

Swine Influenza

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Importance

Swine influenza is an acute respiratory disease caused by influenza A viruses that circulate among pigs. The morbidity rate is usually high, and the case fatality rate low, but more severe outbreaks may be seen, and reduced growth rates in young pigs can cause economic losses.¹⁻⁷ Swine influenza viruses occasionally affect other species including turkeys, mink, ferrets and humans.^{2-4,6,8-42} In people, clinical cases have tended to resemble human influenza.^{2,3,6,9,12,13,17,21,22,24,35-41} Most of these cases were not life-threatening, although serious and fatal illnesses do occur.^{2,3,6,9,12-14,16-19,21,22,24,34-42} Swine influenza viruses are not usually transmitted efficiently in human populations. Most infections are limited to the person who had contact with pigs, although viruses have occasionally spread to family members or others in close contact.^{3,6,9,12-14,17,24,35-39,43} One large outbreak at a U.S. military base in the 1970s was propagated by person-to-person transmission, but the virus did not spread to the community.^{3,6,12,17,25} Nevertheless, these viruses are capable of adapting to humans in rare instances. The 2009-2010 human pandemic was caused by a virus that appears to have resulted from genetic reassortment between North American and Eurasian swine influenza viruses.^{44,45} This virus now circulates in human populations worldwide as a seasonal influenza virus. People have transmitted it to herds of pigs, and it has reassorted with various swine influenza viruses.^{27,46-62} These events and other changes in swine influenza viruses have generated increased viral diversity, especially in North America, where effective vaccination of pigs has become more difficult as a result. The number of swine influenza cases reported in humans has also increased recently, particularly in the U.S. where many infections were acquired from pigs at agricultural fairs.^{35,36,63} Whether this increase is due to genetic changes in the viruses circulating among pigs, increased surveillance for novel influenza viruses in humans, or a combination of factors is still uncertain.^{35,36,63,64}

Etiology

Swine influenza viruses belong to the species *influenza A virus*, genus *Influenzavirus A*, and family Orthomyxoviridae. Other influenza A viruses circulate in birds (avian influenza viruses), horses and other equids (equine influenza viruses), people (human influenza A viruses) or dogs (canine influenza viruses). Influenza A viruses are classified into subtypes based on two surface proteins, the hemagglutinin (HA) and neuraminidase (NA). A virus that has a type 1 HA and type 2 NA, for example, would have the subtype H1N2. At least 16 types of hemagglutinins (H1 to H16), and 9 neuraminidases (N1 to N9) are known to exist in birds, and two additional HA and NA types occur in bats, while small subsets of avian subtypes circulate in other mammals.^{8,65-68} The HA, and to a lesser extent the NA, are major targets for the immune response, and there is ordinarily little or no cross-protection between different HA or NA types.⁶⁹⁻⁷⁸

Influenza A viruses are very diverse, and two viruses that share a subtype may be only distantly related. The high variability is the result of two processes, mutation and genetic reassortment. Mutations cause gradual changes in the HA and NA proteins of the virus, a process called 'antigenic drift.'⁷⁴ Once these proteins have changed sufficiently, immune responses against the former HA and NA may no longer be protective.

Genetic reassortment can cause more rapid changes. The influenza A genome consists of 8 individual gene segments,^{76,77} and when two different viruses infect the same cell, gene segments from both viruses may be packaged into a single, novel virion. This can occur whenever two influenza viruses replicate in the same cell, whether the viruses are adapted to the same host species (e.g., two different swine influenza viruses) or originally came from different hosts (for instance, an avian influenza virus and a swine influenza virus). An important aspect of reassortment is that it can generate viruses containing either a new HA, a new NA, or both. Such abrupt changes, called 'antigenic shifts,' may be sufficient for the novel virus to completely evade the existing immunity in its host species. Antigenic shifts can also occur if one species acquires an influenza virus 'whole' from another, or if a virus disappears for a time and is maintained in another host species, then re-emerges in the



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original host.^{3,6} For example, human viruses can continue to circulate in pigs and could re-emerge into the human population.^{6,79,80} Genetic reassortment can also cause smaller changes in viruses, such as the acquisition of a slightly different HA or NA from another virus circulating in the same species, or a different internal protein.

