

Swine Influenza

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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

Swine influenza is an acute respiratory disease caused by influenza A viruses that circulate among pigs.¹⁻⁶ This disease often has a high morbidity rate and a low case fatality rate, but more severe outbreaks may also be seen.^{1-4,7} Viruses sometimes circulate among pigs with few or no clinical signs.^{1,2,6,8} Swine influenza viruses can occasionally infect other species including humans.^{1-3,6,9-25} Generally, these viruses do not spread efficiently in human populations. One outbreak, with transmission of a virus to approximately 500 people, was reported at Fort Dix in the 1970s; however, most infections are limited to the person who had contact with pigs, or in some cases, to a few family members or others in close contact.^{1,2,10,13-15,19} In April 2009, a novel virus with the subtype H1N1 began circulating in people, causing the first pandemic of the 21st century.^{17,26,27} The genetic analysis of this virus suggests that it originated from North American and Eurasian swine influenza viruses that recombined.²⁸⁻³⁰ Pigs are susceptible to the novel H1N1 virus, and sporadic outbreaks have been reported among swine herds in a number of countries.³¹⁻⁴⁷ Outbreaks have also been reported in turkey flocks, and a few cases have been recognized in pet ferrets, cats and dogs, as well as in a cheetah in a zoo.⁴⁸⁻⁶⁰

Etiology

Viruses in the genus *influenzavirus A* of the family Orthomyxoviridae cause influenza. Viruses in this genus are also called type A influenza viruses. Swine influenza viruses are those influenza A viruses that circulate in pigs. Influenza A viruses are classified into subtypes based on two surface antigens, the hemagglutinin (H) and neuraminidase (N) proteins. These two proteins are involved in cell attachment and release from cells, and are also major targets for the immune response.^{2,61,62} Influenza A viruses may theoretically contain up to 16 hemagglutinin antigens (H1 to H16) and nine neuraminidase antigens (N1 to N9).^{9,63,64} The major circulating swine influenza viruses currently contain H1, H2 or H3, and N1, N2 or N3, but viruses with other hemagglutinin or neuraminidase antigens have also been isolated occasionally from pigs.^{5,65,66} Strains of influenza viruses are described by their type, host, place of first isolation, strain number (if any), year of isolation and antigenic subtype.^{1,3} [e.g., A/Sw/CO/99 (H3N2) is a swine influenza virus with the subtype H3N2 that was first isolated in Colorado in 1999] 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.’³ 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.⁶¹ Reassortment between different strains results in the periodic emergence of novel strains. Reassortment between subtypes can result in the emergence of a new subtype. Swine influenza viruses can recombine with influenza viruses found in other species, including human, avian and equine influenza viruses.^{6,67} This type of reassortment can result in a ‘hybrid’ virus with, for example, both swine 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.^{1,2} For example, human viruses can continue to circulate in pigs and could re-emerge into the human population.^{2,68,69} 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.

Subtypes of swine influenza viruses

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 worldwide.^{2,5,8,61} One H1N1 virus found in North America is the 'classical' H1N1 swine influenza virus. This virus, the first influenza virus known to have infected pigs, was first detected in swine populations in 1918.^{1,2,8,61} Reassortant H1N1 viruses, which contain the same neuraminidase and hemagglutinin as the classical H1N1 virus, but have internal proteins from triple reassortant H3N2 viruses (see below), have recently become prominent among pigs in North America.^{7,70,71} An 'avian-like' H1N1 virus circulates mainly in European pigs.^{2,8,61} This virus seems to be an avian influenza virus that was transmitted whole to pigs.^{8,61,72} It has, in some locations, replaced the classical H1N1 virus.^{8,61} A different 'avian-like' H1N1 virus has been detected, together with the classical H1N1 virus among pigs in Asia.^{8,73} Other variants have also been found. For example, H1N1 reassortant viruses consisting of classical swine influenza virus genes and a human PB1 polymerase gene have been detected in pigs in Canada⁷⁴ and a wholly human lineage H1N1 virus was reported from pigs in China in 2007.⁷⁵

In North America, some of the most important swine influenza viruses are the triple reassortant H3N2 viruses. These viruses first emerged in U.S. pigs in the late 1990s, mainly in the Midwest,^{61,74,76-78} and they have been detected in Canada since 2005.^{12,14,79} The North American H3N2 triple reassortant viruses 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.⁷⁷ The particular combination of internal genes carried by these viruses is known as the triple reassortant internal gene (TRIG) cassette. This cassette seems to be especially efficient in generating swine influenza virus recombinants with new hemagglutinin and neuraminidase genes, including some from human influenza viruses.^{7,71} Viruses with this cassette also have increased antigenic drift compared to other swine influenza viruses.⁷

H3N2 viruses also occur 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.² The European H3N2 viruses contain human H3 and N2 proteins, and internal proteins from the avian virus.² In China, H3N2 viruses that have been detected include double reassortants that contain human H3 and N2 and internal genes from avian influenza viruses, and triple reassortants with human H3 and N2 and internal gene segments from both swine and avian influenza viruses.⁶⁹ Some wholly human-like H3N2 viruses have also been found among pigs in China.⁶⁹

The H1N2 virus in the U.S. is a reassortant of the classical H1N1 swine influenza virus and the North American triple reassortant H3N2 virus.² Other variants have also been detected. Some H1N2 viruses isolated from Canadian pigs contained neuraminidase and hemagglutinin genes from two different human influenza

viruses, the polymerase gene from human H1N2 viruses, and other internal genes from classical H1N1 swine influenza viruses.⁷⁴ The H1N2 virus in Europe is a reassortant of a human H1N1 virus and the 'human-like' European H3N2 virus.^{2,8} In China, both the H1N2 swine influenza virus from North America, and apparent reassortants between the H1N1 classical swine influenza virus and North American H3N2 human influenza viruses have been reported.⁸⁰ Other novel reassortants of swine influenza viruses continue to be discovered.^{81,82}

