swine populations.<sup>55</sup> Recently, H3N1 influenza viruses have also been isolated from pigs in the U.S. and Korea,<sup>56-58</sup> and H2N3 influenza viruses were detected in pigs in the U.S.<sup>59</sup>

One H1N1 virus circulating in the U.S. is the ‘classical H1N1 swine influenza virus. This virus, the first influenza virus known to have infected pigs, was first found in swine populations in 1918.<sup>1,14,16,17</sup> An ‘avian-like’ H1N1 virus circulates in European and U.S. pigs.<sup>14,16,17</sup> This virus seems to be an avian influenza virus that was transmitted whole to pigs.<sup>16,17,60</sup> It has, in some locations, replaced the classical H1N1 virus.<sup>16,17</sup> A different ‘avian-like’ H1N1 virus is co-circulating with the classical H1N1 virus in pigs in Asia.<sup>17</sup> In addition, H1N1 reassortant viruses consisting of classical swine influenza virus genes and a human PB1 polymerase gene have been found in pigs in Canada.<sup>61</sup> A wholly human lineage H1N1 virus was recently reported from pigs in China.<sup>62</sup> This virus, which was responsible for an outbreak of acute respiratory illness in a herd in Guangdong, has been designated A/Swine/Guangdong/96/06 (H1N1).<sup>62</sup>

In North America, H3N2 viruses first emerged in pigs in the U.S. Midwest.<sup>12,16,61,63</sup> The viruses found in the U.S. are triple reassortants.<sup>12,16,63</sup> 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.<sup>63</sup> New triple reassortant H3N2 viruses have recently been found in Canada.<sup>64</sup> These viruses resemble the H3N2 viruses isolated in the U.S., but contain a different neuraminidase gene from a human influenza virus.<sup>64</sup> They have been isolated from pigs, turkeys and a Canadian swine farmer.<sup>64</sup> H3N2 viruses are also found in Europe and Asia, but these viruses 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.<sup>14</sup> The European H3N2 viruses contain human H3 and N2 proteins, and internal proteins from the avian virus.<sup>14</sup>

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.<sup>14</sup> Some H1N2 viruses in Canadian pigs contain neuraminidase and hemagglutinin genes from two different human

influenza viruses, the polymerase gene from human H1N2 viruses, and genes from classical H1N1 swine influenza viruses.<sup>61</sup> The H1N2 virus in Europe is a reassortant of a human H1N1 virus and the 'human-like' European H3N2 virus.<sup>14,17</sup> Other novel reassortants of swine influenza viruses continue to be discovered.<sup>65,66</sup>

New subtypes have also been found in some populations. The novel subtype H3N1 has recently been isolated from pigs in the U.S.<sup>56,57</sup> This subtype appears to contain genes from human, swine and avian influenza viruses.<sup>56,57</sup> A different H3N1 influenza virus, containing human and swine influenza virus genes, has been found in Korea.<sup>58</sup> An H2N3 virus isolated from pigs with respiratory disease in the U.S. contained genes from avian and swine influenza viruses.<sup>59</sup> An avian H9N2 virus has been reported from outbreaks of respiratory disease and paralysis in pigs in southeastern China, and may circulate in swine populations there.<sup>36</sup> This subtype appears to contain neuraminidase and hemagglutinin genes from avian H9N2 viruses and internal genes from a H5N1 virus (Sw/SD/2/03) that also infects pig populations in the area.<sup>36</sup>

## Equine influenza viruses

Equine influenza viruses mainly infect horses and other Equidae (i.e., donkeys, mules and zebras).<sup>1,18,67,68</sup> The two subtypes known to cause disease in horses are H7N7 (equine virus 1) and H3N8 (equine virus 2).<sup>1,18,43</sup> There is less antigenic drift in these viruses than human influenza A viruses.<sup>18,43</sup> The H7N7 virus is currently extinct or present at only very low levels in some parts of the world.<sup>1,18,69</sup> H3N8 viruses have diverged into two distinct evolutionary lineages circulating in Europe or America. Recently, the American lineage has been reported from some outbreaks in Europe.<sup>70</sup> 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.<sup>18,69</sup> This 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 five years without further fatalities.

One equine H3N8 virus recently jumped into dogs.<sup>71-73</sup>

## Canine influenza viruses

A H3N8 canine influenza virus has been reported in canine populations in a number of U.S. states.<sup>74-81</sup> This virus appears to be an equine influenza virus that recently jumped species, and bears a close resemblance to an isolate seen in horses in Wisconsin in 2004.<sup>71,72</sup>

An H3N2 virus, isolated during an outbreak of canine respiratory disease in Korea in 2007, has the potential to become a second canine influenza virus.<sup>45</sup> There is evidence that this virus may have been transmitted between dogs during the outbreak, and dog-to-dog transmission occurs readily in experimentally infected dogs.<sup>45,82</sup> The H3N2 virus seems to have originated in birds.<sup>45</sup> It contains gene segments that may come from

several different avian viruses.<sup>45</sup> At least three different isolates of this virus have been recovered.<sup>45</sup>

## Human influenza A viruses

Human influenza A viruses are mainly found in humans, but they can also infect ferrets and sometimes swine.<sup>1,17,43,61,62,83-87</sup> Experimental infections have been reported in raccoons.<sup>88</sup> Human viruses can also replicate, to a limited extent, in the nasal epithelium of experimentally infected horses.<sup>69</sup> H1N1, H1N2 and H3N2 viruses are currently in general circulation in humans.<sup>4,89</sup> The H1N2 viruses appeared most recently. These viruses were first seen in human populations in 2001, probably as a result of genetic reassortment between the H3N2 and H1N1 viruses.<sup>89,90</sup> H2N2 viruses circulated in the human population between 1957 and 1968.<sup>1</sup>

Human influenza viruses change frequently as the result of antigenic drift, and occasionally as the result of antigenic shift. Epidemics occur every few years, due to small changes in the influenza viruses.<sup>14,91</sup> Human pandemics, resulting from antigenic shifts, 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.<sup>1</sup> In 1984, a H10N4 virus was isolated from mink during an epidemic in Sweden.<sup>1</sup> This virus is thought to have been of avian origin. Raccoons in the U.S. have serological evidence of infection with H1, H3, H4 and H10 viruses, and can be infected experimentally with avian LPAI H4N8 viruses and human H3N2 viruses.<sup>88</sup> Experimental infections with some H6 viruses have been reported in mice and ferrets, as well as human volunteers.<sup>92,93</sup> The currently circulating H5N1 avian influenza viruses appear to have an unusually wide host range, and can infect housecats, tigers, leopards, dogs, foxes, stone martens, palm civets, pigs, ferrets, rodents, rabbits and macaques.<sup>12,22,23,25-27,29-31,44,49,94-101</sup>

## Influenza B viruses

Influenza B viruses are mainly found in humans. These viruses can cause epidemics in human populations, but have not, to date, been responsible for pandemics.<sup>1</sup> They have also been found in animals.<sup>1,14,53,83,102</sup> Influenza B viruses are categorized into lineages rather than subtypes. They are also classified into strains.<sup>4</sup> Influenza B viruses undergo antigenic drift, though it occurs more slowly than in influenza A viruses.<sup>1,89</sup> Until recently, the B/Victoria/2/87 lineage predominated in human populations, and influenza B viruses were said not to undergo antigenic shifts.<sup>4,103</sup> In the 1990s, viruses of the B/Yamagata/16/88 lineage circulated to a very limited extent in Asia.<sup>103</sup> This lineage emerged in various parts of the world in 2001, and is now co-circulating with the B/Victoria/2/87 lineage.<sup>103,104</sup> Recent evidence suggests that recombination between these two lineages is resulting in antigenic shifts.<sup>104,105</sup>

## Influenza C viruses

Influenza C viruses are mainly associated with disease in humans.<sup>1,42,91,106</sup> Until recently, they had never been associated with large scale epidemics.<sup>1,42,91,106</sup> However, a nationwide epidemic of influenza C was reported in Japan between January and July 2004.<sup>107</sup> Influenza C viruses have also been found in animals.<sup>1,14,43,53,83,108-110</sup>

Influenza C viruses are not classified into subtypes, but are classified into strains.<sup>4</sup> Each strain is antigenically stable, and accumulates few changes over time.<sup>111</sup> Recent evidence suggests that reassortment occurs frequently between different strains of influenza C viruses.<sup>111,112</sup>

## Geographic Distribution

Human influenza viruses are found worldwide.<sup>1,2</sup> Avian influenza viruses are also found worldwide in wild birds.<sup>1,2,9,43</sup> The predominant subtypes and strains found in wild populations can change over time.<sup>1</sup> In North America, H3, H4 and H6 viruses are found most often in wild ducks, but H5, H7 and H9 viruses also occur low levels.<sup>113</sup> Avian HPAI viruses have been eradicated from domesticated poultry in most developed nations. However, these viruses can be re-introduced by the recombination or mutation of low pathogenicity viruses from wild waterfowl and shorebirds.<sup>2</sup> The current (2003-2009) HPAI outbreak began in poultry in Southeast Asia in 2003.<sup>7</sup> From 2003 to 2007, HPAI H5N1 viruses spread into domesticated or wild birds in other regions of Asia as well as parts of Europe, the Pacific, the Middle East and Africa.<sup>4</sup> Although some countries have eradicated the viruses from poultry, this epidemic is ongoing and worldwide eradication is not expected in the short term.<sup>4</sup> Unusually, some of these HPAI viruses are also circulating in wild bird populations.<sup>4,7,32-34,114,115</sup>

Swine influenza is common in North and South America, Europe and parts of Asia, and has been reported from Africa.<sup>17,53</sup> 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').

Equine influenza occurs in nearly all countries with substantial numbers of horses.<sup>68</sup> Only a few countries such as New Zealand and Iceland are known to be free from this disease.<sup>67-69,116</sup> The H3N8 subtype is widespread in horse populations.<sup>18,69</sup> The H7N7 subtype is either extinct or present at very low levels in some parts of the world, including North America and Europe.<sup>1,18,67,69</sup> It may still be found at low levels in Central Asia.<sup>1</sup>

The H3N8 canine influenza virus has been reported mainly in the U.S. In 2004-2006, infections were seen in racing greyhounds in a number of states including Florida, Texas, Arkansas, Alabama, Arizona, West Virginia, Kansas, Iowa, Colorado, Rhode Island and Massachusetts.<sup>75,78</sup> Infections were first reported in the general canine population in Florida, but have recently been seen in a number of other states.<sup>75,76,79-81,117</sup> The distribution of this virus in the U.S. is patchy; in some

cases, it caused an outbreak or was detected serologically in a state, but later disappeared from the area.<sup>117</sup> There is no evidence that this virus is currently circulating outside the U.S. In the U.K., an H3N8 virus was responsible for an outbreak of respiratory disease in a quarry hound kennel in 2002.<sup>118</sup> Limited serological evidence also suggests that some foxhounds were exposed to a H3N8 virus in 2003.<sup>119</sup> It is uncertain whether these cases were caused by the H3N8 canine influenza virus or by equine H3N8 strains that did not become established in the canine population.<sup>117</sup> Currently, this virus does not seem to be circulating in the U.K.<sup>117,118</sup> H3N8 infections were also reported from dogs in Australia during an equine influenza outbreak in 2007; however, these were equine viruses that did not become adapted to dogs.<sup>117</sup>

As of January 2009, the H3N2 canine influenza virus has been reported only from Korea.<sup>45</sup>

## Transmission

### Transmission of mammalian influenza viruses

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.<sup>1,17,18,43,55,89-91</sup> Close contact and closed environments favor transmission. Mammalian influenza viruses are relatively labile, but can persist for several hours in dried mucus.<sup>91</sup> In ferrets, *in utero* transmission can occur with high viremia after experimental infection.<sup>87</sup>

### Transmission of avian influenza viruses in birds

In birds, avian influenza viruses are shed in the feces as well as in saliva and nasal secretions.<sup>1,2,4,43</sup> The feces contain large amounts of virus, and fecal-oral transmission is usually the predominant means of spread in wild bird reservoirs.<sup>34</sup> Avian influenza viruses can persist in the environment for a period of time, and have been isolated from the water in ponds where ducks swim.<sup>1,14,120,121</sup> However, some recent isolates of H5N1 have been found in higher quantities in tracheal samples than feces.<sup>34,122,123</sup> This suggests that, at least in some species, these strains may no longer be transmitted primarily by the fecal-oral route. Once an avian influenza virus has entered a poultry flock, it can spread on the farm by both the fecal-oral route and aerosols, due to the close proximity of the birds. Fomites can be important in transmission, and flies may act as mechanical vectors.<sup>2,7,15</sup> Avian influenza viruses have also been found in the yolk and albumen of eggs from HPAI- infected hens, and possibly in eggs from LPAI-infected hens.<sup>2,124,125</sup> Although infected eggs are unlikely to hatch, broken eggs could transmit the virus to other chicks in the incubator.

In countries where HPAI has been eradicated from domesticated poultry, the disease could be introduced into flocks by migratory waterfowl as well as infected poultry or fomites.<sup>2,7,43</sup> Until recently, wild birds were thought to carry only the low pathogenicity form of avian influenza

viruses.<sup>7</sup> Once they were introduced into poultry, these viruses recombined or mutated to produce HPAI viruses. However, some migratory birds carry the currently circulating, high pathogenicity H5N1 strains.<sup>7,114,115</sup> Whether these birds can migrate long distances after being infected is controversial.<sup>126</sup> HPAI H5N2 viruses were also detected recently in some asymptomatic wild ducks and geese in Africa.<sup>127</sup>

## **Transmission of avian influenza viruses to mammals**

Some avian influenza virus strains can be transmitted to mammals by direct or indirect contact. Close contact with dead or sick birds seems to be the principal means of transmission to humans; however, a few cases may have resulted from indirect exposure via contaminated feces, and swimming in contaminated water is theoretically a source of exposure.<sup>4,7</sup> Transmission by ingestion has been reported in felines, dogs, pigs and foxes, and may occur rarely in humans.<sup>4,23,27,97,128</sup> Two people became infected with an avian H5N1 virus after eating uncooked duck blood.<sup>4</sup> One avian H5N1 infection occurred in a dog that had eaten infected duck carcasses.<sup>27</sup> Similarly, leopards and tigers in zoos, as well as housecats, were probably infected with avian H5N1 when they ate raw birds.<sup>23,24,26,28,31,97</sup> Recently, subclinical infections were reported in cats that had been accidentally exposed to a sick swan; the most likely route was ingestion of bird feces while grooming, but aerosol transmission could not be ruled out.<sup>44</sup>

Experimental infections have been established in cats by intratracheal inoculation with avian H5N1 viruses and by feeding them H5N1-infected chicks.<sup>97,129</sup> Cats appear to shed these viruses from the intestinal tract as well as the respiratory tract.<sup>31,129</sup> Pigs and foxes can also be infected by feeding H5N1-infected poultry, as well as by intranasal or intratracheal inoculation.<sup>94,101,128</sup> Infected foxes can excrete this virus in both respiratory secretions and feces, but pigs are known to shed it only from the respiratory tract.<sup>94,101,128</sup> In experimentally infected dogs, avian H5N1 viruses have been found in respiratory secretions, but fecal shedding has not been reported.<sup>99,100</sup> In one experiment, cattle shed small amounts of H5N1 viruses from the respiratory tract after intranasal inoculation; a high dose of the virus, which had been recovered from cats, was used to inoculate the cattle.<sup>130</sup> Fecal shedding of avian H5N1 virus may be possible in humans; this virus has been recovered from a child with diarrhea.<sup>131</sup>

Sustained intraspecies transmission does not occur unless an avian influenza virus becomes adapted to the mammal; however, limited animal-to-animal transmission may be seen. Limited animal-to-animal transmission of avian H5N1 has been reported in zoo tigers and experimentally infected housecats.<sup>28,97</sup> No animal-to-animal transmission was reported in the asymptomatic cats infected by exposure to a sick swan, or in experimentally infected pigs.<sup>44,94</sup> In one study,

avian H5N1 virus was not transmitted to one dog or three cats in contact with four experimentally infected dogs, or to three dogs in contact with infected cats.<sup>100</sup> In humans, a few cases of limited person-to-person spread have been documented after close, prolonged contact.<sup>4,7</sup> Sustained human-to-human transmission has not been reported, as of January 2009.<sup>4,7</sup> Transplacental transmission of avian influenza viruses has not been studied in most species. However, the detection of viral antigens and nucleic acids in the fetus of a pregnant woman who died of an avian H5N1 infection suggests that it may be possible in humans.<sup>132</sup>

There are few reports of mammalian infections with LPAI viruses. Raccoons that were intranasally inoculated with avian LPAI H4N8 viruses shed virus from the respiratory but not the digestive tract.<sup>88</sup> These raccoons could transmit this virus to uninfected raccoons.<sup>88</sup>

## **Transmission of influenza viruses between species – mechanisms and reported cases**

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.<sup>1,4,16,43,53</sup> Cross-species transmission of viruses, without sustained transmission in the unusual host, has been documented for some viruses that can infect humans:

- Human infections with avian influenza viruses are rarely reported.<sup>4,7</sup> Recently, bird-to-human transmission has been reported only with the H5, H7 and H9 viruses.<sup>4,41</sup> Most infections have resulted from 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.<sup>4,13</sup> The virus subtype was H7N7. No sustained person-to-person transmission has been reported, to date, with the viruses currently circulating in bird populations.
- The currently circulating H5N1 avian influenza viruses may be likely to undergo cross-species transmission. These viruses have been isolated nearly 400 times in humans, after contact with infected poultry.<sup>4,7,12,14,15,21</sup> They have also been isolated recently from housecats, zoo tigers, zoo leopards and a dog that ate infected birds, as well as a stone marten and palm civets.<sup>22-24,26-31</sup> Cats, dogs, foxes, pigs, rodents, ferrets, rabbits and macaques have been experimentally infected with viruses from birds.<sup>12,29,49,94-101,128,129</sup> Cattle can be experimentally infected with H5N1 viruses isolated from cats.<sup>130</sup> Serological evidence suggests that pigs have been infected in Vietnam.<sup>94</sup>

- Some currently circulating H9N2 viruses may also undergo frequent cross-species transmission.<sup>36</sup> LPAI H9N2 viruses, which circulate in poultry in parts of Asia and the Middle East, have been associated with disease in Chinese pigs.<sup>36,37</sup> At least 2% of human blood donors in China are seropositive for H9 viruses.<sup>36</sup> Symptomatic infections have also been reported in humans.<sup>4,7,12,35</sup> In general, human LPAI H9N2 infections appear to be clinically indistinguishable from human influenza virus infections.<sup>35</sup>
- Some serological evidence suggests that poultry workers and hunters may be regularly exposed to avian influenza viruses of various subtypes; antibodies to H5, H6, H7 and H11 viruses have been found in healthy people.<sup>133,134</sup> Whether these antibodies result from infections or simply from exposure to antigens remains to be determined.
- Infections with swine influenza viruses are reported sporadically in humans in the U.S., Europe, Asia, New Zealand and other regions.<sup>1,14,41,52,54,64,135-137</sup> One college student transmitted the virus to his roommate, who remained asymptomatic.<sup>52</sup> 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.<sup>1,14,52</sup> 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 serological evidence suggests that swine influenza infections may occur regularly in people who have contact with pigs.<sup>1,14,41,138</sup> If these infections resemble human influenza, they may not be recognized or reported as caused by a swine influenza virus. Since swine influenza became a reportable disease in the U.S., approximately one case per year has been reported to the Centers for Disease Control and Prevention (CDC).<sup>137</sup>
- Pigs are readily infected with human influenza A viruses, but most strains do not spread widely.<sup>1</sup> Pigs can also be infected with human influenza B viruses; serological studies from the U.K. suggest that these infections are sporadic and do not spread to other pigs.<sup>83</sup>

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.<sup>16</sup> 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, pigs and dogs.<sup>1,17-19,45,71</sup> It may also

have been responsible for one pandemic in humans. Some evidence suggests that the H1N1 virus, which caused the deadly 1918 'Spanish flu' pandemic, was probably an avian virus that became adapted to humans.<sup>16,20,139</sup> Other studies question this hypothesis and suggest that this virus may have been a reassortant.<sup>140</sup> In general, dissemination is more likely if the novel virus reassorts with a virus that is already adapted to the host species.<sup>4</sup> Reassortment can occur in the new host's own cells.<sup>4,7,16</sup> It could also occur in an intermediate host, particularly a pig.<sup>4,7,14,16</sup> Pigs have receptors that can bind swine, human and avian influenza viruses.<sup>14,17,41,55</sup> For this reason, they have been called 'mixing vessels' for the formation of new viruses. Recently, quail cells have also been shown to bind both human and avian influenza viruses.<sup>141</sup> 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.<sup>1,12,14</sup> This results in an increased opportunity for virus reassortment.

- Two of the last three human pandemics appear to have been the result of reassortment.<sup>16</sup> The 1957 H2N2 ('Asian flu') virus contained avian hemagglutinin, neuraminidase and an internal protein, and five other proteins from a human H1N1 strain.<sup>14,16</sup> 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.<sup>14,16</sup>
- Repeated reassortment between human, avian and swine influenza viruses has also resulted in novel swine viruses (see 'Etiology' for a description of these viruses).

Reassortant high pathogenicity 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.<sup>12,96</sup> 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. An avian H5N1 virus with the ability to bind human receptors was recently isolated from an infected human in Thailand.<sup>142</sup> Whether this modification would allow the virus to be transmitted more efficiently from person to person is unknown.<sup>142</sup> This particular isolate was found only once, to date, and may have been eliminated by infection control measures.

## Disinfection

Although influenza viruses are enveloped, some of these viruses have been reported to survive for long periods in the environment, particularly when the temperature is low. Virus survival in the environment is influenced by temperature, pH, salinity and the presence

of organic material.<sup>120,121</sup> Mammalian influenza viruses seem to be relatively labile, but can persist for several hours in dried mucus.<sup>91</sup> Avian influenza viruses, which are often transmitted between birds in feces, may be able to survive for long periods in aquatic environments.<sup>121</sup> Currently, there is no consensus on survival times. In one study, LPAI viruses survived in distilled water for more than 100 days at 28°C (82°F) and 200 days at 17°C (63°F).<sup>120</sup> In another study, LPAI viruses remained viable for at least 35 days in peptone water at 4°C (39°F), 30°C (86°F) or 37°C (98.6°F).<sup>120</sup> Various avian influenza viruses were reported to survive for four weeks at 18°C (64°F).<sup>120</sup> A few studies have examined virus persistence in feces. In one study, LPAI viruses (H7N2) persisted for up to two weeks in feces and on cages.<sup>143</sup> These viruses could survive for up to 32 days at 15-20°C (59-68°F), and at least 20 days at 28-30°C (82-86°F), but were inactivated more quickly when mixed with chicken manure.<sup>143</sup> In other studies, LPAI viruses were reported to survive for at least 44 or 105 days in feces.<sup>120</sup> One recent study examined the persistence of HPAI viruses. H5 and H7 HPAI viruses seemed to survive for shorter periods in water than LPAI viruses; however, they still persisted in fresh water for 100 days or more at 17°C (63°F) and for approximately 26-30 days at 28°C (82°F).<sup>121</sup> Avian influenza viruses can survive indefinitely when frozen.<sup>15,120</sup>

Influenza viruses are susceptible to a wide variety of disinfectants including sodium hypochlorite, 70% ethanol, oxidizing agents, quaternary ammonium compounds, aldehydes (formalin, glutaraldehyde, formaldehyde), phenols, acids, povidone-iodine and lipid solvents.<sup>40,43,91,120,144</sup> They can also be inactivated by heat of 56°C (133°F) for a minimum of 60 minutes (or higher temperatures for shorter periods), as well as by ionizing radiation or low pH (pH 2).<sup>40,43,91,120,143</sup>

## Infections in Humans

### Incubation Period

The incubation period for human influenza is usually short; most infections appear after one to four days.<sup>1,89-91</sup>

The incubation period for avian influenza is difficult to determine in humans.<sup>7</sup> Limited data from H5N1 avian influenza virus infections suggest that the incubation period for this virus may range from two to eight days and could be as long as 17 days.<sup>7</sup> The World Health Organization (WHO) currently suggests using an incubation period of seven days for field investigations and monitoring patient contacts.<sup>7</sup>

### Clinical Signs

Uncomplicated infections with 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 and a nonproductive cough.<sup>1,42,87,89-91</sup> Diarrhea,

abdominal pain and photophobia have also been reported.<sup>42,87</sup> Nausea, vomiting and otitis media are common in children, and febrile seizures have been reported in severe cases.<sup>89,90</sup> In young children, the initial signs may mimic bacterial sepsis.<sup>89,90</sup> Most people recover in one to seven days, but in some cases, the symptoms may last up to two weeks or longer.<sup>42,89,91</sup>

More severe symptoms, including pneumonia, can be seen in individuals with chronic respiratory or heart disease.<sup>42,89-91</sup> Secondary bacterial or viral infections may also occur.<sup>1,42,89,90</sup> In addition, influenza A has been associated with encephalopathy, transverse myelitis, Reye syndrome, myocarditis, pericarditis and myositis.<sup>89,91</sup>

Because influenza C viruses are difficult to isolate, there are few reports on their clinical features. These viruses are mainly thought to cause mild upper respiratory disease in children and young adults, but more severe cases similar to influenza A or B have also been seen.<sup>1,106,111,112</sup> Some infections have resulted in bronchitis or pneumonia.<sup>111</sup> In one recent study, the most common clinical signs were fever, cough and rhinorrhea, but 29 of 179 children were hospitalized with more serious illnesses such as pneumonia, bronchitis or bronchiolitis.<sup>145</sup> Serious disease was most common in children less than two years of age.<sup>145</sup> Some influenza C infections may 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.<sup>7</sup> While some infections have been limited to conjunctivitis and/or typical influenza symptoms, others were serious or fatal.<sup>4,7,11-15</sup> HPAI viruses appear to cause more severe infections than LPAI viruses.<sup>4</sup>

The currently circulating avian H5N1 strains tend to cause high fever and upper respiratory symptoms resembling human influenza as the initial signs.<sup>7</sup> In some patients, there may be chest pain, bleeding from the nose and gums, or gastrointestinal symptoms such as diarrhea, vomiting and abdominal pain.<sup>7</sup> Respiratory signs are not always present at diagnosis; two patients from southern Vietnam had acute encephalitis without respiratory disease.<sup>7</sup> Similarly, a patient from Thailand exhibited only fever and diarrhea.<sup>7</sup> Many patients develop lower respiratory tract disease soon after the onset of illness; the symptoms may include dyspnea, hoarseness of the voice and crackles during inspiration.<sup>7</sup> The respiratory secretions and sputum are sometimes blood-tinged.<sup>7</sup> Most patients deteriorate rapidly.<sup>7</sup> Multiorgan dysfunction is common in the later stages, and disseminated intravascular coagulation can occur.<sup>7</sup>

The following human infections were reported between 1997 and 2008:

- In 1997, eighteen human infections were reported during a H5N1 HPAI outbreak among poultry in Hong Kong.<sup>4,7,12,14,15</sup> The symptoms

included fever, sore throat and cough and, in some cases, severe respiratory distress and viral pneumonia.<sup>7</sup> Eighteen people were hospitalized and six died.

- In 1999, avian influenza (LPAI H9N2) was confirmed in two children in Hong Kong.<sup>4,7,12</sup> 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.<sup>4,12</sup>
- In 2002, antibodies to an avian H7N2 virus were found in one person after a LPAI outbreak among poultry in Virginia.<sup>4</sup>
- In 2003, two HPAI H5N1 infections were reported in a Hong Kong family that had traveled to China.<sup>4,7,12</sup> 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 H7N7 HPAI in poultry in the Netherlands.<sup>4,11,13</sup> Most cases occurred in poultry workers, but three family members also became ill.<sup>4,13</sup> In 78 of the confirmed cases, conjunctivitis was the only sign of infection.<sup>13</sup> 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.<sup>13</sup> 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.<sup>13</sup>
- Cases of conjunctivitis have been reported after contact with HPAI H7N7 avian viruses in infected seals.<sup>13,19</sup>
- In 2003, a H9N2 LPAI infection was confirmed in a child in Hong Kong.<sup>4,7,35</sup> The symptoms included mild fever, mild dehydration and cough.<sup>35</sup> The child was hospitalized but recovered.
- In 2003, a LPAI H7N2 infection with respiratory signs was reported in a patient in New York.<sup>4</sup> 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.<sup>4</sup> One virus was LPAI; the other was HPAI. 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.

- From 2004 to 2008, sporadic human illness and deaths were associated with widespread outbreaks of high pathogenicity avian influenza (H5N1) among poultry. As of January 7 2009, 393 confirmed human cases had been reported to WHO; 248 cases were fatal.<sup>21</sup>
- In 2007, a mild case of LPAI H9N2 virus infection was reported in a 9-month-old child in Hong Kong.<sup>4</sup>

## Swine influenza virus infections in humans

Serological evidence suggests that swine influenza virus infections may occur among people who are occupationally exposed.<sup>41,138</sup> However, relatively few infections have been documented.<sup>41,137</sup> It is not known whether infections with swine influenza viruses differ significantly from infections with human influenza viruses.<sup>41</sup> 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.<sup>52</sup> 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.<sup>52</sup> There was no evidence of spread to his family.
- Swine influenza virus was isolated from an immunocompromised child with pneumonia who died.<sup>135</sup> Serological 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 five recruits with respiratory disease, including one who died of pneumonia.<sup>1,14,52</sup> Serological evidence suggested that approximately 500 people on the fort had also been infected by person-to-person spread.
- In 2005, a recombinant swine influenza virus was recovered from a farm worker with influenza symptoms in Canada.<sup>64</sup> The virus, which was also found in sick pigs on the farm, was a triple reassortant H3N2 virus with genes from swine, human and avian influenza viruses.<sup>64</sup> The infected individual was given antiviral drugs, and recovered uneventfully.<sup>64</sup> Other workers on the farm were treated prophylactically and did not become ill.
- In 2004, an Asian H1N2 swine influenza virus was isolated in the Philippines from a 25-year-old man with symptoms of influenza including high fever, dizziness and occasional vomiting.<sup>54</sup> In 2005, an Asian H1N1 swine influenza virus was isolated from a 4-year-old boy in Thailand

with rhinorrhea, fever and myalgia.<sup>54</sup> Both patients recovered without complications. There was no evidence of person-to-person transmission in either case, but comprehensive analyses of the patients' contacts were not done.

## Equine influenza virus infections in humans

Antibodies to equine H3N8 viruses have been reported in humans.<sup>1</sup> Human volunteers inoculated with an equine virus became ill, and virus could be isolated for up to 10 days.<sup>1</sup>

## 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 3-5 days after the initial signs.<sup>89,91</sup> Young children can shed virus for up to six days before, and 10 or more days after they become ill.<sup>89,90</sup> Severely immunocompromised individuals may remain infectious for weeks to months.<sup>89,90</sup> Humans can transmit influenza viruses to ferrets, and occasionally to swine.<sup>1,43,62,84,86</sup>

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.<sup>1,14,52,137</sup> 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.<sup>4,13</sup> Fecal shedding of the avian H5N1 virus has been documented in a child with diarrhea.<sup>131</sup> Transmission of this virus across the placenta may also be possible.<sup>132</sup>

## Diagnostic Tests

Human influenza A and influenza B infections 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.<sup>1,42</sup> Antigens can be detected in respiratory secretions by immunofluorescence or enzyme-linked immunosorbent assays (ELISAs).<sup>42,90</sup> Commercial rapid diagnostic test kits (Directigen® Flu A test) can provide a diagnosis within 30 minutes.<sup>90</sup> Reverse transcription polymerase chain reaction (RT-PCR) techniques are also available.<sup>89,90</sup> Serological tests include complement fixation, hemagglutination inhibition and immunodiffusion.<sup>1,42,90</sup> A rising titer is necessary to diagnose human influenza by serology. RT-PCR or culture can be used for the diagnosis of influenza C.<sup>107</sup>

Avian influenza viruses can be identified by RT-PCR, antigen detection or virus isolation.<sup>4</sup> In the U.S., samples that test positive by PCR or antigen tests are confirmed by the CDC. RT-PCR and antigen testing of avian influenza viruses must be carried out in Biosafety Level (BSL) 2 laboratory conditions.<sup>4</sup> BSL 3+ laboratory

conditions are needed for isolation of HPAI viruses.<sup>4</sup> Serology has been used for surveillance.

## Treatment

Four antiviral drugs are available for influenza treatment in the U.S. Amantadine and rimantadine (adamantanes) are active against human influenza A viruses, if treatment is begun within the first 48 hours.<sup>42,89-91,146</sup> Zanamivir and oseltamivir are effective for both influenza A and influenza B.<sup>77,146</sup> Treatment usually results in milder symptoms and recovery, on average, one day sooner.<sup>42,89,146</sup> Side effects, including neuropsychiatric events, may occur.<sup>90</sup> Drug resistance develops rapidly in viruses exposed to amantadine or rimantadine, and may emerge during treatment.<sup>1,42,89</sup> During the 2006-2008 flu seasons, human influenza viruses circulating in the U.S. and Canada exhibited high resistance to amantadine and rimantadine.<sup>89,90,146</sup> The CDC recommends that these two drugs be avoided until the circulating strains become susceptible again.<sup>89,90,146</sup> Laboratory studies have shown that influenza viruses can also become resistant to zanamivir and oseltamivir; however, this appears to be less common than resistance to adamantanes.<sup>89,90,146</sup>

Limited evidence suggests that oseltamivir may increase the chance of survival in patients infected with avian H5N1 viruses, if it is given within 48 hours of the onset of symptoms.<sup>7</sup> However, further testing, particularly on the optimum dose and duration of treatment, is still needed.<sup>7</sup> The avian HPAI H5N1 viruses now circulating are resistant to amantadine and rimantadine.<sup>4</sup> Although resistance to zanamivir and oseltamivir has also been reported, it is currently uncommon.<sup>4</sup> Recently, an oseltamivir resistant virus was isolated from an Egyptian man and his niece, two days after starting treatment.<sup>147</sup> The timing of the resistance suggests that they may have been infected with a oseltamivir-resistant virus, and resistance did not develop during treatment.