Subtypes and diversity in swine influenza viruses

At present, diverse viruses of the subtypes H1N1, H1N2 and H3N2 circulate in swine populations, although other subtypes have transiently infected pigs in limited locations.^{6,30,52-54,81-90} While the subtypes circulating on each continent are the same, the viruses themselves are different.^{6,52-54,81,82,88-92} Knowledge about the viruses circulating among pigs in the present or the past can be incomplete. Surveillance programs were rare in the past, and while such programs have now been implemented in some areas, they may detect only a portion of the circulating viruses..

North America

The first influenza virus to be recognized in pigs was an H1N1 virus known as the 'classical' swine influenza virus.^{17,20,93} Pigs are thought to have acquired this virus in 1918, at the same time as the severe 'Spanish flu' pandemic in humans.^{3,6,20,81,82,94,95} H1N1 viruses seem to have been transmitted between people and pigs during this pandemic,¹⁷ and although the origin of the virus in pigs is still uncertain, some evidence suggests that they might have acquired it from people.^{20,96} H1N1 viruses circulated in both species after this time, but diverged genetically in the two host populations.^{28,97}

The classical H1N1 swine influenza virus was the major virus among swine populations in North America for approximately 70 years.⁸⁸ Low levels of H3 viruses acquired from humans were also detected during this period, and some of these viruses circulated locally for at least a year; however, they did not become established as stable, widespread lineages in pigs.^{88,98} One recent example is an H3N2 virus of wholly human origins, which may have entered a Canadian swine population around 2000-2002, although it was first recognized in 2009.⁹⁸ Triple reassortant H3N2 viruses first emerged in North American pigs in the late 1990s, mainly in the U.S. Midwest, and spread to other regions.^{11,13,81,83,99-102} These viruses contain HA and NA derived from human influenza viruses, and internal proteins from the classical swine influenza virus, an avian influenza virus and a human influenza virus.¹⁰¹ The particular combination of internal genes carried by these viruses is known as the triple reassortant internal gene (TRIG) cassette. Viruses that contain this cassette seem to be prone to increased antigenic drift.⁷ They also seem to readily acquire new HA and NA genes, which has resulted in new TRIG-containing viruses with various combinations of H1, H3, N1 or N2 from additional human influenza viruses, and/or H1 and N1 from the classical swine influenza virus.^{7,87,88,103-105} The 2009

pandemic H1N1 virus from people has also infected some herds, and it has reassorted with other viruses found in swine.^{27,56-61} As a result, North American H1N1, H1N2 and H3N2 swine influenza viruses have become very diverse, and they are continuing to evolve and change in prevalence.^{7,61,87,88,103,104,106} At present, the North American lineage H3 viruses can be divided into four distinct clusters (I, II, III and IV), which arose from at least three separate introductions of H3 human influenza viruses into pigs,^{88,104} while the H1 viruses belong to the phylogenetic clusters α , β , γ , $\delta 1$ and $\delta 2$, which have limited cross-reactivity.^{7,106}

Other influenza variants and subtypes, such as H2N3 and H3N1 viruses, have been detected occasionally in North American herds, but did not become established in swine populations.^{30,83-86}