New subtypes have also been found in some swine populations. The novel subtype H3N1 has recently been isolated from pigs in the U.S.^{83,84} This subtype appears to contain genes from human, swine and avian influenza viruses.^{83,84} A different H3N1 influenza virus, containing human and swine influenza virus genes, has been found in Korea⁸⁵ and an H3N1 virus which may be a novel reassortant between H3N2 and H1N1 swine influenza viruses has been reported in Italy.⁶⁶ An H2N3 virus isolated from pigs with respiratory disease in the U.S. contained genes from avian and swine influenza viruses.⁸⁶ 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.⁶⁵ This subtype appears to contain neuraminidase and hemagglutinin genes from avian H9N2 viruses and internal genes from an H5N1 virus (Sw/SD/2/03) that also infects pig populations in the area.⁶⁵ Avian (LPAI) H5N2 and an avian/swine H5N2 reassortant viruses have been isolated from pigs in Korea.⁸⁷ The avian H5N2 virus appears to have been circulating among pigs since 2006.⁸⁷

The novel H1N1 virus of swine origin

Swine influenza viruses are occasionally found in humans.^{1-4,6,9-25} In most cases, these viruses are poorly adapted to humans, and little or no person-to-person transmission occurs.^{1,2,10,13,14} In 2009, a novel H1N1 virus, which seems to have originated from one or more swine influenza viruses, emerged in human populations.²⁸⁻³⁰ This virus appears to be a reassortant between North American and Eurasian swine influenza viruses; it contains a hemagglutinin gene that is most closely related to swine influenza viruses in North America, a neuraminidase gene that is related to swine influenza viruses in Eurasia, and internal genes from two or more swine influenza viruses including the North American triple reassortant H3N2 viruses and a Eurasian virus.²⁸⁻³⁰ Similarly to some of the swine influenza viruses described above, the parental swine influenza viruses include some gene segments that originally came from avian and human influenza viruses.^{29,30} In 2009, the novel H1N1 virus was the dominant influenza virus being transmitted in human populations in most parts of the world.⁸⁸ It has also been transmitted to animals, including pigs, apparently from infected humans.^{31-48,50-60}

Geographic Distribution

Swine influenza viruses are enzootic in most areas that have dense populations of pigs.⁸⁹ This disease is common in North and South America, Europe and parts of Asia, and it has been reported from Africa.^{4,8} Although the subtypes of the swine influenza viruses found in the U.S. and Europe are the same, they can actually be different viruses (see 'Etiology').

Novel H1N1 virus of swine origin

The novel H1N1 virus circulating among humans was first reported in Mexico, but it is now found worldwide in people.^{90,91} Sporadic outbreaks in swine herds and/or turkey flocks have also been reported in a number of countries including Canada, the U.S., Mexico, Chile, Japan, Taiwan, Iceland, Finland, Italy, Germany, Ireland, Northern Ireland, Indonesia and Australia.^{31-36,38,39,41-49,56,92} This virus was also found among pigs imported into Singapore from Indonesia.³⁷ An extensive outbreak among swine, with a number of herds believed to be infected, has been reported in Norway.⁴⁰

Transmission

In mammals, influenza viruses are transmitted in aerosols created by coughing and sneezing, and by contact with nasal discharges, either directly or on fomites.^{1,3,5,6,8,93-95} Close contact and closed environments favor transmission. Mammalian influenza viruses are relatively labile, but can persist for several hours in dried mucus.⁹⁵ Swine influenza viruses are inactivated in untreated pig slurry in 1-2.5 hours at 50-55°C (122-131°F), two weeks at 20°C (68°F), and 9 weeks at 5°C (41°F).⁹⁶

Transmission of influenza viruses between species

Ordinarily, swine influenza viruses circulate only among pigs, equine influenza viruses among the Equidae, avian influenza viruses among birds, and human influenza viruses among people. Occasionally, these viruses cross species barriers. Generally, the virus is not well adapted to the new host species and does not undergo sustained transmission. 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.⁶¹

In some instances, a virus has caused a limited outbreak or become established in a population after being transferred 'whole' to a new host species. An avian influenza virus might have been responsible for the deadly 1918 'Spanish flu' (H1N1) pandemic in humans.^{97,98} Pigs are thought to have acquired their first influenza virus, the classical H1N1 virus, at this time.⁶ During the 1918 pandemic, the new H1N1 human influenza virus was transmitted between people and pigs; outbreaks in farm families were often followed immediately by outbreaks in their herds, and outbreaks in

pigs were sometimes followed by illness among humans on the farm.¹⁹ Genetic sequencing of the human virus, as well as the chronology of the epidemics among humans and pigs, support the view that this virus was transmitted from people to pigs.⁶ H1N1 viruses circulated in both species after this time; however, the viruses in the two host populations diverged genetically.^{99,100}

Cross-species 'jumps' are aided if a novel virus reassorts with an influenza virus that is already adapted to that host.⁶⁴ For example, avian influenza viruses or swine influenza viruses are expected to spread more readily in humans if they reassort with human influenza viruses. Two of the last three human pandemics seem to have occurred after reassortment between avian and human influenza viruses.^{2,61} Reassortment can occur in the new host's own cells.^{61,64,101} It could also occur in an intermediate host.^{2,6,61,64,101} Pigs, which are thought to be particularly good intermediate hosts, have receptors that can bind swine, human and avian influenza viruses.^{2,5,6,8,9} For this reason, they have been called 'mixing vessels' for the formation of new viruses.

Transmission of swine influenza viruses to humans

Swine influenza virus infections have been reported sporadically in humans.^{1,2,6,9,10,13-25,102} Most of these infections occur after direct contact with pigs, but viruses may also spread to people through another host. For example, one H1N1 swine influenza virus, which had infected a turkey herd, was then transmitted to a laboratory technician who developed respiratory signs.^{6,103} How often swine influenza viruses infect people is unknown. If most infections resemble human influenza, they may not be investigated and recognized as zoonoses. Before 2005, when swine influenza in humans became reportable in the U.S., approximately one case was reported to the Centers for Disease Control and Prevention (CDC) every 1-2 years.¹⁷ From December 2005 through February 2009, 12 cases were reported to the CDC.¹⁷ Recent serological evidence suggests that swine influenza infections might occur regularly in people who have contact with pigs.^{1,2,9,104-107}

Although many swine influenza virus infections seem to be limited to a single person, sometimes cases are followed by a few infections among close contacts. In Czechoslovakia, five family members of an infected laboratory worker became ill.¹⁹ Similarly, several health care workers developed influenza symptoms after exposure to a pregnant woman with swine influenza in Wisconsin.¹⁹ One college student transmitted the virus to his roommate, who remained asymptomatic.¹³ Until 2009, the most extensive person-to-person transmission was reported in 1976, when approximately 500 of 12,000 people on a military base in Fort Dix, New Jersey became seropositive to a swine influenza virus.^{1,2,13,19} This virus remained limited to the base and did not spread to the surrounding community.