## Prevention

### Preventative measures for human influenza viruses

An annual vaccine is available for influenza A and B.<sup>1,42</sup> Both inactivated (injected) and live (intranasal) vaccines may be available.<sup>89</sup> The vaccine is given in the fall before the flu season.<sup>42</sup> It contains the viral strains that are 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.<sup>89,90</sup>

Three antiviral drugs - amantadine, rimantadine and oseltamivir - can be used for prophylaxis in high risk populations such as the elderly or immunocompromised.<sup>89,90,146</sup> Due to the high resistance of currently circulating viruses to amantadine and rimantadine, the CDC recommends that these two drugs

be avoided in the U.S. until the influenza strains become susceptible again.<sup>89,90,146</sup>

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.<sup>86</sup> If contact is unavoidable, they should wear gloves and face masks to prevent transmitting the virus to the animal.<sup>84</sup> Avoidance of contact with swine may also be considered, as influenza viruses have been transmitted occasionally to or from this species, and recombination can occur between human and swine influenza viruses.

## **Preventative measures for avian influenza viruses**

Controlling avian influenza epidemics in poultry decreases the risk of exposure for humans.<sup>7</sup> People working with infected birds should follow good hygiene practices and wear appropriate protective clothing such as boots (or shoe covers), coveralls, gloves and respirators.<sup>4</sup> In addition, the World Health Organization (WHO) recommends prophylaxis with antiviral drugs in people who cull birds infected with avian H5N1 HPAI viruses.<sup>7</sup> To prevent reassortment between human and avian influenza viruses, people in contact with infected birds should be vaccinated against human influenza.<sup>7,16</sup> They are also discouraged from having contact with sick birds while suffering flu symptoms.<sup>16</sup> One human H5N1 vaccine has been developed and others are in development.<sup>4,148</sup> In the U.S., these vaccines are stockpiled by the government and will be distributed by public health officials if they are needed.<sup>4,148</sup> Avian influenza vaccines for humans are not commercially available in the U.S.

In areas where H5N1 viruses might be present in domesticated poultry, poultry farms and live bird markets should be avoided.<sup>4</sup> Precautions should also be taken when handling raw meat and eggs. Sanitary precautions and cooking methods recommended to destroy *Salmonella* and other poultry pathogens are sufficient to kill avian influenza viruses.<sup>4</sup> The hands should be washed thoroughly with soap and warm water after handling meat or eggs.<sup>4</sup> Cutting boards and utensils should be washed with soap and hot water.<sup>4</sup> Poultry should be cooked to a temperature of at least 74°C (165°F).<sup>4</sup> Eggs should be cooked until the whites and yolks are both firm.<sup>4</sup>

Avian influenza viruses can be carried in wild birds, and these birds could be the initial source of infection in an area. Wild birds should be observed from a distance; close contact is discouraged.<sup>149</sup> If birds or contaminated surfaces are touched, the hands should be washed with soap and water before eating, drinking, smoking, or rubbing the eyes.<sup>149</sup> Dead or diseased wildlife should be reported to state, tribal or federal natural resource agencies.<sup>149</sup> Hunters should not handle or eat sick game, and should always wear rubber or latex gloves while handling and cleaning wild birds.<sup>149</sup> The hands, as well as

equipment and surfaces, should be thoroughly washed after dressing the carcass.<sup>149</sup> All game should be cooked thoroughly.<sup>149</sup>

If an avian influenza pandemic occurs in humans, additional precautions will be necessary. During a pandemic, crowded conditions and close contact with other people should be avoided.<sup>150</sup> Respirators and other protective equipment may be advisable during close contact with an infected individual.<sup>150</sup> In addition, infection control measures such as good hygiene, cancellation of social events and voluntary quarantines of infected individuals can limit the spread of disease.<sup>150,151</sup>

## **Morbidity and Mortality**

Although the morbidity rate for influenza is high, uncomplicated infections with human influenza viruses are rarely fatal in healthy individuals.<sup>1,16,42,87,91</sup> Infections are more severe in the elderly, young children (particularly infants), people with respiratory or cardiac disease, and those who are immunosuppressed.<sup>42,89-91</sup> Influenza-related deaths are usually the result of pneumonia or the exacerbation of a cardiopulmonary condition or other chronic disease.<sup>90</sup> Over 90% of these deaths occur in the elderly.<sup>89</sup> The estimated mortality rate from influenza is 0.0004 - 0.0006% in persons under 50 years old, 0.0075% between the ages of 50 and 64, and 0.1% in those over 65.<sup>89,90</sup> Deaths are rare in children, but can occur.<sup>89,90</sup> Immunity to the viral surface antigens (the hemagglutinin and neuraminidase) reduces the risk of infection and severity of disease. Antibodies offer limited or no protection against other virus types or subtypes.<sup>89</sup>

Human influenza can occur as a localized outbreak, an epidemic, a pandemic or as sporadic cases.<sup>16</sup> 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.<sup>42</sup> During a typical epidemic, influenza appears first among school-aged children, then spreads to preschool children and adults.<sup>1,42</sup> During epidemics, 15% to 40% of the population may be infected.<sup>1,16</sup> The outbreak usually lasts for three to six weeks.<sup>1,42</sup> Epidemics in tropical regions are not usually seasonal.<sup>1</sup>

Antigenic drift is usually responsible for small scale epidemics and localized outbreaks.<sup>14</sup> In North America, an epidemic of influenza A usually occurs every 1-3 years, and an epidemic of influenza B every 3-4 years.<sup>91</sup> Since 1968, the type A (H3N2) viruses have caused the most serious outbreaks with the highest mortality rates.<sup>89,90</sup> Severe pandemics, which last occurred in 1918, 1957 and 1968, are caused by antigenic shifts in influenza A viruses.<sup>16,42</sup> During influenza pandemics, the morbidity and mortality rates can increase dramatically in all age groups.<sup>1,4,14,17,42,90</sup> In the most severe pandemic, in 1918, the morbidity rate was 25-40% and the case fatality rate 2-5%.<sup>16</sup> Approximately 500,000 deaths were reported in the U.S. and an estimated 20-50 million deaths worldwide.<sup>1,4,14,16,17,42</sup> After a pandemic, an influenza

virus usually becomes established in the population and circulates for years.<sup>4</sup>

Less is known about influenza C than influenza A or B. Until recently, these viruses were thought to cause only sporadic cases of influenza and minor localized outbreaks.<sup>1,42,91,106</sup> However, in 2004, a nationwide influenza C epidemic was reported in Japan.<sup>107</sup> Influenza C infections seem to be most serious in very young children. In one study, 30% of the children hospitalized with severe infections were less than two years old, and an additional 12% were between the ages of two and five.<sup>145</sup>

## Zoonotic influenza

Human infections with avian influenza viruses are rarely reported.<sup>7</sup> Although tens of millions of birds were infected with zoonotic avian H5N1 strains from 2003 to 2009, fewer than 400 human cases had been documented as of January 2009.<sup>7,21</sup> Many infections have been reported in children and young adults.<sup>4,152</sup> Most human infections seem to result from close contact with diseased or dead poultry.<sup>7</sup> The risk of infection appears to be particularly high when slaughtering, defeathering or butchering birds, and while preparing them to cook.<sup>7</sup> Exposure to chicken feces may have been the source of infection in a few children, and other routes of exposure have been reported or may be possible.<sup>7</sup>

The severity of the disease seems to depend on the virus subtype and strain. More severe infections have been reported with HPAI viruses, particularly avian H5N1.<sup>4</sup> From 2003 through July 25 2007, 393 confirmed human H5N1 avian virus infections, 248 of them fatal, were reported to WHO.<sup>21</sup> In general, avian H5N1 HPAI infections have had a mortality rate of approximately 60-64%.<sup>4,21</sup> It is possible that milder infections have also occurred, but have not been recognized or reported.<sup>4</sup> Human disease has also been reported after infection with H7N2, H7N3, H7N7 and H9N2 viruses.<sup>4,11-13,19,35,36</sup> The reported infections with H9N2 viruses have resembled human influenza and been non-fatal.<sup>4,7,12,35,36</sup> Most infections with the H7 viruses have been limited to conjunctivitis, but influenza symptoms have also been seen. A single death was reported in an otherwise healthy veterinarian who became infected with a H7N7 virus.<sup>13</sup> Some isolates may also cause asymptomatic or mild, unrecognized infections. During an H7N3 LPAI outbreak in Italy in 2003, 3.8% of poultry workers tested developed antibodies to H7 viruses.<sup>153</sup> Interestingly, no seropositive individuals were identified in serum samples collected during H7N1 epidemics from 1999-2002.<sup>153</sup> In the U.S., antibodies to H5, H6, H7 and H11 avian influenza viruses have been found in poultry workers and waterfowl hunters.<sup>133,134</sup> Whether these antibodies result from infection or simply from exposure to antigens remains to be determined.

The prevalence of swine influenza in humans is unknown. Some serological surveys suggest that these infections may occur regularly among people who work

with pigs.<sup>1,14,41,138</sup> 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.<sup>1,14, 52,135</sup> During the only known outbreak, on a military base in New Jersey, the swine influenza virus was isolated from five people with respiratory disease, including one who died of pneumonia, and serological evidence of infection was found in approximately 500 of 12,000 people on the base.<sup>1,14,52</sup>

## Infections in Animals

### Species Affected

#### *Influenza A viruses*

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

Avian influenza viruses mainly infect birds, but some strains can also infect and/or cause disease in mammals.<sup>1,4,17-19,22-31,92,94-97,100,101,129</sup> Waterfowl and shorebirds, which tend to carry these viruses asymptotically, appear to be the natural reservoir hosts.<sup>1,2,7,14,17</sup> Poultry can develop serious or mild disease, depending on the subtype and strain of virus.<sup>2,8</sup> Some isolates can also cause serious disease in other avian species including gulls, wood ducks, farmed ostriches, emus and passerine birds.<sup>3,29,32,46-48,50,51,154,155</sup>

Swine influenza viruses mainly affect pigs but can also cause disease in turkeys and humans.<sup>1,41,43,54</sup>

Equine influenza viruses mainly affect horses, donkeys and mules.<sup>18,67,68</sup> They have also been reported in zebras.<sup>68</sup> Experimental infections have been established in cattle, dogs and humans.<sup>1,69</sup> Antibodies to the equine H3N8 viruses have been reported in humans.<sup>1</sup> Recently, a H3N8 equine influenza virus appears to have jumped into dogs.<sup>71-73</sup>

Human influenza viruses mainly cause disease in humans and ferrets.<sup>84-87</sup> They can also infect pigs and have been reported in dogs, cattle and birds.<sup>1,43,61,62,83</sup> Experimental infections have been reported in horses and raccoons.<sup>1,69,88</sup>

Canine influenza viruses have been seen only in dogs. To date, there have been no infections reported in other species, including humans.<sup>72</sup>

Serological evidence of infection with H1, H3, H4 and H10 viruses has been reported in wild raccoons.<sup>88</sup> Raccoons have been experimentally infected with avian LPAI H4N8 and human H3N2 viruses.<sup>88</sup>

#### *Host range of the avian H5N1 influenza A viruses*

Two clades of H5N1 viruses are currently circulating in poultry.<sup>4,156</sup> These viruses can infect and cause disease in many species of birds in addition to

poultry. Unusually, they have caused severe disease and deaths in some species of wild waterfowl and shorebirds, which usually carry avian influenza viruses asymptomatically.<sup>4,5,7,33,34,123,157</sup> Most H5N1 viruses have been isolated from birds in the order Anseriformes, particularly the families Anatidae (ducks, swans and geese) and Charadriiformes (shore birds, gulls and terns).<sup>5,6,12,29,32,33,114,115</sup> Symptomatic or fatal infections have also been reported in pheasants, partridges, quail, guineafowl and peafowl (order Galliformes); egrets, storks and herons (order Ciconiiformes); pigeons (order Columbiformes); eagles, falcons and buzzards (order Falconiformes); owls (order Strigiformes); cranes, moorhens and sultans (order Gruiformes); cormorants (order Pelecaniformes), emus (order Struthioniformes), grebes (order Podicipediformes), budgerigars (order Psittaciformes) and flamingos. (order Phoenicopteriformes).<sup>3,29,32,34,49</sup> Disease can also occur in passeriform birds including zebra finches, house finches, house sparrows, Eurasian tree sparrows, mynahs, crows, magpie robins, munias, orioles and magpies.<sup>29,32,51,155</sup>

Symptomatic infections with avian H5N1 viruses have been reported in mammals including zoo tigers, zoo leopards, housecats, a dog, a stone marten and captive palm civets.<sup>4,22-31</sup> Asymptomatic infections have also been reported in cats.<sup>44</sup> During outbreaks in poultry, serological evidence of infection or exposure has been reported in cats, dogs and swine.<sup>94,158</sup> Experimental infections have been established in housecats, dogs, foxes, pigs, cattle, ferrets, rodents, cynomolgus macaques and rabbits.<sup>12,29,49,94-101,128-130</sup> The currently circulating H5N1 strains are continuing to evolve, and other species may also be susceptible to infection and/or disease.

## Influenza B viruses

Influenza B viruses can cause disease in humans, ferrets and seals, and these viruses have also been isolated from pigs and a horse.<sup>1,14,53,102</sup> Serological evidence of infection has been found in pigs, dogs and horses.<sup>1,83</sup>

## Influenza C viruses

Influenza C viruses have been isolated from humans and swine.<sup>1,14,43,53,106,108</sup> These viruses can cause disease in experimentally infected dogs.<sup>1</sup> Serological evidence of infection has been found in pigs, dogs and horses.<sup>1,83,109,110</sup>

## Incubation Period

In poultry, the incubation period can be a few hours to a week.<sup>2,9,43</sup> The incubation period for mammalian influenza viruses is generally short. The clinical signs usually appear within 1 to 3 days in horses, pigs or seals.<sup>1,18,43,53,55,67,69,144,159</sup> Rarely, incubation periods up to seven days have been reported in some horses.<sup>67</sup> The incubation period for H3N8 canine influenza can be two to five days, but most cases appear in 2 to 3 days.<sup>76,117</sup> Little is known about H3N2 influenza virus in dogs; however, fever first appeared at 24 hours in

experimentally infected dogs, and other clinical signs began 2 to 8 days after inoculation.<sup>82</sup>

## Clinical Signs

### 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.<sup>1,2</sup> The clinical signs are variable.<sup>2,8,10,43</sup> Respiratory and systemic signs are often seen in chickens and turkeys. Sinusitis, lacrimation, edema of the head, cyanosis of the head, comb and wattle, and green to white diarrhea may be present in some birds.<sup>2,9,10,15,43</sup> Hemorrhagic lesions may be found on the comb and wattles of turkeys.<sup>2,43</sup> Other clinical 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.<sup>1,2,9,15,43</sup> However, none of these signs is pathognomonic, and sudden death may occur with few other signs.<sup>10</sup> Most of the flock usually dies.<sup>2</sup> Clinical signs tend to be minimal in ducks and geese infected with most avian influenza viruses. In ducks, the most common signs are sinusitis, diarrhea and increased mortality.<sup>2,33,43</sup> Some recent H5N1 isolates have caused severe acute disease with neurological signs and high mortality rates in domesticated ducks.<sup>3,32-34,49,123,160</sup>

LPAI viruses usually cause subclinical infections or mild illness in poultry.<sup>8</sup> The clinical signs may include decreased egg production or increased mortality rates.<sup>4,9</sup> More severe disease, mimicking high pathogenicity avian influenza, can be seen if the birds are concurrently infected with other viruses or there are other exacerbating factors.<sup>8,10</sup>

Avian influenza is often subclinical in wild birds, but some strains can cause illness and death.<sup>1-7</sup> Strains known to cause fatal illness include some of the currently circulating H5N1 viruses.<sup>3,5,7,33,34</sup> Experimental infections in call ducks (*Anas platyrhynchos* var. *domestica*), a cross between wild and domesticated ducks, resulted in drowsiness, ataxia, torticollis, circling and seizures.<sup>160</sup> Experimental infections in wood ducks (*Aix sponsa*) caused severe weakness and incoordination, cloudy eyes, ruffled feathers, rhythmic dilation and constriction of the pupils, tremors, seizures and death.<sup>3</sup> Other indigenous North American ducks including mallards (*Anas platyrhynchos*), northern pintails (*Anas acuta*), blue-winged teals (*Anas crecca*) and redheads (*Aythya americana*) remained asymptomatic when inoculated with the same strain.<sup>3</sup> Swans have been severely affected by H5N1 viruses in Europe; these birds are generally found dead.<sup>5,6</sup> Experimental infection with H5N1 viruses resulted in severe neurological disease in some mute swans and sudden death in others, while some birds shed virus subclinically.<sup>157</sup>