Europe

Different H1N1, H1N2 and H3N2 swine influenza viruses circulate in Europe. While some viruses are widespread, there is regional variability, and some variants only occur in limited areas.^{82,89,91,92} The classical H1N1 swine influenza virus was found in Europe at one time (although records of its isolation and times of circulation are scarce), but an H1N1 virus of wholly avian origins has become widespread since the 1970s.^{6,52,54,81,82,89,91,92,107-111} The 2009 pandemic H1N1 virus and its reassortants have also been detected frequently, and currently seem to be maintained in some populations of pigs.^{54,55,89,91,92,110} Several H1N2 viruses also circulate, either transiently or long-term.^{6,54,55,89,91,92,107,110,112} Various human-origin H3N2 viruses have been detected sporadically, and some of these viruses have circulated for a time; however, a reassortant that contains human-origin H3 and N2 and internal gene segments from the avian-origin H1N1 virus has now become the dominant H3N2 swine influenza virus in much of Europe.^{6,54,89,91,92,107,110} Additional subtypes (e.g., H3N1 viruses) are also found occasionally.^{54,110,113} One particularly unique variant was an H1N7 virus, which was apparently a reassortant between swine and equine influenza viruses.^{54,110} One isolate with gene segments comparable to North American TRIG-containing viruses was detected recently.⁹¹ However, such viruses are not common in Europe, and virus diversity is not thought to be as extensive as in North America. Nevertheless, the introduction of pandemic H1N1 appears to have resulted in new opportunities for reassortment.⁹¹ In 2010-2013, approximately 14% of the viruses analyzed during passive surveillance were reassortants between pandemic H1N1 and/or the major swine influenza lineages.⁹² A previous analysis of the viruses isolated from several countries in 2006-2008 found that only 3% were novel.⁸⁹

Asia

Information about swine influenza viruses in Asia is limited, especially for some regions, but H1N1, H3N2 and H1N2 viruses are known to circulate. Various North American and European lineage viruses belonging to these

three subtypes have been reported, as well as reassortants between North American and Eurasian lineages, and viruses unique to Asia.^{52,53,80,82,90,114-117} Some of these viruses contain the North American TRIG cassette. Some viruses have infected Asian pigs only transiently, and different swine influenza viruses may predominate in different regions.^{52,53} One notable Asian-origin H1N2 virus caused a major outbreak in Japan in 1989-1990, became established in Japanese swine populations, and has spread to some other countries.^{52,53} It is a reassortant between the classical H1N1 virus and early human-like H3N2 viruses.⁵² The pandemic H1N1 virus, as well as its reassortants, have been found, and novel subtypes (e.g., H3N1 viruses) have been isolated occasionally.^{52,53,118,119}

Avian influenza viruses have been detected a number of times in Asian pigs. H9N2 viruses and Asian lineage H5N1 highly pathogenic avian influenza (HPAI) viruses from poultry have been documented most often, but other subtypes (e.g., H4, H5N2, H6N6, H7, H10N5, H11N2), have been isolated, and antibodies to avian H3, H4, H5, H6 and H9 viruses occur in some herds.^{32,52,53,120-131} Whether a virus is circulating in pigs or represents a one-time event can sometimes be difficult to determine without long-term surveillance, which is not always available.⁵² However, these avian influenza viruses seem to infect herds only transiently at present, although the H9 and H5 viruses have been introduced repeatedly.^{52,53} One outbreak in China was caused by an H3N8 equine influenza virus.¹³² An extensive analysis conducted in Hong Kong abattoirs, where the majority of the pigs originate from China, suggests that swine influenza viruses reassort frequently, but only a few of these viruses persist, and that the population of viruses gradually changes.⁹⁰ This is also likely to be true of other regions and continents.

Other regions

At present, there is limited information about swine influenza viruses in other regions, such as Latin America or Africa. H3N2 and H1N1 viruses are known to circulate in Latin America, although genetic characterization has rarely been reported.¹³³ A recent study found that the composition of viruses in northwestern Mexico included H3N2 viruses similar to those in the U.S., and H1N1 viruses that had 89% nucleotide identity with U.S. viruses.¹³⁴ One H3N2 virus isolated from an outbreak of respiratory disease in Argentina was of wholly human influenza virus origins, although it was highly transmissible in pigs.¹³³ Whether this was a limited outbreak, or the virus circulates there in swine populations is not known. Pandemic H1N1 virus and/or its reassortants with human-like H1N1 swine influenza viruses, as well as a reassortant human-like H1N2 influenza virus, have been detected in Argentina and Brazil.^{47,62,135,136} H1 viruses were documented in one report from Africa, and some recent studies report the presence of 2009 pandemic H1N1 virus there in pigs.^{49,137,138}