In 2009, a novel H1N1 virus with genes of swine origin became established in human populations.^{91,108} Genetic analysis suggests that this virus was probably transmitted to people very recently, and that it might have been circulating among pigs in an unknown location for years before it emerged in humans.^{29,30} As of December 2009, this swine population has not been found, and it is not known how humans acquired the novel H1N1 virus.²⁹ There is no evidence that pigs are playing an significant role in the spread of this virus among people,¹⁰⁹ but people might be involved in disseminating the virus to pigs.^{34,35,39,44,110}

Transmission of swine influenza viruses to other species

Swine influenza viruses may also infect other species. These viruses occur regularly among turkeys,^{1,3} and outbreaks have been reported recently in mink and ferrets.^{11,12} Mink might have been exposed via uncooked swine tissues in their diet.¹² How the ferrets became infected is not known, but the outbreak occurred near a swine farm.¹¹ In addition, the ferrets were fed uncooked turkey.

Disinfection

Influenza viruses are susceptible to many common disinfectants including sodium hypochlorite, 70% ethanol, oxidizing agents, quaternary ammonium compounds, aldehydes (formalin, glutaraldehyde, formaldehyde), phenols, acids, povidone-iodine and lipid solvents.^{3,95,111-113} 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).^{3,95,111,113,114}

For the disinfection of the novel H1N1 virus in laboratories, the CDC recommends the agents used for human influenza viruses, such as chlorine-containing disinfectants, alcohols, peroxygen, detergents, iodophors, quaternary ammonium or phenolic compounds.¹¹⁵

Infections in Humans

Incubation Period

The incubation period for swine influenza in people is unknown; however, influenza generally becomes apparent within a few days of exposure in all mammals. The incubation period for the novel H1N1 virus circulating in humans appears to be 2-7 days.^{116,117}

Clinical Signs

Because few infections with swine influenza viruses have been described, it is not known whether the symptoms caused by these viruses differ significantly from human influenza.⁹ Reported cases of swine influenza include the following. It should be noted that more severe or fatal cases are more likely to be investigated than mild illnesses that resemble human seasonal influenza.¹¹⁶

- A localized outbreak was reported at Fort Dix, New Jersey in 1976. An H1N1 swine influenza virus was isolated from five recruits with respiratory disease, including one who died of pneumonia.^{1,2,13} Other people on the base may also have been ill with the same infection.^{19,102} Serological evidence suggests that approximately 500 people on the fort had been infected by person-to-person spread. (This virus is not the same virus involved in the swine-origin H1N1 pandemic of 2009.)
- A self-limiting illness with influenza symptoms was reported in a college student infected with an H1N1 virus in 1979.¹³ There was evidence that his roommate had been infected but remained asymptomatic.
- In 1980, an H1N1 virus infection with influenza symptoms including diarrhea occurred in a young boy, who recovered.¹³ There was no evidence of spread to his family.
- Swine influenza virus (H1N1) was isolated from an immunocompromised child with fulminant pneumonia who died in 1982.¹⁵ Serological evidence of possible infection was found in five contacts, but the infection did not spread further.
- In 1986, an H1N1 virus caused severe viral pneumonia in a 29-year-old swine farmer in The Netherlands.²¹ The farmer had been in contact with pigs showing signs of respiratory disease.
- In 1988, an H1N1 swine influenza virus was isolated from a pregnant woman with viral pneumonia in Wisconsin.²⁰ She apparently became infected while attending an agricultural fair, and died shortly after giving birth. Several health care workers developed influenza-symptoms after exposure.¹⁹
- In 1991, a healthy young laboratory animal caretaker in Maryland died of pneumonia caused by an H1N1 influenza virus.¹⁸ He had close contact with pigs in a research facility. The virus appeared to be a reassortant, but all of the gene segments were of swine influenza virus origin. No one who had been in contact with the caretaker became ill, and only one person was seropositive.
- In 1993, an H1N1 swine influenza virus caused severe viral pneumonia in a 5-year-old child who lived on a pig farm in The Netherlands.²¹
- 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.¹⁰ He recovered without complications. There was no evidence of person-to-person transmission.
- In 2005, an Asian H1N1 swine influenza virus was isolated from a 4-year-old boy in Thailand with rhinorrhea, fever and myalgia.¹⁰ The child recovered without complications, and there was no evidence that the virus had infected others.

- In 2005, a recombinant swine influenza virus was recovered from a farm worker with influenza symptoms in Canada.¹⁴ 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. The infected individual was given antiviral drugs, and recovered uneventfully. Other workers on the farm were treated prophylactically and did not become ill.
- In 2007, an H3N2 swine influenza virus was isolated from an infant with respiratory disease in Canada.²² The child was hospitalized but recovered. He had no direct contact with animals, but lived on a communal farm. Four of 7 household members and 4 of 46 other people on the farm had antibodies to this virus.
- In November 2008, a mild, self-limited case of H1N1 swine influenza was reported from a 50-year-old woman who worked on a swine farm in Spain.²³ This case was diagnosed only because the physician participated in an influenza surveillance program and collected a laboratory sample for virus identification.²⁴ The physician who treated her reported an influenza-like illness shortly afterward, but was not tested for the virus. No other potential cases were associated with this infection.
- Between 2005 and February 2009, 11 human infections with triple reassortant H1N1 swine influenza viruses were reported to the U.S. Centers for Disease Control and Prevention (CDC).²⁵ The symptoms included fever, coughing, sore throat, headache, diarrhea, vomiting, myalgia, shortness of breath and conjunctivitis. Two children were hospitalized for dehydration, but recovered without other complications. Two patients, a 26-year-old previously healthy woman and a 48-year-old woman with asthma and a history of smoking, experienced severe illness with pneumonia and respiratory failure, but recovered. Nine of the patients had a history of contact with pigs, and one case was thought to have been transmitted from person to person. One patient had three family members with suspected but unconfirmed swine influenza virus infections.