Symptomatic infections with H5N1 viruses have also been reported in experimentally infected gulls and passerine or psittacine birds.<sup>49,51,155</sup> Laughing gulls (*Larus atricilla*) developed severe neurological disease; the clinical signs included weakness, cloudy eyes, ruffled feathers, incoordination and torticollis.<sup>3</sup> Most infected gulls died. One gull that recovered had a persistent head tilt; the other recovered completely. Anorexia and depression occurred in experimentally infected zebra finches, and all of the birds died within five days of inoculation.<sup>51</sup> House finches and budgerigars developed anorexia, depression and neurologic signs, and died rapidly.<sup>51</sup> In one study, H5N1 infections were mild in house sparrows, which experienced only mild depression and survived, and starlings, which remained asymptomatic.<sup>51</sup> In another study, house sparrows but not starlings had severe, often fatal infections.<sup>155</sup> Other subtypes can also be pathogenic. A H7N1 (HPAI) virus caused conjunctivitis, apathy and anorexia, with a high mortality rate, in canaries and a siskin.<sup>50</sup>

## Swine influenza

Swine influenza is an acute upper respiratory disease characterized by fever, lethargy, anorexia, weight loss and labored breathing.<sup>1,14,43,53,55</sup> Coughing may be seen in the later stages of the disease.<sup>14</sup> Sneezing, nasal discharge and conjunctivitis are less common clinical signs.<sup>14</sup> Abortions may also occur.<sup>53,55</sup> Some strains can circulate in pigs with few or no clinical signs.<sup>1,14,17</sup> Complications may include secondary bacterial or viral infections.<sup>14,53,55</sup> Severe, potentially fatal bronchopneumonia is occasionally seen.<sup>43</sup>

Turkeys infected with swine influenza viruses may develop respiratory disease, have decreased egg production, or produce abnormal eggs.<sup>43</sup>

## Equine influenza

Equine influenza usually spreads rapidly in a group of animals. In naïve horses, the first sign is usually a high fever, followed by a deep, dry cough.<sup>18,68,144</sup> Other clinical signs may include a serous to mucopurulent nasal discharge, myalgia, inappetence, photophobia, corneal opacity and enlarged submandibular lymph nodes.<sup>1,18,43,67,144</sup> There may be edema of the legs and scrotum, and enteritis (spasmodic impaction colic) has been reported in some epidemics.<sup>18,144</sup> Animals with partial immunity can have milder, atypical infections with little or no coughing or fever.<sup>18</sup> Equine influenza is sometimes complicated by secondary bacterial infections.<sup>68</sup>

Healthy adult horses usually recover within 1-3 weeks, but the cough may persist longer.<sup>1,18,67,144</sup> In severely affected animals, convalescence can take up to six months.<sup>67</sup> Secondary bacterial infections prolong recovery.<sup>18,43,67</sup> Death in adult horses usually results from bacterial pneumonia, pleuritis or purpura hemorrhagica.<sup>18</sup> Sequelae may include chronic pharyngitis, chronic bronchiolitis and emphysema.<sup>18,67,144</sup> Interstitial myocarditis can occur during or after the infection.<sup>1,144</sup>

Loss of eyesight has also been reported.<sup>144</sup> Young foals without maternal antibodies can develop rapidly fatal viral pneumonia.<sup>1,18,144</sup> Postinfection encephalopathy has also been reported in foals.<sup>144</sup>

Horses experimentally infected with human influenza virus (H3N2 'Hong Kong') developed a mild febrile illness.<sup>1</sup> The virus could be isolated for up to five days.

## Influenza in dogs

Canine influenza is an emerging disease in dogs. The most common presentation seen with H3N8 viruses resembles kennel cough.<sup>71,74,75,77,117</sup> In this milder form, an initial (usually low grade) fever is followed by a persistent cough and, sometimes, a purulent nasal discharge.<sup>71,76,117</sup> The cough can last for up to three weeks regardless of treatment.<sup>76</sup> The nasal discharge appears to resolve with antibiotics, suggesting that secondary bacterial infections may be important in this disease.<sup>76</sup> More severely affected dogs exhibit a high fever with an increased respiratory rate and other signs of pneumonia or bronchopneumonia.<sup>73,75,77,117</sup> Lethargy and anorexia are common.<sup>117</sup> Some dogs have been found dead peracutely with evidence of hemorrhages in the respiratory tract; this syndrome has been seen in racing greyhounds, but does not seem to be prominent in pets.<sup>71,117</sup> Asymptomatic seroconversion also occurs.<sup>71</sup>

The only known outbreak of H3N2 canine influenza was characterized by severe respiratory disease with fever, nasal discharge, sneezing, coughing and anorexia.<sup>45</sup> Four of five pet dogs seen at veterinary clinics died.<sup>45</sup> Fever, sneezing, coughing and nasal discharges occurred in experimentally inoculated dogs, and severe pathologic changes were seen in the lungs.<sup>45,82</sup>

The clinical signs in dogs experimentally infected with influenza C virus included nasal discharge and conjunctivitis, which persisted for 10 days.<sup>1</sup>

## Influenza in ferrets

Ferrets are susceptible to human influenza viruses. The clinical signs may include fever, anorexia, depression, listlessness, sneezing, purulent nasal discharge and coughing.<sup>84,85,87</sup> The infection is not usually fatal in adult animals, which generally recover in five days to two weeks.<sup>84,86,87</sup> More severe or fatal disease can be seen in neonates.<sup>87</sup>

## Influenza in mink

In 1984, a H10N4 avian influenza virus caused an epidemic on 33 mink farms in Sweden.<sup>1</sup> The clinical signs included anorexia, sneezing, coughing, nasal and ocular discharges, and numerous deaths.

## Influenza in raccoons

Serological evidence of infection with H1, H3, H4 and H10 viruses has been reported in wild raccoons, but whether clinical signs occur is unknown.<sup>88</sup> Raccoons that were experimentally infected with avian LPAI H4N8 or human H3N2 viruses shed these viruses but remained asymptomatic.<sup>88</sup>

## *Influenza in marine mammals*

Influenza A viruses have been associated with outbreaks of pneumonia in seals and disease in a pilot whale.<sup>1,19,159</sup> The viruses appeared to be of avian origin.<sup>19</sup> Clinical signs in seals included weakness, incoordination, dyspnea and swelling of the neck.<sup>159</sup> A white or bloody nasal discharge was seen in some animals. In the single known case in a whale, the signs were nonspecific and included extreme emaciation, difficulty maneuvering and sloughing skin.<sup>159</sup>

## *Avian H5N1 influenza in mammals*

Symptomatic avian H5N1 virus infections have been reported in several species of mammals. Fatal infections have been seen in felids including tigers, leopards and housecats.<sup>23,24,26,28,31</sup> Captive tigers and leopards exhibited respiratory distress and high fever before death.<sup>24</sup> Little is known about the clinical signs in naturally infected housecats. One cat had fever, depression, dyspnea, convulsions and ataxia.<sup>26</sup> Several infected housecats were found dead.<sup>25</sup> One of these cats was apparently well up to 24 hours before its death.<sup>25</sup> In experimentally infected housecats, the clinical signs included fever, lethargy, conjunctivitis, protrusion of the third eyelid, dyspnea and death.<sup>97,100,129</sup> Recently, asymptomatic infections were reported in housecats that had been accidentally exposed to a sick, H5N1-infected swan.<sup>44</sup>

Other carnivores may also be affected by avian H5N1 viruses. A dog that ate infected poultry developed a high fever, panting and lethargy, and died the following day.<sup>27</sup> Experimentally infected dogs have been asymptomatic or developed only transient fever and conjunctivitis.<sup>4,99,100</sup> The clinical signs in wild animals such as palm civets and stone marten are usually not known; these animals are generally found dead. Some experimentally infected foxes developed fever but no other clinical signs; however, lung lesions were reported at necropsy.<sup>101</sup>

Experimental avian H5N1 virus infections in ferrets ranged from mild upper respiratory infections to severe, fatal disease; the pathogenicity varied with the specific isolate.<sup>95</sup> The clinical signs in severe cases included high fever, extreme lethargy, anorexia, weight loss and diarrhea.<sup>95</sup> Some infections in ferrets were fatal.<sup>95</sup>

Avian H5N1 infections in pigs appear to be mild or asymptomatic. Mild respiratory signs including cough, fever and transient anorexia were observed in some experimentally infected pigs.<sup>94</sup> In another study, some avian H5N1 strains caused slight and transient weight loss, but other clinical signs were not seen, and lung lesions were much less severe than those caused by swine influenza viruses.<sup>128</sup> One group reported that miniature pigs were resistant to infection.<sup>49</sup> Cattle inoculated with high titers of H5N1 virus isolated from infected cats remained asymptomatic but could transiently shed virus.<sup>130</sup>

## *H9N2 influenza in mammals*

An avian H9N2 virus caused respiratory disease and paralysis in pigs in southeastern China.<sup>36</sup>

## *Communicability*

Influenza viruses are readily transmitted between animals in the species to which they are adapted. Chickens can begin shedding avian influenza viruses as soon as 1-2 days after infection.<sup>161</sup> Most chickens shed LPAI influenza viruses for only a week, but a minority of the flock can excrete the virus in feces for up to two weeks.<sup>143</sup> Birds infected with HPAI viruses usually die before this time. Ducks can shed avian influenza viruses for up to 30 days.<sup>14</sup> Pigs may begin excreting swine influenza viruses within 24 hours of infection, and typically shed the viruses for 7-10 days.<sup>17,55</sup> Shedding up to four months has been documented in one pig.<sup>17</sup> Horses begin excreting equine influenza viruses during the incubation period, and usually shed these viruses for 4-5 days or less after the onset of clinical signs.<sup>18,43,144</sup>

Rarely, influenza viruses are transmitted to other species. In this case, how efficiently the virus spreads depends on how well it is adapted to the new species. Limited animal-to-animal transmission seems to occur, under some conditions, with the currently circulating avian H5N1 viruses. Cats can shed these viruses from the intestinal tract as well as the respiratory tract.<sup>31,100,129</sup> Experimentally infected cats shed avian H5N1 viruses by the third day post-inoculation, and were able to infect sentinel cats in close contact.<sup>97,129</sup> However, naturally infected, asymptomatic cats appeared to shed avian H5N1 viruses only sporadically, and for less than two weeks.<sup>44</sup> Horizontal transmission was not observed in this instance.<sup>44</sup> Limited animal-to-animal transmission was reported among tigers in a zoo.<sup>28</sup>

Horizontal transmission of avian H5N1 has not been reported in other mammals including experimentally infected dogs and pigs.<sup>94,100</sup> However, several species are reported to shed this virus in respiratory secretions, and in some cases, in feces. In experimentally infected foxes, avian H5N1 virus has been detected in both respiratory secretions and feces.<sup>101</sup> In experimentally infected dogs, pigs and cattle, this virus was found only in respiratory secretions.<sup>99,100,128,130</sup> In cattle, the shedding was transient and occurred after high dose inoculation with a virus isolated from cats.<sup>130</sup> As of January 2009, sustained or prolonged transmission of avian H5N1 viruses has not been reported in any species of mammal including cats.

Raccoons may be able to transmit some influenza viruses. Raccoons that were experimentally infected with an avian LPAI H4N8 virus shed this virus in respiratory secretions but not from the digestive tract, and could infect other raccoons in contact.<sup>88</sup> Raccoons that were inoculated with a human H3N2 virus shed virus mainly from respiratory secretions, but minimal intestinal shedding was also reported.<sup>88</sup> The H3N2 virus was not transmitted to uninfected raccoons.<sup>88</sup>

## Post Mortem Lesions

### *Avian influenza*

The lesions in chickens and turkeys are highly variable and can resemble other avian diseases.<sup>2</sup> 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. Birds that die peracutely and young birds may have few or no lesions.

Experimentally infected wood ducks had multiple petechial hemorrhages in the pancreas.<sup>3</sup> More extensive lesions were reported in experimentally infected laughing gulls; in these birds, petechial hemorrhages were found in the ventriculus, apex of the heart, cerebrum and pancreas.<sup>3</sup> In naturally infected swans, the most consistent lesions are multifocal hemorrhagic necrosis in the pancreas, subepicardial hemorrhages, and pulmonary congestion and edema.<sup>6</sup> Mild or absent gross lesions were reported in experimentally infected zebra finches, house finches and budgerigars despite high mortality rates in these species.<sup>51</sup>

### *Swine influenza*

In uncomplicated infections, the gross lesions are mainly those of a viral pneumonia.<sup>14</sup> Affected parts of the lungs are depressed and consolidated, dark red to purple-red, and sharply demarcated.<sup>14,53</sup> The lesions may be found throughout the lungs, but are usually more extensive in the ventral regions.<sup>14,53</sup> Other parts of the lungs may be pale and emphysematous.<sup>53</sup> The airways are often dilated and filled with mucopurulent exudate.<sup>53</sup> The bronchial and mediastinal lymph nodes are typically edematous but not congested.<sup>14,53</sup> Severe pulmonary edema, as well as serous or serofibrinous pleuritis, may also be seen.<sup>53</sup> Some strains of swine influenza viruses produce more marked lesions than others.<sup>14</sup> Generalized lymphadenopathy, hepatic congestion and pulmonary consolidation were reported in one outbreak of severe disease in swine.<sup>1</sup>

### *Equine influenza*

The gross lesions are typically of an upper respiratory infection (including nasal discharge), and are often accompanied by enlargement of the lymph nodes of the head.<sup>144</sup> Interstitial pneumonia, bronchitis and bronchiolitis have been reported in fatal cases.<sup>18,69,144</sup> Ventral edema of the trunk and lower limbs can also occur.<sup>144</sup> Severe necrotizing myocarditis, as well as

catarrhal or hemorrhagic enteritis, have been reported with some strains.<sup>69,144</sup>

### *Canine influenza*

In fatal cases of H3N8 virus infection, hemorrhages may be found in the lungs, mediastinum and pleural cavity.<sup>71,73</sup> The lungs may exhibit signs of severe pneumonia, and can be dark red to black.<sup>73,117</sup> Fibrinous pleuritis can also be seen in some cases.<sup>73,117</sup> On histologic examination, there may be tracheitis, bronchitis, bronchiolitis, and severe interstitial or bronchointerstitial pneumonia.<sup>71,73,117</sup> There is limited information on the lesions found in mild cases. In experimentally infected puppies with this form, the bronchial lymph nodes were edematous, and cranioventral lung consolidation was rarely seen.<sup>117</sup> The most severely affected puppies had small focal areas of pulmonary hemorrhage scattered throughout the lungs, but there was no evidence of severe hemorrhagic pneumonia.<sup>117</sup>

In dogs that were inoculated with H3N2 viruses, multifocal to coalescing reddish consolidation was found in the lungs.<sup>45,82</sup> The histopathologic lesions included severe multilobular or diffuse necrotizing tracheobronchitis, and severe multilobular bronchiolitis and alveolitis.<sup>82</sup> Mild to moderate thickening of the alveolar septa was also seen.<sup>45,82</sup> No lesions were found outside the respiratory tract.<sup>45</sup>

### *Avian H5N1 influenza in mammals*

Pulmonary edema; pneumonia; conjunctivitis; cerebral, renal and splenic congestion; multifocal hepatic necrosis; hemorrhages in the intestinal serosa, lymph nodes, perirenal tissue and/or diaphragm; and severe hemorrhagic pancreatitis have been reported in naturally infected cats.<sup>25,26,31</sup> Multiple to coalescing foci of pulmonary consolidation were reported in experimentally infected cats.<sup>97,129</sup> These lesions were similar whether the cats were infected intratracheally or by the ingestion of infected chicks. In one study, cats infected by ingestion also had enlarged tonsils, which contained multifocal petechial hemorrhages, and enlarged mandibular and/or retropharyngeal lymph nodes.<sup>129</sup> Petechial hemorrhages occurred in the liver of some cats.<sup>129</sup> In one cat, the liver lesions were accompanied by generalized icterus.<sup>129</sup> In naturally infected tigers and leopards, the gross lesions included severe pulmonary consolidation and multifocal hemorrhages in multiple organs including the lung, heart, thymus, stomach, intestines, liver and lymph nodes.<sup>24</sup>

Bloody nasal discharge; severe pulmonary congestion and edema, and congestion of the spleen, kidney and liver were reported in a dog.<sup>27</sup> Pulmonary lesions including interstitial pneumonia have been reported in some experimentally infected pigs.<sup>94</sup> In one study, avian H5N1-infected pigs had mild to minimal gross lung lesions, with mild to moderate bronchiolitis and alveolitis detected on histopathologic examination.<sup>128</sup> Experimentally infected foxes developed lesions mainly in the lung.<sup>101</sup> More severe lesions were seen in foxes inoculated

intratracheally than in animals fed infected birds, and some of these animals also had histopathologic evidence of encephalitis and myocarditis.<sup>101</sup>

## **Influenza in marine mammals**

In seals, pneumonia with necrotizing bronchitis, bronchiolitis and hemorrhagic alveolitis have been reported.<sup>19,159</sup> In a single case in a whale, the lungs were hemorrhagic and a hilar lymph node was greatly enlarged.<sup>159</sup>