Influenza B and C viruses in pigs

Serological and virological evidence indicates that influenza B and C viruses from humans can occasionally infect pigs.^{3-6,139-145;146 cited in 145} Although serological evidence suggested that one outbreak in pigs might have been caused by influenza B viruses acquired from humans,^{146 cited in 145} experimentally infected pigs had mild or no clinical signs.^{144,145} A novel cattle-associated influenza C-like virus, with the proposed designation “influenza D” has been found in some pigs with respiratory signs, although they are not thought to be reservoir hosts.¹⁴⁷⁻¹⁴⁹ For further information on influenza B, C and D viruses, please see the ‘Influenza’ factsheet.

Species Affected

Swine influenza viruses mainly affect pigs, but some viruses can also cause disease in turkeys, ferrets and mink.^{3,4,10,11,26-33} Once a virus has entered turkey flocks, it can propagate within this species.³² Some viruses in turkeys, but not others, can be transmitted back to pigs.³² Chicken flocks infected with swine influenza viruses have not been reported, and these viruses do not seem to replicate efficiently in experimentally infected chickens.³² One H1N1 swine influenza virus, which was avirulent for both poultry and pigs, was isolated from a duck in Hong Kong,¹⁵⁰ and ducks can be infected experimentally.¹⁵¹ Two H3N2 viruses isolated from pet dogs in China had high homology to human-like H3N2 swine influenza viruses.¹⁵² Experimental infections have been reported in calves,^{150,153} and in a recent study, antibodies to H3 viruses found in cattle might have been caused by exposure to swine influenza viruses, although definitive identification of the virus source was not possible.¹⁵⁴

Zoonotic Potential

Infections with various H1N1, H3N2 and H1N2 swine influenza viruses are reported sporadically in humans.^{3,6,8,9,12-25,34-37,42,63,155,156} It is possible that certain genotypes are more likely to infect people. Many recent infections in the U.S. were caused by North American triple reassortant H3N2 viruses (and occasionally other subtypes) that contained the ‘M’ gene from the 2009 pandemic H1N1 virus.^{35,36,39,64} (The M gene codes for the viral matrix proteins.) While there is evidence for limited person-to-person transmission of some swine influenza viruses, including one large outbreak at the Fort Dix military base in the 1970s,^{3,6,12,17,24,35-39,43} the only virus known to have adapted to humans is the 2009 pandemic H1N1 virus.

The 2009 pandemic H1N1 virus

In 2009, a novel H1N1 virus emerged in human populations.^{44,45,105,157} This virus appears to be a reassortant between North American H1N2 and Eurasian H1N1 swine influenza viruses; it contains an HA that is most closely related to swine influenza viruses in North America, an NA that is related to swine influenza viruses in Eurasia, and internal proteins from two or more swine influenza viruses

including the North American triple reassortant H3N2 viruses and a Eurasian virus.^{44,45} This virus caused a human pandemic in 2009-2010, then became established as a seasonal human influenza virus. It is currently the predominant H1N1 virus circulating in people.¹⁵⁸ For further information about the effects of this virus on humans and animals other than pigs, please see the 'Influenza' factsheet.

Geographic Distribution

Swine influenza has been reported from North and South America, Europe, parts of Asia and Africa.^{5,52-54,82,88} Swine influenza viruses are thought to be enzootic in most areas that have dense populations of pigs,¹⁵⁹ but they might remain undetected in some regions, as infected herds can be asymptomatic or have only mild clinical signs.