A recent literature review summarized 49 cases of swine influenza that had been documented in scientific journals as of April 2006 (including many of the cases described above), and one additional case identified in an ongoing survey of swine influenza among farmers.¹⁹ Thirteen of the cases were from the outbreak at Fort Dix; the other 37 were described as ‘cases in civilians.’ Twenty of the 37 civilian patients were previously healthy; others had immunosuppressive conditions including cancer and pregnancy. Four cases involved H3N2 viruses; the remainder were H1N1. All cases were described in the literature as upper respiratory disease, acute respiratory disease or pneumonia. Most patients recovered, but seven deaths were reported.

Novel H1N1 virus of swine origin

In most people, the novel H1N1 virus causes relatively mild disease that resembles seasonal human influenza.^{88,90,117,118} The symptoms may include fever, chills, cough, sore throat, rhinorrhea, malaise, headache and myalgia.^{88,90,117,119,120} Vomiting and diarrhea have also been reported in a significant number of cases.^{90,117,119,120} Most people have a self-limiting illness, and recover within a week.¹¹⁸ Severe primary viral pneumonia and/or acute respiratory distress syndrome occur in a small percentage of cases, and may be fatal.^{88,117,120-123} Patients who become severely ill usually begin to deteriorate 3-5 days after the onset of the symptoms, and their condition rapidly becomes serious, often progressing to respiratory failure within 24 hours.^{118,122} Multiple organ failure may be seen.^{118,123} Like other influenza viruses, the novel H1N1 virus can also exacerbate chronic medical conditions, especially respiratory diseases such as asthma or chronic obstructive pulmonary disease, and some cases may be complicated by secondary bacterial infections.^{118,119,123,124} Underlying health conditions, very young age or pregnancy increase the risk of severe disease.^{88,118,122,125-128} A significant number of serious or fatal cases have been reported in healthy children or young adults, who would not be expected to have a high risk of complications.^{88,118,122,125,126}

Communicability

Most swine influenza viruses have been transmitted only to a few close contacts.^{13,15,19} There are two known outbreaks with more extensive spread. One was a localized outbreak among recruits infected with an H1N1 virus at a military base in Fort Dix, New Jersey.^{1,2,6,13,17} Approximately 500 people on the base, which contained approximately 12,000 people, were infected or exposed; however, the virus did not spread to the surrounding community.^{1,2,13} The other is the 2009 H1N1 pandemic in humans.

Novel H1N1 virus of swine origin

For the novel (2009 pandemic) H1N1 virus, the estimated period of communicability is from 1 day before the symptoms appear, to as long as 7 days after their onset.^{17,108} People may shed this virus for as long as they are ill, and in some cases, for 2-3 days after the fever has resolved.^{17,129} Children and people who are immunocompromised might be infectious for longer.¹⁰⁸ One study presented at a recent conference found that viral nucleic acids could be detected by reverse transcription polymerase chain reaction (RT-PCR) assays in children for 1 to 13 days after they became febrile, and virus could be isolated for 1 to 7 days.¹²⁹ Atypical prolonged shedding up to 28 days (by PCR) has been reported in healthy adults with severe or relatively severe cases.¹³⁰ Humans can transmit the novel H1N1 virus to animals as well as people. Swine herds, turkeys, ferrets, felids and dogs have apparently been infected from human contacts.^{34,35,39,41,44,48,50-60,110}

Diagnostic Tests

Swine influenza viruses

Influenza A infections may be diagnosed by virus isolation. These viruses can be isolated in cell lines or chicken embryos, and they may be identified by hemagglutination and neuraminidase inhibition tests, or RT-PCR.^{1,2,5,62} Nucleic acids can be detected in respiratory secretions by RT-PCR, and viral antigens can be found using immunofluorescence or enzyme-linked immunosorbent assays (ELISAs).^{62,131} Infections can also be diagnosed retrospectively by serology with a fourfold rise in titer.^{131,132} Because humans are not expected to have antibodies to swine influenza viruses, a single titer might be suggestive. An influenza test that is positive for influenza A, but does not detect the hemagglutinins in common human influenza viruses also suggests a novel, possibly zoonotic, influenza virus.¹³²

Novel H1N1 virus of swine origin

Infections with the novel H1N1 virus can be confirmed by RT-PCR or virus isolation, using respiratory secretions.^{131,133} Samples should be collected as early as possible after the onset of illness. The current immunofluorescence or rapid antigen tests for human influenza cannot distinguish other human influenza viruses from the novel H1N1 virus.^{131,133} Serology is used mainly in epidemiology and research.¹³¹

Treatment

Supportive care for uncomplicated influenza in humans includes fluids and rest. Most people infected with the novel H1N1 virus recover within a week without additional treatment.^{118,134} More severe cases, or infections in people at an elevated risk of complications, are treated with antiviral drugs.^{134,135} Four drugs - amantadine, rimantadine, zanamivir and oseltamivir - are active against influenza A viruses.^{62,93-95,136} Testing must be done to determine each virus's drug susceptibility. The novel H1N1 virus circulating among humans in 2009 is resistant to amantadine and rimantadine (adamantanes), but it is usually sensitive to oseltamivir and zanamivir.^{119,135,137,138} Oseltamivir-resistant isolates have been reported sporadically, but they are currently uncommon.^{88,137} Antiviral drugs are most effective if treatment is begun within the first 48 hours of illness,^{62,93-95,136} but these drugs may also be used later in some cases.^{134,135} Side effects including neuropsychiatric events may occur.^{94,134} Hospitalization and extensive supportive therapy are also necessary in some cases,^{88,117,120-123} and antibiotics may be needed to control secondary bacterial infections.^{118,124} Current recommendations for the treatment of infections with the novel H1N1 virus, including the use of antiviral drugs, are available on the CDC and World Health Organization (WHO) Web sites (see Internet Resources).^{134,135}