## **Diagnostic Tests**

### **Avian influenza**

Avian influenza can be diagnosed by virus isolation.<sup>9,10</sup> The virus can be recovered from oropharyngeal and/ or cloacal swabs in live birds. Feces can be substituted in small birds if cloacal samples are not practical. Oropharyngeal or cloacal swabs (or intestinal contents), and pooled or individual organ samples (trachea, lungs, air sacs, intestine, spleen, kidney, brain, liver and heart) are tested in dead birds.<sup>2,10</sup> Virus isolation is performed in embryonated eggs; hemagglutinating activity indicates the presence of influenza virus.<sup>9,10</sup> The identity of the virus can be confirmed with agar gel immunodiffusion (AGID) or ELISAs. Avian influenza viruses are subtyped with specific antisera in AGID or hemagglutination and neuraminidase inhibition tests.<sup>10</sup> An immunofluorescence assay was used to identify the neuraminidase type during an outbreak in Italy.<sup>162</sup> Virulence tests in susceptible birds, together with genetic tests to identify characteristic patterns in the hemagglutinin, are used to differentiate LPAI from HPAI viruses.<sup>10</sup>

RT-PCR assays can identify avian influenza viruses in clinical samples, and can replace virus isolation in some cases.<sup>10,163</sup> These tests can also distinguish some subtypes.<sup>10</sup> Real-time RT-PCR is the method of choice in many laboratories.<sup>10</sup>

Viral antigens can be detected with ELISAs including rapid tests.<sup>10,163</sup> As of 2008, the World Organization for Animal Health (OIE) recommended that antigen detection tests be used to identify avian influenza only in flocks and not in individual birds.<sup>10</sup> Some rapid tests, including various PCR assays, were evaluated and compared in a recent review.<sup>163</sup>

Serological tests including agar gel immunodiffusion, hemagglutination, hemagglutination inhibition and ELISAs are useful as supplemental tests.<sup>10</sup> Although most poultry and other susceptible birds die before developing antibodies, serology can be valuable for surveillance and to demonstrate freedom from infection. AGID tests can recognize all avian influenza subtypes in poultry, but hemagglutination inhibition tests are subtype specific and may miss some infections. In wild birds, some serological tests may underestimate the prevalence of H5N1 infections.<sup>3</sup>

### **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.<sup>14,55</sup> Swine influenza viruses are often recovered in Madin–Darby canine kidney cells, but other cell types can also be used.<sup>55</sup> These viruses can be isolated from lung tissues at necropsy, or nasal or pharyngeal swabs from acutely ill pigs.<sup>43,53,55</sup> Recovery is best from an animal with a fever, 24–48 hours after the onset of disease.<sup>55</sup> Isolated viruses are subtyped with hemagglutination inhibition and neuraminidase inhibition tests or RT-PCR.<sup>14,55</sup>

Immunofluorescent techniques can detect antigens in fresh lung tissue, nasal epithelial cells or bronchoalveolar lavage.<sup>14,55</sup> Other antigen detection tests include immunohistochemistry on fixed tissue samples, and ELISAs.<sup>14,55</sup> RT-PCR assays are used to detect viral RNA.<sup>14,55</sup>

Serology on paired samples can diagnose swine influenza retrospectively.<sup>53</sup> The hemagglutination inhibition test, which is subtype specific, is most often used.<sup>14,53,55</sup> It may not detect new viruses.<sup>14</sup> ELISA kits are available. Uncommonly used serological tests in swine include agar gel immunodiffusion, the indirect fluorescent antibody test and virus neutralization.<sup>55</sup>

### **Equine influenza**

Equine influenza may tentatively be diagnosed based on the clinical signs.<sup>67</sup> As in swine, the disease is confirmed by virus isolation, the detection of viral antigens (e.g., by ELISA), or the detection of nucleic acids by RT-PCR.<sup>18,67,68</sup> Equine influenza viruses can be isolated from nasopharyngeal swabs or nasal and tracheal washes. In horses, peak virus shedding is thought to occur during the first 24 to 48 hours of fever; whenever possible, samples should be collected within the first 3–5 days after the onset of clinical signs.<sup>18,68</sup> Ideally, recovery of virus should be attempted in both embryonated eggs and cell cultures.<sup>68</sup> Equine influenza can also be diagnosed retrospectively by serology, using paired serum samples.<sup>18,67,68</sup> The most commonly used serological tests in horses are the hemagglutination inhibition test and a single-radial hemolysis (SRH) test.<sup>18,68</sup>

### **Canine influenza**

At this time, serology and RT-PCR are the most reliable methods for detecting H3N8 canine influenza.<sup>75,117,164</sup>

Hemagglutination inhibition is the most commonly used serological test.<sup>117</sup> Virus neutralization (microneutralization test) can also be done, but this test is usually too cumbersome for routine use.<sup>117</sup> Acute and convalescent titers should be submitted if possible.<sup>117,164</sup> Since this is an emerging disease, most dogs are not expected to have pre-existing titers to the canine influenza virus; however, single titers are still considered to be less useful.<sup>117,164</sup>

RT-PCR is the most reliable method to detect the virus directly.<sup>117</sup> This test can be used on nasal swabs from live animals or lung tissue samples at necropsy.<sup>117,164</sup> Virus isolation may also be successful in some dogs, but only during the early stages of disease before antibodies develop.<sup>117</sup> The H3N8 canine influenza virus can be found in lung tissue samples taken post-mortem, but virus isolation fails to detect the virus in many infected dogs that do not die of the disease.<sup>71,75,117,164</sup> In experimental infections, nasal swabs have been more likely to yield virus than nasopharyngeal swabs.<sup>117,164</sup> H3N8 canine influenza virus has been isolated in both embryonated eggs and cell cultures (MDCK cells).<sup>117</sup> Antigen-capture ELISA tests do not seem to be reliable in individual dogs, probably because the amount of virus shed is low.<sup>117</sup> However, these tests may be able to detect H3N8 canine influenza during outbreaks at kennels or other large facilities.<sup>117</sup>

Little is known about testing for H3N2 viruses in dogs. Some H3N2 viruses were isolated from nasal swabs taken from dogs during an outbreak.<sup>45</sup> In experimentally infected dogs, these viruses are shed in nasal secretions from one to six days after inoculation.<sup>45</sup> RT-PCR can also detect this virus.<sup>45</sup> Serology is expected to be useful.

## Treatment

Animals with influenza are usually treated with supportive care and rest.<sup>9,18,53,67</sup> Rest is particularly important in horses; prolonged recovery and more severe disease has been associated with increased stress.<sup>144</sup> Antibiotics may be used to control secondary infections; they seem to be particularly important in the treatment of canine influenza.<sup>9,18,53,67,77</sup> Antiviral drugs are not generally given to animals; however, ferrets may be given amantadine as well as antihistamines, antibiotics and other supportive therapy.<sup>84</sup> Antiviral drugs could also be of use in valuable horses.<sup>2,165</sup>

Poultry flocks with high pathogenicity avian influenza are depopulated and are not treated.<sup>4,43</sup>

## Prevention

### Vaccines

Inactivated influenza vaccines are available for pigs, horses and, in some countries, birds.<sup>1,18,43,53,55,67,68</sup> The vaccines do not always prevent infection or virus shedding, but the disease is usually milder if it occurs. Influenza vaccines may 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.<sup>14,18,43</sup>

In the U.S., avian influenza vaccines are used most often in turkeys and are intended only to prevent infection by LPAI viruses.<sup>10</sup> HPAI vaccines are not used routinely in the U.S. or most other countries; however, nations may consider vaccination as a preventative or adjunct control measure during an outbreak.<sup>10,166</sup> Avian vaccines are

usually autogenous or from viruses of the same subtype or hemagglutinin type.<sup>10</sup> Currently licensed vaccines in the U.S. include inactivated whole virus and recombinant fowlpox- H5 vaccines. The use of these vaccines requires the approval of the state veterinarian and, in the case of H5 and H7 vaccines, USDA approval. Because vaccines may allow birds to shed virus while remaining asymptomatic, good surveillance and movement controls are critical in a vaccination campaign.<sup>166-168</sup> Methods used to recognize infections with field viruses in vaccinated flocks include “DIVA” (differentiating vaccinated from infected animals) strategies, and the use of sentinel birds.<sup>162,166,167</sup> Vaccination may place selection pressures on avian influenza viruses, and might eventually result in the evolution of vaccine-resistant isolates.<sup>168,169</sup>

### Other preventative measures

Poultry can be infected by contact with newly introduced birds or fomites, as well as by contact with wild birds, particularly waterfowl.<sup>7,15,43</sup> Illegal poultry movements may be of primary importance in transmission in some regions.<sup>170,171</sup> 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.<sup>2,15</sup> Keeping flocks indoors is often recommended in areas where the H5N1 virus has been isolated from wild birds. Poultry should not be returned to the farm from live bird markets or other slaughter channels.<sup>15</sup> In addition, strict hygiene and biosecurity measures are necessary to prevent virus transmission on fomites.<sup>2,7,15,120</sup>

In pigs and horses, influenza is usually introduced into a facility in a new animal.<sup>14,17,43,53</sup> Isolation of newly acquired animals can decrease the risk of transmission to the rest of the herd.<sup>67</sup> Good biosecurity is also important.<sup>53,67</sup> Once a herd of swine has been infected, the virus usually persists in the herd and causes periodic outbreaks; however, good management can decrease the severity of disease.<sup>1,14,17,53</sup> Infected swine herds can be cleared of influenza viruses by depopulation.<sup>17</sup>

Ferrets can be infected by the human influenza viruses, and people with influenza should avoid contact with this species.<sup>86</sup> If contact is unavoidable, a face mask and gloves should be worn.<sup>84</sup>

Mammals should not be fed poultry or other birds that may be infected with the avian influenza viruses.<sup>23</sup> They should also be kept from contact with potentially infected flocks and wild birds. During outbreaks of avian H5N1, cats and dogs should be kept indoors whenever possible.

### Eradication and prevention of virus transmission during outbreaks

During an outbreak of influenza among mammals, quarantines and isolation of infected animals help prevent virus dissemination.<sup>18,43</sup> Good hygiene can keep the virus from spreading on fomites. Rest decreases virus shedding in horses.<sup>18</sup> Infected facilities should be cleaned and disinfected after the outbreak.

In poultry, outbreaks of high pathogenicity avian influenza are controlled by eradication.<sup>4,43</sup> 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. Because H5 and H7 LPAI viruses can mutate to become HPAI viruses, these infections are reportable to the OIE, and are being controlled similarly by many countries.<sup>10</sup>

## 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.<sup>1,14,18,43,53,55,67,69</sup> Secondary bacterial infections can exacerbate the clinical signs, prolong recovery and result in complications such as pneumonia.

### Avian influenza

Avian influenza outbreaks occur in most countries including the U.S. Low pathogenicity forms are seen most often, but outbreaks with high pathogenicity H5 and H7 viruses are also reported occasionally.<sup>2,4</sup> Seasonality has been reported in the current H5N1 epidemic; this virus has tended to reemerge during colder temperatures in the Northern Hemisphere.<sup>147</sup> The reason for the seasonality is unknown, but it may be the result of multiple factors such as increased virus survival in the cold, increased poultry trade during winter festivals, and wild bird movements.<sup>147</sup> In domesticated poultry (particularly chickens), HPAI viruses are associated with very high morbidity and mortality rates, up to 90-100%.<sup>2,4</sup> Any surviving birds are usually in poor condition. LPAI viruses usually result in mild or asymptomatic infections, but may also mimic HPAI viruses.<sup>8,10</sup>

Symptomatic infections are unusual in wild birds; however, some of the currently circulating H5N1 viruses have caused outbreaks with high mortality rates.<sup>1,2,4,7,14,33,34</sup> In April 2005, an outbreak that began at Qinghai Lake in central China resulted in the death of more than 6000 migratory wild birds.<sup>7</sup> H5N1 viruses have also been isolated sporadically from other dead birds, including waterfowl, in a number of countries.<sup>4,6,29,32,34</sup> High mortality rates have been reported in some but not all experimentally infected wild birds. All six laughing gulls infected with recent strains of H5N1 became severely ill, and four died.<sup>3</sup> Four of six infected wood ducks also became severely ill while two others remained asymptomatic.<sup>3</sup> Three of the sick ducks died and one recovered. Mallard, northern pintail, blue-winged teal and redhead ducks inoculated with the same viral strains did not become ill.<sup>3</sup> Morbidity and mortality rates in passerine and psittacine birds have varied with the species. In one study, mortality rates approached 100% in zebra finches, house finches and budgerigars, but all house sparrows experienced mild disease and survived, and all starlings remained asymptomatic.<sup>51</sup> In a study with a different

H5N1 virus, the mortality rate was 66-100% in house sparrows, but no deaths were seen in starlings.<sup>155</sup>

### 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.<sup>1,17</sup> High seroprevalence rates to swine influenza viruses have also been reported in other countries.<sup>1,14,17,83</sup> In addition, pigs can be infected with the human influenza A, B and C viruses.<sup>1,14,43,53,83,106,108,110</sup> In the U.K., a study found antibodies to both swine and human influenza viruses in 14% of all pigs.<sup>17</sup> Approximately 10% of the pigs were seropositive for influenza C viruses, but only sporadic infections with the human influenza B viruses were found.<sup>71</sup> In Japan, a similar study found antibodies to the type C viruses in 19% of pigs.<sup>110</sup>

Swine influenza viruses are usually introduced into a herd in an infected animal, and can survive in carrier animals for up to three months.<sup>17,43,53</sup> In a newly infected herd, up to 100% of the animals may become ill but most animals recover within 3-7 days if there are no secondary bacterial infections or other complications.<sup>14,43,53,55</sup> In uncomplicated cases, the case fatality rate has ranged from less than 1% to 4%.<sup>1,43,53</sup>

Once the virus has been introduced, it usually persists in the herd.<sup>1,14,17</sup> Annual outbreaks are often seen, and in temperate regions, occur mainly during the colder months.<sup>1,14,17,53</sup> Many infections in endemically infected herds are subclinical; typical signs of influenza may occur in only 25% to 30% of the pigs.<sup>14,17</sup> Maternal antibodies decrease the severity of disease in young pigs.<sup>14</sup> Some viruses can infect the herd with few or no clinical signs.<sup>1,14,17</sup>

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.<sup>1,17</sup> In the epidemic form, the virus spreads rapidly in pigs of all ages.<sup>55</sup> In the 1918 epizootic, millions of pigs developed influenza, and thousands of the infections were fatal.<sup>1</sup> Recently, a novel H3N2 entered pigs in the Midwest and has caused serious illness and reproductive losses in sows.<sup>14</sup>

### Equine influenza

In horses, influenza outbreaks are not as seasonal as they are in pigs or humans.<sup>18</sup> Most outbreaks are associated with sales, races and other events where horses congregate.<sup>18,43</sup> Close contact with other horses, crowding and transportation are typical risk factors for disease.<sup>69</sup> Widespread epidemics can be seen, with morbidity rates of 60-90% or greater, in naïve populations.<sup>1,18,144</sup> In 1987, an equine influenza epidemic in India affected more than 27,000 animals and killed several hundred.<sup>18</sup> In populations that have been previously exposed, cases are seen mainly in young and newly introduced animals.<sup>1,18</sup>

Unless there are complications, healthy adult horses usually recover within 1-3 weeks, although coughing can persist.<sup>1,18,67,144</sup> The H3N8 viruses usually cause more severe disease than the H7N7 viruses.<sup>1,18</sup> Deaths are rare in adult horses, and are usually the result of secondary bacterial infections.<sup>1,18,67</sup> Higher mortality rates have been reported in foals, animals in poor condition, donkeys and zebras.<sup>18,67</sup> In horses, tracheal clearance rates can be depressed for up to a month after infection.<sup>18</sup>

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.<sup>18,69</sup> The morbidity rate was at least 80% and the mortality rate was 20-35%.<sup>18,69</sup> 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 five years without further fatalities.

## Canine influenza

Canine H3N8 influenza was first reported in racing greyhounds and, at first, appeared to be confined to this breed.<sup>75,117</sup> Although this disease was first reported in 2004, new evidence suggests that the H3N8 virus may have been circulating in U.S. greyhound populations as early as 1999.<sup>71,78,172</sup> Researchers have found antibodies to this virus in 33% of greyhound sera from 1999, and 1-44% of greyhound sera collected between 2000 and 2004.<sup>172</sup> More recently, H3N8 canine influenza has been seen in a variety of breeds at veterinary clinics and animal shelters in several states.<sup>71,77,79,81,117</sup> All dogs regardless of breed or age are now considered to be susceptible.<sup>76,77,117</sup> The prevalence of this disease in the U.S. is not yet known. One study suggests that canine influenza is rare, if it exists at all, in Canada. In the province of Ontario, a survey found antibodies to the H3N8 virus in only one of 225 dogs in 2006.<sup>173</sup> This dog was a greyhound that had come from a racetrack in Florida, and may have been infected there. It had no recent history of respiratory disease.