Prevention

Preventing infection with influenza viruses found in pigs

Good hygiene and sanitation, including frequent hand washing, can help prevent human infections with swine influenza viruses. Protective clothing, gloves and other personal protective equipment also reduce exposure. When investigating a possible outbreak of the novel 2009 H1N1 virus in pigs, the Canadian Food Inspection Agency (CFIA) recommends that veterinarians use N95 masks, eye protection, gloves, impermeable coveralls, and protective clothing and footwear, in addition to good hygiene and sanitation.¹⁰⁹

There is no indication that any swine influenza virus can be acquired by eating well-cooked pork.^{139,140} In pigs, swine influenza viruses replicate in the lungs and upper respiratory tract, and are not ordinarily expected to occur outside these tissues (e.g., in meat).⁸⁹ Ordinary food safety precautions including hand washing before and after handling raw meat, the prevention of cross-contamination of foods or surfaces used for food preparation, and the use of hot soapy water to wash contaminated surfaces would be protective if any viruses survived long enough to reach consumers.¹³⁹ Influenza viruses are also killed by sanitizing cutting boards with 1 tbsps bleach in a gallon of water, and by cooking pork to an internal temperature of 160°F (71.1°C).¹³⁹

Preventing infection with the novel H1N1 virus circulating in humans

Preventative measures include the avoidance of close contact (approximately 6 feet) with people who have flu-like illnesses, as well as frequent hand washing, the avoidance of unnecessary hand contact with the eyes, nose or mouth, and other common sense hygiene measures.^{17,108,141} To protect others, the mouth and nose should be covered when coughing or sneezing.^{17,108,141} There appears to be little or no cross-reactivity with the H1N1 strains in the current seasonal human influenza vaccine,¹⁴² but vaccines for the novel H1N1 virus became available in Fall 2009. Where limited quantities of these vaccines are available, specific risk groups may be targeted first for vaccination.¹⁴³ Antiviral drugs may be used for prophylaxis in some high risk populations after exposure.¹⁴⁴ In other cases, people may be monitored, and treated at the first sign of disease.¹⁴⁴ The CDC Web site has detailed information on the current recommendations.¹⁴⁴

In areas where infections with the novel H1N1 virus are common, people at an increased risk for complications should consider avoiding crowded conditions or close contact with others.¹⁴⁵ The CDC currently recommends that anyone infected with the novel H1N1 virus and anyone who has an undiagnosed flu-like illness limit contact with others, and stay home except for necessities (for instance, seeking medical care).^{108,146,147} The CDC has published specific guidelines for self-isolation and

treatment, as well as recommendations for infection control measures in health care settings (see Internet Resources).^{119,121,147,148} People who remain home should minimize contact with others in the household during their illness.¹⁴⁸ Face masks and respirators are no longer recommended in homes, communities or non-healthcare occupational settings, but they may be used voluntarily by individuals at risk for complications.¹⁴¹ To prevent virus transmission to pigs, anyone who has a flu-like illness should avoid contact with this species. Care should also be taken to avoid spreading the virus to other animals, particularly turkeys, ferrets, cats (both housecats and other felines) and dogs.

Guidelines for laboratory work with the novel H1N1 virus have been updated, and are less stringent than during the initial stages of the outbreak when the risk to humans was poorly understood. Some simple diagnostic procedures may be done with splash protection and ordinary laboratory precautions; more complex procedures require the use of a Class II biosafety cabinet in a BSL-2 laboratory.¹¹⁵ Personal protective equipment recommendations and additional details on laboratory safety are available from the CDC.¹¹⁵

Morbidity and Mortality

The overall prevalence of swine influenza virus infections in humans is unknown; however, serological evidence suggests that exposure may be relatively common among people who work with pigs.^{1,2,9,104-107} Swine influenza infections have been reported among farm workers, laboratory workers, visitors at agricultural fairs or livestock shows, and a meat packer.¹⁹ Infections not associated with swine contact have included instances of limited person-to-person transmission and some published cases with no known connection to swine.^{13,19,25} Most sporadic cases of swine influenza have been relatively mild and some may have been asymptomatic, but some severe illnesses and a few deaths have been reported.^{1,2,10,13-15,18-25} During the outbreak at the Fort Dix military base, one person died of pneumonia, at least twelve additional cases thought to be swine influenza were reported, other probable cases were suspected, and serological evidence of infection was found in approximately 500 of 12,000 people on the base.^{1,2,13,19,102} One review reported that, of 37 other cases reported in the literature, six cases were fatal.¹⁹ Four of these patients had primary viral pneumonia, one had secondary bacterial infection, and one had extensive involvement of the abdominal organs.¹⁹ Two patients who died were described as previously healthy, one was pregnant, and two were immunosuppressed by cancer.^{1,2,13,15,18,19} The health status of one person was not known. In a series of 11 infections with North American triple reassortant H1N1 swine influenza viruses between 2005 and 2009, two children were hospitalized for dehydration, and severe illnesses were reported in a previously healthy 26-year-old woman and a 48-year-old woman with asthma

and a history of smoking.²⁵ All of the patients in the latter study recovered.

Novel H1N1 virus of swine origin

The initial outbreak with the novel H1N1 virus occurred in Mexico in April.^{17,26,27,90,149-151} This was followed by the identification of the virus among travelers in other countries, then by the recognition of sustained person-to-person transmission outside Mexico.^{26,27,149-151} In June, a human pandemic was declared.¹⁵² As of November 27 2009, more than 622,000 cases and 7,800 deaths attributed to this virus have been reported to the World Health Organization.¹⁵³ Because many countries no longer count or report individual cases, this underestimates the number of cases, particular those that are mild.^{91,138,153}

Cases were reported in both the Northern and Southern Hemispheres during the initial stage of the outbreak. However, like other human influenza viruses, the novel H1N1 virus has been transmitted most widely during the traditional flu season, which begins in the autumn. Because the virus emerged in April, this occurred first in the Southern Hemisphere. During the flu season in the Southern Hemisphere, the reported hospitalization rates from various countries ranged from 2.0 to 31.8 per 100,000 population.¹²⁷ The mortality rate in the Southern Hemisphere was relatively low, with less than 1 death per 100,000 population in most countries; individual countries reported mortality rates from 0 to 36.1 per million population.¹²⁷ In Victoria, Australia, approximately 5% of the population is thought to have become ill, and 0.3% of those infected were hospitalized, with 20% of hospitalized patients transferred to an intensive care unit (ICU).¹²³ In Victoria, 85% of these critically ill patients survived.¹²³ In Taiwan, the mortality rate among 91 hospitalized patients was approximately 10%.¹⁵⁴ In New South Wales, Australia, the overall mortality rate from influenza was lower than in previous years, but severe illness was seen in some high risk groups.¹²⁷ Peru reported 8381 confirmed cases and 143 deaths, most (75%) in people who had other health issues.¹²⁷ A small number of H1N1 infections may be asymptomatic.¹²⁷ Transmission of the novel H1N1 virus appears to have declined normally after the flu season in the temperate regions of the Southern Hemisphere.¹³⁸ The autumn flu season in the Northern Hemisphere has been very active in the initial stages.^{91,138,153,155} The impact of the novel H1N1 virus has been greater among indigenous people in both the Northern and Southern Hemispheres, with hospitalization and mortality rates that were 3-7 times greater than in non-indigenous groups.¹²⁷

Although the vast majority of cases have been mild and uncomplicated, viral pneumonia has been a significant concern with this virus.^{88,118,122,154} Secondary bacterial infections have also contributed to some severe cases and deaths.^{118,124} The risk of severe illness has been greatest in children under the age of 2 years (especially infants under a year of age), pregnant women, people with

underlying health conditions such as chronic respiratory disease, some cardiovascular conditions or immunosuppression, and those who are obese.^{88,118,120,122,123,125-128,138,141,154,155} HIV infection was linked to more severe illness in South Africa,¹²⁷ but data from other countries suggest that this is not necessarily the case among HIV-infected individuals who are receiving antiretroviral drugs.⁸⁸ Unusually, severe or fatal cases have also been reported among some young, previously healthy individuals, who are not ordinarily expected to be at high risk.^{88,90,120,122,123,125,126,138,155} The reported percentage of hospitalized patients who have had no significant pre-existing conditions ranges from approximately 24% to 59%, depending on the country and the conditions that are defined as predisposing.^{117,155,156} Some older people may have some immunity to the novel H1N1 virus,^{157,158} and this group has had lower morbidity rates than expected, but they are more likely to have severe symptoms if they become ill.^{88,108,118,122,127}

For comparison, the morbidity rate for seasonal human influenza is high, but uncomplicated infections with human influenza viruses are rarely fatal in healthy individuals.^{1,61,62,95,159} Infections with human influenza viruses are more severe in the elderly, young children (particularly infants), people with respiratory or cardiac disease, and those who are immunosuppressed.^{62,93-95} Influenza-related deaths are usually the result of pneumonia or the exacerbation of a cardiopulmonary condition or other chronic disease.⁹⁴ During influenza pandemics, the morbidity and mortality rates can increase dramatically in all age groups.^{1,2,8,62,64,94} After a pandemic, an influenza virus usually becomes established in the population and circulates for years.⁶⁴

Infections in Animals

Species Affected

Swine influenza viruses mainly affect pigs, but they can also cause disease in turkeys.^{1,3} Outbreaks have been described recently in ferrets and mink.^{11,12} One H1N1 swine influenza virus, which was avirulent for both poultry and pigs, was isolated from a duck in Hong Kong.¹⁶⁰ Experimental infections have been reported in calves.¹⁶¹

Novel H1N1 virus of swine origin

The novel H1N1 virus has infected pigs and turkeys.^{31-49,56,92,162} A few clinical cases have also been reported in pet ferrets, cats, a cheetah in a zoo, and dogs.^{50-55,57-60} Experimental infections have been established in ferrets, mice and cynomolgus macaques (*Macaca fascicularis*).^{120,158,163} In one experiment, chickens exposed to infected pigs did not become infected.¹⁶⁴

Incubation Period

The clinical signs usually appear within 1-3 days in pigs infected with most swine influenza viruses.^{1,3-5} Pigs

that were experimentally infected with the novel H1N1 virus developed clinical signs beginning on the third day after inoculation.¹⁶⁴

Clinical Signs

Swine influenza is an acute upper respiratory disease characterized by a variety of clinical signs, which may include fever, lethargy, anorexia, weight loss and labored breathing.^{1-5,89} Coughing can occur in the later stages of the disease.^{2,89} Sneezing, nasal discharge, conjunctivitis and abortions may also be seen.^{2,4,5} Some outbreaks are more severe than others, and swine influenza viruses can circulate in pigs with few or no clinical signs.^{1,2,7,8} Complications may include secondary bacterial or viral infections.^{2,4,5} Severe, potentially fatal bronchopneumonia is occasionally seen.³

Turkeys infected with swine influenza viruses may develop respiratory disease, have decreased egg production, or produce abnormal eggs.³

In ferrets that were naturally infected with a triple reassortant H1N1 swine influenza virus, the clinical signs included sneezing, coughing, crusting of the nose and eyes, and severe dyspnea.¹¹ Mink naturally infected with a Canadian triple reassortant H3N2 virus had respiratory signs including pneumonia, with increased mortality particularly on ranches where the mink were co-infected with other pathogens.¹²

Novel H1N1 virus of swine origin

A number of swine herds have been infected with the novel H1N1 virus circulating in humans.^{31-42,46-49,92,162} The illness has been mild, with little or no mortality, and the clinical signs have resembled those caused by other swine influenza viruses.^{31,34,36,39,41,44-47,92,165} Coughing, nasal discharge, fever, weakness and decreased appetite have been reported.^{34,38,39,42,44,45,110} Abortions or diarrhea have also been seen in some herds.^{34,42} Experimentally infected pigs developed mild disease, with nasal discharge, sneezing and fever as the most prominent signs.^{164,166} Diarrhea was reported in some experimentally infected animals.¹⁶⁴ In one study, miniature pigs remained asymptomatic although they shed the virus.¹⁵⁸