Because dogs have not been exposed to the canine influenza virus before, most of the population is expected to be fully susceptible.<sup>75,76</sup> In kennels, the infection rate may reach 100% and clinical signs can occur in 60-80% of the dogs infected.<sup>76,117</sup> Most dogs are expected to develop the less severe form of the disease, and recover; however, a more severe form with pneumonia may occur in a minority.<sup>75,77,117</sup> In dogs with severe disease, the overall mortality rate is thought to be 1-5%.<sup>71,73,74,77</sup> Higher case fatality rates have been reported in small groups of greyhounds.<sup>117</sup> At one Florida greyhound racetrack, the case fatality rate was 36%.<sup>71</sup> High case fatality rates are not expected in most canine populations; however, severe disease is more likely in dogs that are in poor condition or are concurrently exposed to other pathogens.

The H3N2 virus has been reported from outbreaks at three veterinary hospitals and a kennel in South Korea.<sup>45</sup> Cases were described in a miniature schnauzer, a cocker spaniel, a Yorkshire terrier and two Jindo dogs (a Korean breed of hunting dog), as well as 13 dogs of unknown breed at an animal shelter.<sup>45</sup> Only one of the five dogs seen at veterinary clinics survived. The fate of the dogs in the animal shelter was not stated.

## 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.<sup>1</sup> The morbidity rate was nearly 100%. 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.<sup>1</sup> Explosive epidemics in seals are thought to be exacerbated by high population densities and unseasonably warm temperatures.<sup>159</sup>

The morbidity and mortality rates in cats or dogs infected with avian influenza viruses are unknown. In an unpublished study from Thailand, antibodies to H5N1 viruses were found in 8 of 11 cats and 160 of 629 dogs.<sup>158</sup> In contrast, no antibodies were found in 171 cats from areas of Austria and Germany where H5N1 infections had been reported in wild birds.<sup>174</sup> Fatal infections with avian H5N1 viruses have been reported in housecats, a dog, tigers and leopards.<sup>23-28,31</sup> Experimentally infected cats also exhibited severe disease and high mortality rates.<sup>97,129</sup> However, asymptomatic infections were recently reported in cats exposed to an infected swan in an animal shelter.<sup>44</sup> Few cats shed virus, and none became ill despite the presence of other viral and bacterial infections, and high stress levels in this population.<sup>44</sup> Asymptomatic or mild infections have also been reported in experimentally infected dogs.<sup>99,100</sup>

In pigs, experimental avian H5N1 infections suggest that disease may be mild.<sup>94,128</sup> A serological study conducted in Vietnam found that a low percentage of pigs (0.25%) had been exposed to the avian H5N1 influenza virus in 2004.<sup>94</sup> Miniature pigs were resistant to infection in one study.<sup>49</sup> Cattle do not appear to be susceptible to disease: although they shed virus, cattle inoculated with high titers of H5N1 avian influenza virus remained asymptomatic.<sup>130</sup>

## Internet Resources

Centers for Disease Control and Prevention (CDC). Avian Influenza

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

Medical Microbiology

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

Prevention and Control of Influenza. Recommendations of the Advisory Committee on Immunization Practices, 2006  
<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5510a1.htm>

Public Health Agency of Canada. Material Safety Data Sheets

<http://www.phac-aspc.gc.ca/msds-ftss/index.html>

The Merck Manual

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

The Merck Veterinary Manual

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

United States Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS). Avian Influenza.

[http://www.aphis.usda.gov/newsroom/hot\\_issues/avian\\_influenza/avian\\_influenza.shtml](http://www.aphis.usda.gov/newsroom/hot_issues/avian_influenza/avian_influenza.shtml)

USDAAPHIS. Avian Influenza Portal

[http://www.usda.gov/wps/portal/!ut/p/\\_s.7\\_0\\_A/7\\_0\\_1OB?navid=AVIAN\\_INFLUENZA&navtype=SU](http://www.usda.gov/wps/portal/!ut/p/_s.7_0_A/7_0_1OB?navid=AVIAN_INFLUENZA&navtype=SU)

USDA APHIS. Biosecurity for the Birds

[http://www.aphis.usda.gov/animal\\_health/birdbiosecurity/](http://www.aphis.usda.gov/animal_health/birdbiosecurity/)

United States Animal Health Association. Foreign Animal Diseases.

[http://www.vet.uga.edu/vpp/gray\\_book02/fad/index.php](http://www.vet.uga.edu/vpp/gray_book02/fad/index.php)

United States Geological Survey. National Wildlife Health Center. List of species affected by H5N1 (avian influenza)

[http://www.nwhc.usgs.gov/disease\\_information/avian\\_influenza/affected\\_species\\_chart.jsp](http://www.nwhc.usgs.gov/disease_information/avian_influenza/affected_species_chart.jsp)

World Health Organization

[http://www.who.int/csr/disease/avian\\_influenza/en/](http://www.who.int/csr/disease/avian_influenza/en/)

World Organization for Animal Health (OIE)

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

OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals

[http://www.oie.int/eng/normes/mmanual/a\\_summry.htm](http://www.oie.int/eng/normes/mmanual/a_summry.htm)

virus subtype H5N1 in mute swans in the Czech Republic. *Vet Microbiol.* 2007;120:9-16.

6. Teifke JP, Klopfeisch R, Globig A, Starick E, Hoffmann B, Wolf PU, Beer M, Mettenleiter TC, Harder TC. Pathology of natural infections by H5N1 highly pathogenic avian influenza virus in mute (*Cygnus olor*) and whooper (*Cygnus cygnus*) swans. *Vet Pathol.* 2007;44:137-43.

7. World Health Organization [WHO]. Avian influenza ("bird flu") fact sheet [online]. WHO; 2006 Feb. Available at: [http://www.who.int/mediacentre/factsheets/avian\\_influenza/en/index.html#humans](http://www.who.int/mediacentre/factsheets/avian_influenza/en/index.html#humans). Accessed 1 Aug 2007.

8. Alexander DY. A review of avian influenza [monograph online]. Available at: [http://www.esvv.unizh.ch/gent\\_abstracts/Alexander.html](http://www.esvv.unizh.ch/gent_abstracts/Alexander.html). Accessed 30 Aug 2004.

9. Kahn CM, Line S, editors. The Merck veterinary manual [online]. Whitehouse Station, NJ: Merck and Co; 2003. Avian influenza. Available at: <http://www.merckvetmanual.com/mvm/index.jsp?cfile=htm/bc/206200.htm>. Accessed 29 Dec 2006.

10. World Organization for Animal Health [OIE]. Manual of diagnostic tests and vaccines for terrestrial animals [online]. Paris; OIE; 2008. Avian influenza. Available at: [http://www.oie.int/eng/normes/mmanual/2008/pdf/2.03.04\\_AI.pdf](http://www.oie.int/eng/normes/mmanual/2008/pdf/2.03.04_AI.pdf). Accessed 31 Dec 2008.

11. Abbott, A. Human fatality adds fresh impetus to fight against bird flu. *Nature* 2003;423:5.
12. Chen H, Deng G, Li Z, Tian G, Li Y, Jiao P, Zhang L, Liu Z, Webster RG, Yu K. The evolution of H5N1 influenza viruses in ducks in southern China. *Proc Natl Acad Sci USA.* 2004;101:10452-7.
13. Fouchier RAM, Schneeberger PM, Rozendaal FW, Broekman JM, Kemink SAG, Munster V, Kuiken T, Rimmelzwaan GF, Schutten M, van Doornum GJJ, Koch G, Bosman A, Koopmans M, Osterhaus ADME. Avian influenza A virus (H7N7) associated with human conjunctivitis and a fatal case of acute respiratory distress syndrome. *Proc Natl Acad Sci U S A.* 2004;101:1356-61.
14. Heinen P. Swine influenza: a zoonosis. *Vet Sci Tomorrow* [serial online]. 2003 Sept 15. Available at: <http://www.vetscite.org/publish/articles/000041/print.html>. Accessed 26 Aug 2004.
15. U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Veterinary Services [USDA APHIS, VS]. Highly pathogenic avian influenza. A threat to U.S. poultry [online]. USDA APHIS, VS; 2002 Feb. Available at: <http://www.aphis.usda.gov/oa/pubs/avianflu.html>. Accessed 30 Aug 2004.
16. Reid AH, Taubenberger JK. The origin of the 1918 pandemic influenza virus: a continuing enigma. *J Gen Virol.* 2003;84:2285-92.
17. Brown IH. (OIE/FAO/EU International Reference Laboratory for Avian Influenza). Influenza virus

## References

1. Acha PN, Szyfres B (Pan American Health Organization [PAHO]). Zoonoses and communicable diseases common to man and animals. Volume 2. Chlamydiosis, rickettsioses and viroses. 3rd ed. Washington DC: PAHO; 2003. Scientific and Technical Publication No. 580. Influenza; p. 155-72.
2. Beard CW. Avian influenza. In: Foreign animal diseases. Richmond, VA: United States Animal Health Association; 1998. p. 71-80.
3. Brown JD, Stallknecht DE, Beck JR, Suarez DL, Swayne DE. Susceptibility of North American ducks and gulls to H5N1 highly pathogenic avian influenza viruses. *Emerg Infect Dis.* 2006;12:1663-70.
4. Centers for Disease Control and Prevention [CDC]. Avian flu [Website online]. CDC. Available at: <http://www.cdc.gov/flu/avian/index.htm>. Accessed 1 Aug 2007.
5. Nagy A, Machova J, Hornickova J, Tomci M, Nagl I, Horyna B, Holko I. Highly pathogenic avian influenza

- infections of pigs. Part 1: swine, avian & human influenza viruses [monograph online]. Available at: <http://www.pighealth.com/influenza.htm>. Accessed 31 Dec 2006.
18. Daly JM, Mumford JA. Influenza infections [online]. In: Lekeux P, editor. Equine respiratory diseases. Ithaca NY: International Veterinary Information Service [IVIS]; 2001. Available at: [http://www.ivis.org/special\\_books/Lekeux/toc.asp](http://www.ivis.org/special_books/Lekeux/toc.asp). Accessed 10 Jan 2006.
19. Hinshaw VS, Bean WJ, Webster RG, Reh JE, Fiorelli P, Early G, Geraci JR, St Aubin DJ. Are seals frequently infected with avian influenza viruses? *J Virol*. 1984;51:863-5.
20. Taubenberger JK, Reid AH, Lourens RM, Wang R, Jin G, Fanning TG. Characterization of the 1918 influenza virus polymerase genes. *Nature*. 2005;437:889-93.
21. World Health Organization [WHO]. Cumulative number of confirmed human cases of avian influenza A/(H5N1) reported to WHO [online]. WHO; 7 Jan 2009. Available at: [http://www.who.int/csr/disease/avian\\_influenza/en/](http://www.who.int/csr/disease/avian_influenza/en/). Accessed 8 Jan 2009.
22. Amonsin A, Songserm T, Chutinimitkul S, Jam-On R, Sae-Heng N, Pariyothorn N, Payungporn S, Theamboonlers A, Poovorawan Y. Genetic analysis of influenza A virus (H5N1) derived from domestic cat and dog in Thailand. *Arch Virol*. 2007;152:1925-33.
23. Enserink M, Kaiser J. Avian flu finds new mammal hosts. *Science*. 2004;305:1385.
24. Keawcharoen J, Oraveerakul K, Kuiken T, Fouchier RA, Amonsin A, Payungporn S, Noppornpanth S, Wattanodorn S, Theamboonlers A, Tantilertcharoen R, Pattanarangsarn R, Arya N, Ratanakorn P, Osterhaus DM, Poovorawan Y. Avian influenza H5N1 in tigers and leopards. *Emerg Infect Dis*. 2004;10:2189-91.
25. Klopfeisch R, Wolf PU, Uhl W, Gerst S, Harder T, Starick E, Vahlenkamp TW, Mettenleiter TC, Teifke JP. Distribution of lesions and antigen of highly pathogenic avian influenza virus A/Swan/Germany/R65/06 (H5N1) in domestic cats after presumptive infection by wild birds. *Vet Pathol*. 2007;44:261-8.
26. Songserm T, Amonsin A, Jam-on R, Sae-Heng N, Meemak N, Pariyothorn N, Payungporn S, Theamboonlers A, Poovorawan Y. Avian influenza H5N1 in naturally infected domestic cat. *Emerg Infect Dis*. 2006;12:681-3.
27. Songserm T, Amonsin A, Jam-on R, Sae-Heng N, Pariyothorn N, Payungporn S, Theamboonlers A, Chutinimitkul S, Thanawongnuwech R, Poovorawan Y. Fatal avian influenza A H5N1 in a dog. *Emerg Infect Dis*. 2006;12:1744-7.
28. Thanawongnuwech R, Amonsin A, Tantilertcharoen R, Damrongwatanapokin S, Theamboonlers A, Payungporn S, Nanthapornphiphat K, Ratanamungkalanon S, Tunak E, Songserm T, Vivatthanavanich V, Lekdumrongsak T, Kesdangsakonwut S, Tunhikorn S, Poovorawan Y. Probable tiger-to-tiger transmission of avian influenza H5N1. *Emerg Infect Dis*. 2005;11:699-701.
29. United States Geological Survey [USGS]. National Wildlife Health Center. List of species affected by H5N1 (avian influenza) [online]. USGS; 2006 Nov. Available at: [http://www.nwhc.usgs.gov/disease\\_information/avian\\_influenza/affected\\_species\\_chart.jsp](http://www.nwhc.usgs.gov/disease_information/avian_influenza/affected_species_chart.jsp). Accessed 1 Aug 2007.
30. World Health Organization [WHO] Avian influenza – H5N1 infection found in a stone marten in Germany [online]. WHO; 2006 March. Available at: [http://www.who.int/csr/don/2006\\_03\\_09a/en/index.html](http://www.who.int/csr/don/2006_03_09a/en/index.html). Accessed 8 Jan 2006.
31. Yingst SL, Saad MD, Felt SA. Qinghai-like H5N1 from domestic cats, northern Iraq. *Emerg Infect Dis*. 2006;12:1295-7.
32. Ellis TM, Bousfield RB, Bissett LA, Dyrting KC, Luk GS, Tsim ST, Sturm-Ramirez K, Webster RG, Guan Y, Malik Peiris JS. Investigation of outbreaks of highly pathogenic H5N1 avian influenza in waterfowl and wild birds in Hong Kong in late 2002. *Avian Pathol*. 2004;33:492-505.
33. Liu J, Xiao H, Lei F, Zhu Q, Qin K, Zhang XW, Zhang XL, Zhao D, Wang G, Feng Y, Ma J, Liu W, Wang J, Gao GF. Highly pathogenic H5N1 influenza virus infection in migratory birds. *Science*. 2005;309:1206.
34. Sturm-Ramirez KM, Ellis T, Bousfield B, Bissett L, Dyrting K, Reh JE, Poon L, Guan Y, Peiris M, Webster RG. Reemerging H5N1 influenza viruses in Hong Kong in 2002 are highly pathogenic to ducks. *J Virol*. 2004;78:4892-901.
35. Butt KM, Smith GJ, Chen H, Zhang LJ, Leung YH, Xu KM, Lim W, Webster RG, Yuen KY, Peiris JS, Guan Y. Human infection with an avian H9N2 influenza A virus in Hong Kong in 2003. *J Clin Microbiol*. 2005;43:5760-7.
36. Cong YL, Pu J, Liu QF, Wang S, Zhang GZ, Zhang XL, Fan WX, Brown EG, Liu JH. Antigenic and genetic characterization of H9N2 swine influenza viruses in China. *J Gen Virol*. 2007;88:2035-41.
37. Monne I, Cattoli G, Mazzacan E, Amarín NM, Al Maaitah HM, Al-Natour MQ, Capua I. Genetic comparison of H9N2 AI viruses isolated in Jordan in 2003. *Avian Dis*. 2007;51:451-4.
38. Banet-Noach C, Perk S, Simanov L, Grebenyuk N, Rozenblut E, Pokamunski S, Pirak M, Tendler Y, Panshin A. H9N2 influenza viruses from Israeli poultry: a five-year outbreak. *Avian Dis*. 2007;51:290-6.
39. Naeem K, Siddique N, Ayaz M, Jalalee MA. Avian influenza in Pakistan: outbreaks of low- and high-pathogenicity avian influenza in Pakistan during 2003-2006. *Avian Dis*. 2007;51:189-93.
40. International Committee on Taxonomy of Viruses [ICTV]. Universal virus database, version 3. 00.046. Orthomyxoviridae [online]. ICTV; 2003. Available at:

- <http://www.ncbi.nlm.nih.gov/ICTVdb/ICTVdb>. Accessed 25 Aug 2004.
41. Olsen CW, Brammer L, Easterday BC, Arden N, Belay E, Baker I, Cox NJ. Serologic evidence of H1 swine influenza virus infection in swine farm residents and employees. *Emerg Infect Dis* 2002;8:814-9.
  42. Couch RB. Orthomyxoviruses [monograph online]. In: Baron S, editor. *Medical microbiology*. 4th ed. New York: Churchill Livingstone; 1996. Available at: <http://www.gsbs.utmb.edu/microbook/>. Accessed 29 Dec 2006.
  43. Fenner F, Bachmann PA, Gibbs EPJ, Murphy FA, Studdert MJ, White DO. *Veterinary virology*. San Diego, CA: Academic Press Inc.; 1987. Orthomyxoviridae; p. 473-484.
  44. Leschnik M, Weikel J, Möstl K, Revilla-Fernández S, Wodak E, Bagó Z, Vanek E, Benetka V, Hess M, Thalhammer JG. Subclinical infection with avian influenza A (H5N1) virus in cats. *Emerg Infect Dis* [serial online]. 2007;13. 243-7.
  45. Song D, Kang B, Lee C, Jung K, Ha G, Kang D, Park S, Park B, Oh J. Transmission of avian influenza virus (H3N2) to dogs. *Emerg Infect Dis*. 2008;14:741-6.
  46. Panigrahy B, Senne DA, Pedersen JC. Avian influenza virus subtypes inside and outside the live bird markets, 1993-2000: a spatial and temporal relationship. *Avian Dis*. 2002;46:298-307.
  47. Promed Mail. Avian influenza, ostriches - South Africa. Aug 7, 2004. Archive Number 20040807.2176. Available at <http://www.promedmail.org>. Accessed 10 Jan 2007.
  48. Promed Mail. Avian influenza, ostriches – South Africa (H5N2)(03): OIE. July 18, 2006. Archive Number 20060718.1970. Available at: <http://www.promedmail.org>. Accessed 10 Jan 2007.
  49. Isoda N, Sakoda Y, Kishida N, Bai GR, Matsuda K, Umemura T, Kida H. Pathogenicity of a highly pathogenic avian influenza virus, A/chicken/Yamaguchi/7/04 (H5N1) in different species of birds and mammals. *Arch Virol*. 2006;151:1267-79.
  50. Kaleta EF, Honicke A. A retrospective description of a highly pathogenic avian influenza A virus (H7N1/Carduelis/Germany/72) in a free-living siskin (*Carduelis spinus* Linnaeus, 1758) and its accidental transmission to yellow canaries (*Serinus canaria* Linnaeus, 1758). *Dtsch Tierarztl Wochenschr*. 2005;112:17-9.
  51. Perkins LE., Swayne DE. Varied pathogenicity of a Hong Kong-origin H5N1 avian influenza virus in four passerine species and budgerigars. *Vet. Pathol*. 2003;40:14-24.
  52. Dacso CC, Couch RB, Six HR, Young JF, Quarles JM, Kasel JA. Sporadic occurrence of zoonotic swine influenza virus infections. *J Clin Microbiol*. 1984;20:833-5.
  53. Komadina N, Roque V, Thawatsupha P, Rimando-Magalong J, Waicharoen S, Bomasang E, Sawanpanyalert P, Rivera M, Iannello P, Hurt AC, Barr IG. Genetic analysis of two influenza A (H1) swine viruses isolated from humans in Thailand and the Philippines. *Virus Genes*. 2007;35:161-5.
  54. Kahn CM, Line S, editors. *The Merck veterinary manual* [online]. Whitehouse Station, NJ: Merck and Co; 2003. Swine influenza. Available at: <http://www.merckvetmanual.com/mvm/index.jsp?cfile=html/bc/121407.htm>. Accessed 9 Jan 2007.
  55. World Organization for Animal Health [OIE]. *Manual of diagnostic tests and vaccines for terrestrial animals* [online]. Paris;OIE; 2008. Swine influenza. Available at: [http://www.oie.int/eng/normes/mmanual/2008/pdf/2.08.08\\_SWINE\\_INFLUENZA.pdf](http://www.oie.int/eng/normes/mmanual/2008/pdf/2.08.08_SWINE_INFLUENZA.pdf). Accessed 7 Jan 2008.
  56. Lekcharoensuk P, Lager KM, Vemulapalli R, Woodruff M, Vincent AL, Richt JA. Novel swine influenza virus subtype H3N1, United States. *Emerg Infect Dis*. 2006;12:787-94.
  57. Ma W, Gramer M, Rossow K, Yoon KJ. Isolation and genetic characterization of new reassortant H3N1 swine influenza virus from pigs in the midwestern United States. *J Virol*. 2006;80:5092-6.
  58. Shin JY, Song MS, Lee EH, Lee YM, Kim SY, Kim HK, Choi JK, Kim CJ, Webby RJ, Choi YK. Isolation and characterization of novel H3N1 swine influenza viruses from pigs with respiratory diseases in Korea. *J Clin Microbiol*. 2006;44:3923-7.
  59. Ma W, Vincent AL, Gramer MR, Brockwell CB, Lager KM, Janke BH, Gauger PC, Patnayak DP, Webby RJ, Richt JA. Identification of H2N3 influenza A viruses from swine in the United States. *Proc Natl Acad Sci USA*. 2007;104:20949-54.
  60. Janke, BH. Relative prevalence of reassortants and subtypes. In: *Proceedings of the Twelfth Annual Swine Disease Conference for Swine Practitioners*; 2004 Nov 11-12; Ames, IA.
  61. Karasin AI, Carman S, Olsen CW. Identification of human H1N2 and human-swine reassortant H1N2 and H1N1 influenza A viruses among pigs in Ontario, Canada (2003 to 2005). *J Clin Microbiol*. 2006;44:1123-6.
  62. Yu H, Zhang GH, Hua RH, Zhang Q, Liu TQ, Liao M, Tong GZ. Isolation and genetic analysis of human origin H1N1 and H3N2 influenza viruses from pigs in China. *Biochem Biophys Res Commun*. 2007;356:91-6.
  63. Karasin AI, Schutten MM, Cooper LA, Smith CB, Subbarao K, Anderson GA, Carman S, Olsen CW. Genetic characterization of H3N2 influenza viruses isolated from pigs in North America, 1977-1999: evidence for wholly human and reassortant virus genotypes. *Virus Res*. 2000;68:71-85.
  64. Olsen CW, Karasin AI, Carman S, Li Y, Bastien N, Ojkie D, Alves D, Charbonneau G, Henning BM, Low DE, Burton L, Broukhanski G. Triple reassortant H3N2

- influenza A viruses, Canada, 2005. *Emerg Infect Dis*. 2006;12:1132-5.
65. Zell R, Bergmann S, Krumbholz A, Wutzler P, Dürrwald R. Ongoing evolution of swine influenza viruses: a novel reassortant. *Arch Virol*. 2008;153:2085-92.
66. Zell R, Motzke S, Krumbholz A, Wutzler P, Herwig V, Dürrwald R. Novel reassortant of swine influenza H1N2 virus in Germany. *J Gen Virol*. 2008;89:271-6.
67. Kahn CM, Line S, editors. The Merck veterinary manual [online]. Whitehouse Station, NJ: Merck and Co; 2003. Equine influenza. Available at: <http://www.merckvetmanual.com/mvm/index.jsp?cfile=html/bc/121303.htm>. Accessed 9 Jan 2007.
68. World Organization for Animal Health [OIE]. Manual of diagnostic tests and vaccines for terrestrial animals [online]. Paris: OIE; 2008. Equine influenza. Available at: [http://www.oie.int/eng/normes/mmanual/2008/pdf/2.05.07\\_EQ\\_INF.pdf](http://www.oie.int/eng/normes/mmanual/2008/pdf/2.05.07_EQ_INF.pdf). Accessed 31 Dec 2008.
69. Rooney, JR. Equine pathology. Ames, IA: Iowa State University Press; 1996. Influenza; p. 36-38.
70. Martella V, Elia G, Decaro N, Di Trani L, Lorusso E, Campolo M, Desario C, Parisi A, Cavaliere N, Buonavoglia C. An outbreak of equine influenza virus in vaccinated horses in Italy is due to an H3N8 strain closely related to recent North American representatives of the Florida sub-lineage. *Vet Microbiol*. 2007;121:56-63.
71. Crawford PC, Dubovi EJ, Castleman WL, Stephenson I, Gibbs EPJ, Chen L, Smith C, Hill RC, Ferro P, Pompey J, Bright RA, Medina M-J, Johnson CM, Olsen CW, Cox NJ, Klimov AI, Katz JM, Donis RO. Transmission of equine influenza virus to dogs. *Science*. 2005;310:482-5.
72. Enserink M. Flu virus jumps from horses to dogs [online]. Science Now. American Association for the Advancement of Science; 26 September 2005. Available at: <http://sciencenow.sciencemag.org/cgi/content/full/2005/926/2>. Accessed 27 Sept 2005.
73. Yoon KJ, Cooper VL, Schwartz KJ, Harmon KM, Kim WI, Janke BH, Strohschein J, Butts D, Troutman J. Influenza virus infection in racing greyhounds. *Emerg Infect Dis*. 2005;11:1974-6.
74. American Veterinary Medical Association. Canine influenza virus emerges in Florida [online]. *J Am Vet Med Assoc News Express*. Sept. 22, 2005. Available at: <http://www.avma.org/onlnews/javma/oct05/x051015b.asp>. Accessed 27 Sept 2005.
75. Carey S. UF researchers: equine influenza virus likely cause of Jacksonville greyhound deaths [online]. News Releases, University of Florida College of Veterinary Medicine. Available at: [http://www.vetmed.ufl.edu/pr/nw\\_story/greyhds.htm](http://www.vetmed.ufl.edu/pr/nw_story/greyhds.htm).\* Accessed 27 Sept 2005.
76. Cornell University College of Veterinary Medicine. Canine influenza virus detected [online]. Animal Health Diagnostic Center Announcements. Sept 21, 2005. Available at: <http://www.diaglab.vet.cornell.edu/issues/civ-dect.asp>.\* Accessed 27 Sept 2005.
77. Lamb S, McElroy T. Bronson alerts public to newly emerging canine flu. Florida Department of Agriculture and Consumer Services; 2005 Sept. Available at: <http://doacs.state.fl.us/press/2005/09202005.html>. Accessed 27 Sept 2005.
78. Promed Mail. Influenza, canine-USA (Florida). June 20, 2006. Archive Number 20060620.1703. Available at: <http://www.promedmail.org>. Accessed 10 Jan 2007.
79. Promed Mail. Influenza, canine-USA (multistate). March 25, 2006. Archive Number 20060325.0921. Available at: <http://www.promedmail.org>. Accessed 10 Jan 2007.
80. Promed Mail. Influenza, canine-USA (multistate). October 2, 2005. Archive Number 20051002.2883. Available at: <http://www.promedmail.org>. Accessed 3 Oct 2005.
81. Promed Mail. Influenza, canine-USA (Wyoming). May 3, 2006. Archive Number 20060503.1279. Available at: <http://www.promedmail.org>. Accessed 10 Jan 2007.
82. Song D, Lee C, Kang B, Jung K, Oh T, Kim H, Park B, Oh J. Experimental infection of dogs with avian-origin canine influenza A virus (H3N2). *Emerg Infect Dis*. 2009;15:56-8.
83. Brown IH, Harris PA, Alexander DJ. Serological studies of influenza viruses in pigs in Great Britain 1991-2. *Epidemiol Infect*. 1995;114:511-20.
84. Kahn CM, Line S, editors. The Merck veterinary manual [online]. Whitehouse Station, NJ: Merck and Co; 2003. Ferrets: Influenza. Available at: <http://www.merckvetmanual.com/mvm/index.jsp?cfile=html/bc/170303.htm>. Accessed 9 Jan 2007.
85. Michigan Department of Agriculture, Animal Industry Division. Ferret health advisory sheet. 2 p. Available at: [http://www.michigan.gov/documents/MDA\\_FerretHealthAdvisorySheet\\_31881\\_7.pdf](http://www.michigan.gov/documents/MDA_FerretHealthAdvisorySheet_31881_7.pdf).\* Accessed 20 Aug 2004.
86. Randolph RW. Medical and surgical care of the pet ferret: Influenza. In: Kirk RW, editor. Current veterinary therapy X. Philadelphia: WB Saunders; 1989. p. 775.
87. Sweet C, Smith H. Pathogenicity of influenza virus. *Microbiol Rev*. 1980;44: 303-30.
88. Hall JS, Bentler KT, Landolt G, Elmore SA, Minnis RB, Campbell TA, Barras SC, Root JJ, Pilon J, Pablonia K, Driscoll C, Slate D, Sullivan H, McLean RG. Influenza infection in wild raccoons. *Emerg Infect Dis*. 2008;14:1842-8.
89. Smith NM, Bresee JS, Shay DK, Uyeki TM, Cox NJ, Strikas RA. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP) Morb Mortal Wkly Rep. 2006;55(RR-10):1-42. Available at:

- <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5510a1.htm>. Accessed 29 Dec 2006.
90. Centers for Disease Control and Prevention [CDC]. Influenza. Information for health care professionals [Website online]. CDC; 2006. Available at: <http://www.cdc.gov/flu/professionals/background.htm>. Accessed 1 Aug 2007.
  91. Public Health Agency of Canada. Material Safety Data Sheet – Influenza virus. Office of Laboratory Security; 2001 Sept. Available at: <http://www.phac-aspc.gc.ca/msds-ftss/index.html>. Accessed 24 Aug 2004.
  92. Gillim-Ross L, Santos C, Chen Z, Aspelund A, Yang CF, Ye D, Jin H, Kembler G, Subbarao K. Avian influenza H6 viruses productively infect and cause illness in mice and ferrets. *J Virol*. 2008;82:10854-63.
  93. Beare, A. S., and R. G. Webster. 1991. Replication of avian influenza viruses in humans. *Arch Virol*. 1991;119:37–42.
  94. Choi YK, Nguyen TD, Ozaki H, Webby RJ, Puthavathana P, Buranathai C, Chaisingh A, Auewarakul P, Hanh NT, Ma SK, Hui PY, Guan Y, Peiris JS, Webster RG. Studies of H5N1 influenza virus infection of pigs by using viruses isolated in Vietnam and Thailand in 2004. *J Virol*. 2005;79:10821-5.
  95. Govorkova EA, Rehg JE, Krauss S, Yen HL, Guan Y, Peiris M, Nguyen TD, Hanh TH, Puthavathana P, Long HT, Buranathai C, Lim W, Webster RG, Hoffmann E. Lethality to ferrets of H5N1 influenza viruses isolated from humans and poultry in 2004. *J Virol*. 2005;79:2191-8.
  96. Guan Y, Peiris JS, Lipatov AS, Ellis TM, Dyrting KC, Krauss S, Zhang LJ, Webster RG, Shortridge KF. Emergence of multiple genotypes of H5N1 avian influenza viruses in Hong Kong SAR. *Proc Natl Acad Sci U S A*. 2002;99:8950-5.
  97. Kuiken T, Rimmelzwaan G, van Riel D, van Amerongen G, Baars M, Fouchier R, Osterhaus A. Avian H5N1 influenza in cats. *Science*. 2004;306:241.
  98. Perkins LE, Swayne DE. Comparative susceptibility of selected avian and mammalian species to a Hong Kong-origin H5N1 high-pathogenicity avian influenza virus. *Avian Dis*. 2003;47(3 Suppl):956-67.
  99. Maas R, Tacken M, Ruuls L, Koch G, van Rooij E, Stockhofe-Zurwieden N. Avian influenza (H5N1) susceptibility and receptors in dogs. *Emerg Infect Dis*. 2007;13:1219-21.
  100. Giese M, Harder TC, Teifke JP, Klopfeisch R, Breithaupt A, Mettenleiter TC, Vahlenkamp TW. Experimental infection and natural contact exposure of dogs with avian influenza virus (H5N1). *Emerg Infect Dis*. 2008;14:308-10.
  101. Reperant LA, van-Amerongen G, van-de-Bildt MW, Rimmelzwaan GF, Dobson AP, Osterhaus AD, Kuiken T. Highly pathogenic avian influenza virus (H5N1) infection in red foxes fed infected bird carcasses. *Emerg Infect Dis*. 2008;14:1835-41.
  102. Jakeman KJ, Tisdale M, Russell S, Leone A, Sweet C. Efficacy of 2'-deoxy-2'-fluororibosides against influenza A and B viruses in ferrets. *Antimicrob Agents Chemother*. 1994;38:1864-7.
  103. Chi XS., Bolar TV, Zhao P, Rappaport R, Cheng SM. Co-circulation and evolution of two lineages of influenza B viruses in Europe and Israel in the 2001-2002 season. *J. Clin. Microbiol*. 2003;41:5770-3.
  104. Chi XS, Hu A, Bolar TV, Al-Rimawi W, Zhao P, Tam JS, Rappaport R, Cheng SM. Detection and characterization of new influenza B virus variants in 2002. *J Clin Microbiol*. 2005;43:2345-9.
  105. Matsuzaki Y, Sugawara K, Takashita E, Muraki Y, Hongo S, Katsushima N, Mizuta K, Nishimura H. Genetic diversity of influenza B virus: the frequent reassortment and cocirculation of the genetically distinct reassortant viruses in a community. *J. Med. Virol*. 2004;74:132-40.
  106. Greenbaum E, Morag A, Zakay-Rones Z. Isolation of influenza C virus during an outbreak of influenza A and B viruses. *J Clin Microbiol*. 1998;36:1441-2.
  107. Matsuzaki Y, Abiko C, Mizuta K, Sugawara K, Takashita E, Muraki Y, Suzuki H, Mikawa M, Shimada S, Sato K, Kuzuya M, Takao S, Wakatsuki K, Itagaki T, Hongo S, Nishimura H. A nationwide epidemic of influenza C virus in Japan in 2004. *J Clin Microbiol*. 2007;45:783-8.
  108. Kimura H, Abiko C, Peng G, Muraki Y, Sugawara K, Hongo S, Kitame F, Mizuta K, Numazaki Y, Suzuki H, Nakamura K. Interspecies transmission of influenza C virus between humans and pigs. *Virus Res*. 1997;48:71-9.
  109. Manuguerra JC, Hannoun C, Simon F, Villar E, Cabezas JA. Natural infection of dogs by influenza C virus: a serological survey in Spain. *New Microbiol*. 1993;16:367-71.
  110. Yamaoka M, Hotta H, Itoh M, Homma M. Prevalence of antibody to influenza C virus among pigs in Hyogo Prefecture, Japan. *J Gen Virol*. 1991;72:711-4.
  111. Matsuzaki Y, Mizuta K, Sugawara K, Tsuchiya E, Muraki Y, Hongo S, Suzuki H, Nishimura H. Frequent reassortment among influenza C viruses. *J. Virol*. 2003;77: 871–81.
  112. Matsuzaki Y, Sugawara K, Mizuta K, Tsuchiya E, Muraki Y, Hongo S, Suzuki H, Nakamura K. Antigenic and genetic characterization of influenza C viruses which caused two outbreaks in Yamagata City, Japan, in 1996 and 1998. *J Clin Microbiol*. 2002;40:422-9.
  113. Hanson BA, Stallknecht DE, Swayne DE, Lewis LA, Senne DA. Avian influenza viruses in Minnesota ducks during 1998–2000. *Avian Dis*. 2003;47(3 Suppl):867-71.