Infected turkey flocks reported in Chile and Canada experienced only decreased egg production and reduced quality of the eggs, with no mortality or other clinical signs.^{48,49} Decreased egg production was also reported in a turkey flock in the U.S.⁵⁶

Respiratory disease was reported in naturally infected ferrets; the clinical signs included fever, coughing, sneezing, nasal discharge and weakness.^{50,53} Lethargy, decreased appetite, sneezing, nasal discharge and ruffled fur were seen in some experimentally infected ferrets.¹²⁰ In another experimental study, lethargy and weight loss were the most apparent signs, and sneezing was rare.¹⁶³

Upper or lower respiratory signs including sneezing and coughing in some cases, and pneumonia in others, have been described in cats.^{54,58,60} One cat became

dyspneic and severely ill, and two other cats died.^{54,60} Some cats with respiratory disease have not had a fever.⁵⁴ The illness can last for several weeks in some animals.⁵⁸ An infected cheetah developed lethargy, anorexia and a cough, but recovered.⁶⁰ There is little information on cases in dogs, but the novel H1N1 virus was isolated from sick animals in China,⁵⁵ and a dog in the U.S. was ill with clinical signs of lethargy, anorexia, fever and coughing, and radiological evidence of pneumonia.⁵⁹ The dog in the U.S. was hospitalized and treated with supportive care including antibiotics, and recovered.⁵⁹

Communicability

Swine influenza viruses are readily transmitted between pigs. These viruses are normally found only in respiratory secretions.⁸⁹ In one group of experimentally infected pigs, a swine influenza virus was found in the feces of a single animal; however, there is no evidence that these viruses can replicate in the intestinal tract.^{89,167} Virus excretion may begin within 24 hours of infection, and typically continues for 7-10 days.^{5,6,8} Shedding up to four months has been documented in one pig, although this is unusual.^{6,8}

Novel H1N1 virus of swine origin

In pigs that were experimentally infected with the novel H1N1 virus, PCR could detect nucleic acids beginning 1 day after inoculation (two days before the development of clinical signs), and virus could be isolated from day 3 to day 11 after inoculation.¹⁶⁴ Studies from the United States Department of Agriculture, which have not yet been published, have not detected the novel H1N1 virus in swine tissues other than the respiratory tract.^{168,169}

Post Mortem Lesions [Click to view images](#)

Swine influenza

In uncomplicated infections, the gross lesions are mainly those of a viral pneumonia.² Affected parts of the lungs are depressed and consolidated, dark red to purple-red, and sharply demarcated.^{2,4} Lesions may be found throughout the lungs but they are usually more extensive in the ventral regions.^{2,4} Other parts of the lungs may be pale and emphysematous.⁴ The airways are often dilated and filled with mucopurulent exudate.⁴ The bronchial and mediastinal lymph nodes are typically edematous but not congested.^{2,4} Severe pulmonary edema, as well as serous or serofibrinous pleuritis, may also be seen.⁴ Some strains of swine influenza viruses produce more marked lesions than others.² Generalized lymphadenopathy, hepatic congestion and pulmonary consolidation were reported in one outbreak of severe disease in swine.¹

Novel H1N1 virus of swine origin

Typical swine influenza lesions in the lungs, including a diffusely non-collapsed parenchyma, rubbery texture and areas of bronchiopneumonia were reported in pigs experimentally infected with the novel H1N1

virus.¹⁶⁴ Salpingitis, peritonitis and interrupted follicular development were the only lesions reported in turkeys.⁴⁸

Diagnostic Tests

Swine influenza can be diagnosed by virus isolation, the detection of viral antigens or nucleic acids, and serology. Mammalian influenza viruses can be isolated in embryonated chicken eggs or cell cultures.^{2,5} Swine influenza viruses are often recovered in Madin–Darby canine kidney cells, but other cell types can also be used.⁵ These viruses can be isolated from lung tissues at necropsy, and from nasal or pharyngeal swabs collected from acutely ill pigs.³⁻⁵ Recovery is best from an animal with a fever, 24-48 hours after the onset of disease.⁵ Isolated viruses can be subtyped with hemagglutination inhibition and neuraminidase inhibition tests or RT-PCR.^{2,5}

Immunofluorescence can detect antigens in fresh lung tissue, nasal epithelial cells or bronchoalveolar lavage.^{2,5} Other antigen detection tests include immunohistochemistry and ELISAs.^{2,5} RT-PCR assays are used to detect viral RNA.^{2,5}

Serology on paired samples can diagnose swine influenza retrospectively.^{4,5} The hemagglutination inhibition test, which is subtype specific, is most often used.^{2,4,5} It may not detect new viruses.² ELISA kits are also available. Uncommonly used serological tests in swine include agar gel immunodiffusion, the indirect fluorescent antibody test and virus neutralization.⁵

Treatment

Animals with influenza are usually treated with supportive care and rest.⁴ Antibiotics may be used to control secondary infections. Antiviral drugs are not generally given to animals.

Prevention

Common swine influenza viruses

Vaccines are available for some influenza virus infections in pigs.^{1,3-5} These 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 viruses display less antigenic drift than human viruses, and these vaccines are changed less often.^{2,3,89}

Because influenza is usually introduced into a facility in an infected animal, isolating newly acquired pigs can decrease the risk of transmission to the rest of the herd.^{2-4,6,8} Good biosecurity is also important to prevent transmission on fomites and mechanical vectors.⁴ Once a herd of swine has been infected, the virus usually persists in the herd and periodically causes outbreaks in young animals and other susceptible pigs; however, good management can decrease the severity of disease.^{1,2,4,6,8} Infected swine herds can be cleared of influenza viruses by depopulation.^{6,8}

Influenza viruses from humans, birds and other species

Pigs can be infected with human and avian influenza viruses. Infections with equine H3N8 viruses have also been reported among pigs in China.¹⁷⁰ As much as possible, pigs should be protected from these viruses, which can become established in swine populations or recombine to generate new swine influenza variants. Birds, which can carry avian influenza viruses asymptotically, should be excluded from swine facilities. These viruses are found especially in waterfowl, shorebirds and poultry, but they can also occur in other avian species.^{1-3,8,63,171-174} Avian influenza viruses can survive for long periods in aquatic environments,^{113,175} and pigs should not be allowed to contact water where waterfowl have been swimming. To prevent human influenza viruses from entering a herd, swine workers who are ill should avoid contact with pigs, and the public should be restricted from entering swine operations.¹⁷⁶ Vaccination against human influenza is encouraged for swine workers, to reduce the risk that recombination could occur between these viruses and swine influenza viruses.¹⁷⁶

Biosecurity measures to prevent swine influenza would also protect pigs from other influenza viruses on fomites.

Novel H1N1 virus of swine origin

To prevent the novel H1N1 virus from infecting swine, anyone who has influenza-like symptoms, including mild disease, should avoid contact with pigs.^{176,177} Workers who have been exposed to influenza should also stay away from pigs until they have been checked by a healthcare provider.¹⁷⁷ Excellent cleaning, disinfection and hygiene, particularly washing of the arms and hands, is important before and while working with pigs.¹³⁹ The use of farm-specific clothing is recommended.¹⁷⁶ At a minimum, dedicated shoes should be used while on the farm.¹⁷⁶ The Canadian Food Inspection Agency has published biosecurity recommendations, including recommended waiting periods before visiting other herds, for veterinarians who examine herds that may be infected (see Internet Resources).¹⁰⁹

Good biosecurity can help prevent the novel H1N1 virus and other viruses from entering a farm. As a reminder, only essential workers and vehicles should be allowed on the premises, and vehicles or equipment should not be borrowed from other farms.^{139,176,177} If another farm must be visited, or if a vehicle that visits other swine farms enters the property, diligent cleaning and disinfection are important.¹³⁹ Swine premises and equipment should be cleaned and disinfected regularly to prevent the spread of disease, and ventilation should be optimized.^{109,176,177} The benefits of vaccination should be discussed with a swine veterinarian; it is uncertain how much protection the current swine vaccines will offer

against the novel H1N1 strain circulating in humans.^{109,176,177}

Sick animals should be identified and isolated as soon as possible.^{109,177} Herds that may be infected with the novel H1N1 virus should be reported immediately to a swine veterinarian or to government authorities. Some countries may implement movement controls, quarantines or other measures to prevent the novel H1N1 virus from spreading among pigs.^{40,42,43,46,47} When an infected herd is found, the source of the infection should be determined, and potential transmission to other herds should be investigated.

Morbidity and Mortality

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.^{1,8} High seroprevalence rates to swine influenza viruses have also been reported in other countries.^{1,2,8,178}

Swine influenza viruses are usually introduced into a herd in an infected animal.^{3,4,6,8} 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.²⁻⁵ In uncomplicated illness, the case fatality rate varies from less than 1% to 4%.^{1,3,4} Once the virus has been introduced, it usually persists in the herd.^{1,2,6,8} Annual outbreaks are often seen, and in temperate regions, occur mainly during the colder months.^{1,2,4,6,8} Many infections in endemically infected herds are subclinical; typical signs of influenza may occur in only 25% to 30% of the pigs.^{2,6,8} Maternal antibodies decrease the severity of disease in young animals.² Viruses may also infect the herd with few or no clinical signs.^{1,2,6,8}

Influenza epizootics 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.^{1,6,8} In the epizootic form, the virus spreads rapidly in pigs of all ages.⁵ In the 1918 epizootic, millions of pigs developed influenza, and thousands of these infections were fatal.^{1,2,7}

Little is known about the morbidity and mortality rates in species other than swine. In an outbreak caused by a triple reassortant H1N1 swine influenza virus in ferrets, the morbidity rate was 8% and the mortality rate was 0.6%.¹¹

Novel H1N1 virus of swine origin

The H1N1 virus circulating in humans appears to cause mild disease in pigs.^{34,38,39,165} Morbidity rates from less than 1% to as high as 90% have been reported, but little or no mortality has been seen.^{33-35,38,39,42-47,92,110} Experimental studies support this view; deaths have not been reported among experimentally infected pigs.^{158,164,166}

Decreased egg production may be the main effect in turkeys. In a turkeys flock in Chile, the morbidity rate was 61%, but no deaths were seen.⁴⁸ Egg production in this flock dropped from 70% to 31%. Similarly, egg production dropped by approximately 80%, in affected turkey flocks in Canada.⁴⁹ Although a slight increase in flock mortality occurred in the latter case, it may have been unrelated to the H1N1 infection.¹⁷⁹ Decreased egg production and no mortality was reported in a U.S. turkey flock.⁵⁶

A few cats, pet ferrets and dogs have been infected naturally with the novel H1N1 virus.^{50-55,58-60} Several ferrets recovered, but one died.^{50,51,53} Two infected cats died, another developed severe illness with dyspnea but recovered with medical care, and some cats apparently had milder cases.^{52,54,60} An infected cheetah also recovered.⁶⁰ An infected dog in the U.S. was ill with pneumonia, and required hospitalization and supportive care, but recovered.⁵⁹ Experimental studies in mice, ferrets and nonhuman primates suggest that this virus might cause more severe lung pathology and/or clinical signs than seasonal human H1N1 viruses, or that the illness might last longer.^{120,158,163}

Internet Resources

- Canadian Food Inspection Agency.H1N1 Flu Virus (Human Swine Influenza) Questions and Answers [includes biosecurity and waiting period recommendations for veterinarians examining potentially infected herds]
<http://www.inspection.gc.ca/english/anima/disemala/swigri/queste.shtml>
- Centers for Disease Control and Prevention (CDC). H1N1 Flu (Swine Flu)
<http://www.cdc.gov/h1n1flu/>
- Medical Microbiology
<http://www.gsbs.utmb.edu/microbook>
- Public Health Agency of Canada (PHAC). H1N1 Flu Virus
<http://www.phac-aspc.gc.ca/alert-alerte/h1n1/index-eng.php>
- PHAC 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).
<http://www.aphis.usda.gov>
- USDA APHIS. H1N1 Flu
http://www.usda.gov/wps/portal/?navid=USDA_H1N1
- World Health Organization
<http://www.who.int/csr/disease/swineflu/en/index.html>
- 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

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