114. Gilbert M, Xiao X, Domenech J, Lubroth J, Martin V, Slingenbergh J. Anatidae migration in the western Palearctic and spread of highly pathogenic avian influenza H5N1 virus. *Emerg Infect Dis.* 2006;12:1650-6.
115. Lei F, Tang S, Zhao D, Zhang X, Kou Z, Li Y, Zhang Z, Yin Z, Chen S, Li S, Zhang D, Yan B, Li T. Characterization of H5N1 influenza viruses isolated from migratory birds in Qinghai province of China in 2006. *Avian Dis.* 2007;51:568-72.
116. World Organization for Animal Health [OIE]. World Animal Health Information Database (WAHID) Interface [database online]. OIE; 2008. Equine influenza. Available at: [http://www.oie.int/wahis/public.php?page=disease\\_status\\_lists](http://www.oie.int/wahis/public.php?page=disease_status_lists). Accessed 8 Jan 2008.
117. Dubovi EJ, Njaa BL. Canine influenza. *Vet Clin North Am Small Anim Pract.* 2008;38:827-35, viii.
118. Smith KC, Daly JM, Blunden AS, Laurence CJ. Canine influenza virus. *Vet Rec.* 2005;157:599.
119. Newton R, Cooke A, Elton D, Bryant N, Rash A, Bowman S, Blunden T, Miller J, Hammond TA, Camm I, Day M. Canine influenza virus: cross-species transmission from horses. *Vet Rec.* 2007;161:142-3.
120. De Benedictis P, Beato MS, Capua I. Inactivation of avian influenza viruses by chemical agents and physical conditions: a review. *Zoonoses Public Health.* 2007;54:51-68.
121. Brown JD, Swayne DE, Cooper RJ, Burns RE, Stallknecht DE. Persistence of H5 and H7 avian influenza viruses in water. *Avian Dis.* 2007;51:285-9.
122. Antarasena C, Sirimujalin R, Prommuang P, Blacksell SD, Promkuntod N, Prommuang P. Tissue tropism of a Thailand strain of high-pathogenicity avian influenza virus (H5N1) in tissues of naturally infected native chickens (*Gallus gallus*), Japanese quail (*Coturnix coturnix japonica*) and ducks (*Anas spp.*). *Avian Pathol.* 2006;35:250-3.
123. Sturm-Ramirez KM, Hulse-Post DJ, Govorkova EA, Humbert J, Seiler P, Puthavathana P, Buranathai C, Nguyen TD, Chaisingh A, Long HT, Naipospos TS, Chen H, Ellis TM, Guan Y, Peiris JS, Webster RG. Are ducks contributing to the endemicity of highly pathogenic H5N1 influenza virus in Asia? *J Virol.* 2005;79:11269-79.
124. Cappucci DT, Johnson DC, Brugh M, Smith TM, Jackson CF, Pearson JE, Senne DA. Isolation of avian influenza virus (subtype H5N2) from chicken eggs during a natural outbreak. *Avian Dis.* 1985; 29:1195-1200.
125. Moses HE, Brandley CA, Jones EE. The isolation and identification of fowl plague virus. *Am J Vet Res.* 1948;9:314-28.
126. Weber TP, Stilianakis NI. Ecologic immunology of avian influenza (H5N1) in migratory birds. *Emerg Infect Dis.* 2007;13:1139-43.
127. Gaidet N, Cattoli G, Hammoumi S, Newman SH, Hagemeijer W, Takekawa JY, Cappelle J, Dodman T, Joannis T, Gil P, Monne I, Fusaro A, Capua I, Manu S, Micheloni P, Ottosson U, Mshelbwala JH, Lubroth J, Domenech J, Monicat F. Evidence of infection by H5N2 highly pathogenic avian influenza viruses in healthy wild waterfowl. *PLoS Pathog.* 2008;4(8):e1000127.
128. Lipatov AS, Kwon YK, Sarmiento LV, Lager KM, Spackman E, Suarez DL, Swayne DE. Domestic pigs have low susceptibility to H5N1 highly pathogenic avian influenza viruses. *PLoS Pathog.* 2008;4(7):e1000102.
129. Rimmelzwaan GF, van Riel D, Baars M, Bestebroer TM, van Amerongen G, Fouchier RA, Osterhaus AD, Kuiken T. Influenza A virus (H5N1) infection in cats causes systemic disease with potential novel routes of virus spread within and between hosts. *Am J Pathol.* 2006;168:176-83.
130. Kalthoff D, Hoffmann B, Harder T, Durban M, Beer M. Experimental infection of cattle with highly pathogenic avian influenza virus (H5N1). *Emerg Infect Dis.* 2008;14:1132-4.
131. de Jong MD, Bach VC, Phan TQ, Vo MH, Tran TT, Nguyen BH, Beld M, Le TP, Truong HK, Nguyen VV, Tran TH, Do QH, Farrar J: Fatal avian influenza A (H5N1) in a child presenting with diarrhea followed by coma. *N Engl J Med* 2005, 352:686-91.
132. Gu J, Xie Z, Gao Z, Liu J, Korteweg C, Ye J, Lau LT, Lu J, Gao Z, Zhang B, McNutt MA, Lu M, Anderson VM, Gong E, Yu AC, Lipkin WI. H5N1 infection of the respiratory tract and beyond: a molecular pathology study. *Lancet.* 2007;370:1137-45.
133. Gray GC, McCarthy T, Capuano AW, Setterquist SF, Alavanja MC, Lynch CF. Evidence for avian influenza A infections among Iowa's agricultural workers. *Influenza Other Respir Viruses.* 2008;2:61-9.
134. Gill JS, Webby R, Gilchrist MJ, Gray GC. Avian influenza among waterfowl hunters and wildlife professionals. *Emerg Infect Dis.* 2006;12:1284-6.
135. Patriarca PA, Kendal AP, Zakowski PC, Cox NJ, Trautman MS, Cherry JD, Auerbach DM, McCusker J, Belliveau RR, Kappus KD. Lack of significant person-to-person spread of swine influenza-like virus following fatal infection in an immunocompromised child. *Am J Epidemiol.* 1984;119:152-8.
136. Schnirring L. (Center for Infectious Disease Research and Policy [CIDRAP]. University of Minnesota). South Dakota reports swine flu case. *CIDRAP*; 2009 Jan 14. Available at: <http://www.cidrap.umn.edu/cidrap/content/influenza/general/news/jan1509swine-ms.html>. Accessed 19 Jan 2009.
137. Centers for Disease Control and Prevention [CDC]. Key facts about swine influenza (swine flu). CDC; 2006 Dec. Available at: <http://www.cdc.gov/flu/swine/>. Accessed 19 Jan 2009.

138. Myers KP, Olsen CW, Setterquist SF, Capuano AW, Donham KJ, Thacker EL, Merchant JA, Gray GC. Are swine workers in the United States at increased risk of infection with zoonotic influenza virus? *Clin Infect Dis*. 2006;42:14-20.
139. Chatterjee R. Portrait of a killer [online]. ScienceNOW Daily News. American Association for the Advancement of Science; 17 Jan 2007. Available at: <http://sciencenow.sciencemag.org/cgi/content/full/2007/117/2>. Accessed 19 Jan 2007.
140. Vana G, Westover KM. Origin of the 1918 Spanish influenza virus: a comparative genomic analysis. *Mol Phylogenet Evol*. 2008;47:1100-10.
141. Wan H, Perez DR. Quail carry sialic acid receptors compatible with binding of avian and human influenza viruses. *Virology*. 2006;346:278-86.
142. Auewarakul P, Suptawiwat O, Kongchanagul A, Sangma C, Suzuki Y, Ungchusak K, Louisirirochanakul S, Lerdsamran H, Pooruk P, Thitithanyanont A, Pittayawonganon C, Guo CT, Hiramatsu H, Jampangern W, Chunsutthiwat S, Puthavathana P. An avian influenza H5N1 virus that binds to human-type receptor. *J Virol*. 2007;81:9950-9955.
143. Lu H, Castro AE, Pennick K, Liu J, Yang Q, Dunn P, Weinstock D, Henzler D. Survival of avian influenza virus H7N2 in SPF chickens and their environments. *Avian Dis*. 2003;47(3 Suppl):1015-21.
144. Ardans AA. Equine influenza. In: Hirsch DC, Zee YC, editors. *Veterinary microbiology*. Malden, MA: Blackwell Science; 1999. p. 398-399.
145. Matsuzaki Y, Katsushima N, Nagai Y, Shoji M, Itagaki T, Sakamoto M, Kitaoka S, Mizuta K, Nishimura H. Clinical features of influenza C virus infection in children. *J Infect Dis*. 2006;193:1229-35.
146. National Institute of Allergy and Infectious Diseases [NIAID], National Institutes of Health [NIH]. Flu drugs [online]. NIAID, NIH; 2003 Feb. Available at: <http://www.niaid.nih.gov/factsheets/fludrugs.htm>.\* Accessed 11 Nov 2006.
147. Normile D, Enserink M. With change in the seasons, bird flu returns. *Science*. 2007;315:448.
148. United States Food and Drug Administration [FDA]. FDA approves first U.S. vaccine for humans against the avian influenza virus H5N1. Press release P07-68. FDA; 2007 Apr. Available at: <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01611.html>. Accessed 31 Jul 2007.
149. United States Geological Survey [USGS]. National Wildlife Health Center. Wildlife health bulletin #05-03 [online]. USGS; 2005 Aug. Available at: [http://www.nwhc.usgs.gov/publications/wildlife\\_health\\_bulletins/WHB\\_05\\_03.jsp](http://www.nwhc.usgs.gov/publications/wildlife_health_bulletins/WHB_05_03.jsp). Accessed 25 Jan 2007.
150. United States Department of Health and Human Services [USDHHS]. Interim public health guidance for the use of facemasks and respirators in non-occupational community settings during an influenza pandemic. USDHHS; 2007 May. Available at: <http://www.pandemicflu.gov/plan/community/maskguidancecommunity.html>. Accessed 2 Aug 2007.
151. United States Department of Health and Human Services [USDHHS]. Pandemic flu mitigation. USDHHS; 2007 Feb. Available at: <http://www.pandemicflu.gov/plan/community/mitigation.html>. Accessed 31 Jul 2007.
152. Smallman-Raynor M, Cliff AD. Avian influenza A (H5N1) age distribution in humans. *Emerg Infect Dis*. 2007 13:510-2.
153. Puzelli S, Di Trani L, Fabiani C, Campitelli L, De Marco MA, Capua I, Aguilera JF, Zambon M, Donatelli I. Serological analysis of serum samples from humans exposed to avian H7 influenza viruses in Italy between 1999 and 2003. *J Infect Dis*. 2005;192:1318-22.
154. Capua I, Mutinelli F, Terregino C, Cattoli G, Manvell RJ, Burlini F. Highly pathogenic avian influenza (H7N1) in ostriches farmed in Italy. *Vet Rec*. 2000;146:356.
155. Boon AC, Sandbulte MR, Seiler P, Webby RJ, Songserm T, Guan Y, Webster RG. Role of terrestrial wild birds in ecology of influenza A virus (H5N1). *Emerg Infect Dis*. 2007;13:1720-4.
156. Smith GJ, Fan XH, Wang J, Li KS, Qin K, Zhang JX, Vijaykrishna D, Cheung CL, Huang K, Rayner JM, Peiris JS, Chen H, Webster RG, Guan Y. Emergence and predominance of an H5N1 influenza variant in China. *Proc Natl Acad Sci U S A*. 2006; 103: 16936-41.
157. Kalthoff D, Breithaupt A, Teifke JP, Globig A, Harder T, Mettenleiter TC, Beer M. Highly pathogenic avian influenza virus (H5N1) in experimentally infected adult mute swans. *Emerg Infect Dis*. 2008;14:1267-70.
158. Butler D. Thai dogs carry bird-flu virus, but will they spread it? *Nature*. 2006;439:773.
159. Kahn CM, Line S, editors. *The Merck veterinary manual* [online]. Whitehouse Station, NJ: Merck and Co; 2003. Marine mammals: Influenza virus. Available at: <http://www.merckvetmanual.com/mvm/index.jsp?cfile=htm/bc/170811.htm>. Accessed 9 Jan 2007.
160. Yamamoto Y, Nakamura K, Kitagawa K, Ikenaga N, Yamada M, Mase M, Narita M. Severe nonpurulent encephalitis with mortality and feather lesions in call ducks (*Anas platyrhynchos* var. *domestica*) inoculated intravenously with H5N1 highly pathogenic avian influenza virus. *Avian Dis*. 2007;51:52-7.
161. Spickler AR, Trampel DW, Roth JA. The onset of virus shedding and clinical signs in chickens infected with high-pathogenicity and low-pathogenicity avian influenza viruses. *Avian Pathol*. 2008;37:555-77.
162. Capua I, Marangon S. Vaccination policy applied to the control of avian influenza in Italy. *Dev Biol (Basel)*. 2003;114:213-9.

163. Suarez DL, Das A, Ellis E. Review of rapid molecular diagnostic tools for avian influenza virus. *Avian Dis.* 2007;51:201-8.
164. Cornell University College of Veterinary Medicine. Canine influenza virus. Appropriate samples for detection [online]. Animal Health Diagnostic Center – Emerging Issues. Available at: <http://www.diaglab.vet.cornell.edu/issues/civ.asp#samp>. Accessed 8 Jan 2006.
165. Yamanaka T, Tsujimura K, Kondo T, Hobo S, Matsumura T. Efficacy of oseltamivir phosphate to horses inoculated with equine influenza A virus. *J Vet Med Sci.* 2006;68:923-8.
166. Capua I, Marangon S. Control of avian influenza in poultry. *Emerg Infect Dis.* 2006;12:1319-24.
167. Suarez DL. Overview of avian influenza DIVA test strategies. *Biologicals.* 2005;33:221-6.
168. van der Goot JA, Koch G, de Jong MC, van Boven M. Quantification of the effect of vaccination on transmission of avian influenza (H7N7) in chickens. *Proc Natl Acad Sci U S A.* 2005;102:18141-6.
169. Lee CW, Senne DA, Suarez DL. Effect of vaccine use in the evolution of Mexican lineage H5N2 avian influenza virus. *J Virol.* 2004;78:8372-81.
170. Promed Mail. Avian influenza – Eurasia: wild birds, fish feed. Dec 28, 2005. Archive Number 20051228.3700. Available at <http://www.promedmail.org>. Accessed 10 Jan 2007.
171. Promed Mail. Avian influenza, poultry vs migratory birds. May 12, 2006. Archive Number 20060512.1350. Available at: <http://www.promedmail.org>. Accessed 10 Jan 2007.
172. Sliwa J (American Society for Microbiology [ASM]). Canine influenza was around as early as 1999. Press Release, International Conference on Emerging Infectious Diseases; 2008 Mar 16-19; Atlanta, GA. Available at: <http://www.asm.org/Media/index.asp?bid=57269>. Accessed 13 Jan 2009.
173. Kruth SA, Carman S, Weese JS. Seroprevalence of antibodies to canine influenza virus in dogs in Ontario. *Can Vet J.* 2008;49:800-2.
174. Marschall J, Schulz B, Harder Priv-Doz TC, Vahlenkamp Priv-Doz TW, Huebner J, Huisinga E, Hartmann K. Prevalence of influenza A H5N1 virus in cats from areas with occurrence of highly pathogenic avian influenza in birds. *J Feline Med Surg.* 2008;10:355-8.

\*link defunct as of 2009