Transmission

In mammals, influenza viruses are transmitted in droplets and aerosols created by coughing and sneezing, and by contact with nasal discharges, either directly or on fomites.^{1,3,4,20,82,160,161} While most viruses are thought to enter the body through the respiratory tract, the eye might act as an additional entry point, based on evidence from humans and laboratory animals.¹⁶²⁻¹⁶⁵ Close contact and closed environments favor transmission. One group found no evidence for transplacental transmission of swine influenza viruses in pigs.¹⁶⁶

The relative importance of the various routes in each host species is still incompletely understood, but swine influenza viruses are thought to be transmitted between pigs mainly during direct contact, and to a lesser extent on fomites.^{58,167} Virus shedding can begin within 1-3 days after infection, and typically continues for 4-5 days and up to 7-10 days.^{1,20,82,168} While there are rare reports of pigs that shed viruses for as long as four months,^{20,82} this is unusual, and long-term carrier pigs do not seem to exist or play any role in virus maintenance.^{58,168} There is some evidence that aerosol transmission might be possible, at least within densely populated pig barns, and possibly over longer distances in swine-dense regions.^{167,169,170} Swine influenza viruses have been isolated from air samples inside barns and immediately outside exhaust fans.¹⁶⁹ Based on RNA quantification, the amount of virus decreases significantly with distance outside the barn.^{169,170} One study found small amounts of viral RNA up to 2 km downwind of infected barns.¹⁶⁹ Another group did not detect viral RNA in samples taken outside barns during influenza outbreaks, at a distance of 25 m either upwind or downwind.¹⁷⁰

Carnivores such as mink and ferrets might be infected by feeding tissues from pigs or swine influenza virus-infected turkeys, although this is still speculative.^{10,11,26} Other possible sources of exposure, such as nearby pig farms, were also found in some outbreaks.¹⁰

Environmental survival of influenza viruses can differ with the type of surface, ambient conditions and presence of

organic matter. Low temperatures and protection from sunlight enhance survival.¹⁷¹⁻¹⁷⁷ Swine influenza viruses were inactivated in untreated pig slurry in 1-2.5 hours at 50-55°C (122-131°F), 2 weeks at 20°C (68°F), and 9 weeks at 5°C (41°F).¹⁷⁸ Their persistence on fomites or in water is likely to be similar to other mammalian influenza viruses. Human influenza A viruses seem to remain viable for less than 24-48 hours on most surfaces, with recovery from porous surfaces sometimes lasting less than 8-12 hours.¹⁷⁹⁻¹⁸² Nevertheless, some data indicate that influenza viruses might survive longer on some fomites or in some conditions.¹⁸³ Avian influenza viruses and human influenza A viruses can persist for weeks or months in some types of water (e.g., distilled), although they might be inactivated faster in aquatic environments that contain normal microbial flora.¹⁷²⁻¹⁷⁷ Additional details on virus survival on fomites is available in the 'Influenza' factsheet.

Transmission to humans

People are usually infected with viruses from other species during close contact with the living host or its tissues, although indirect contact via fomites or other means is also thought to be possible.^{3,6,9,12,13,24,34-39,63,184,185} During recent cases associated with fairs, many (though not all) patients had been exposed to pigs for more than one day.³⁹ Person-to-person transmission of swine influenza viruses has occasionally been reported to family members or other close contacts, and a limited outbreak occurred on a military base; however, most viruses were not transmitted to other people.^{3,6,9,12,13,17,24,25,35-39}

Disinfection

Influenza A viruses are susceptible to a wide variety of disinfectants including sodium hypochlorite, 60% to 95% ethanol, quaternary ammonium compounds, aldehydes (glutaraldehyde, formaldehyde), phenols, acids, povidone-iodine and other agents.^{4,173,186-189} Common household agents, including 1% bleach, 10% malt vinegar or 0.01-0.1% dishwashing liquid (washing up liquid), as well as antimicrobial wipes, were found to destroy the viability of human influenza viruses, although hot water (55°C; 131°F) alone was ineffective in rapidly eliminating these viruses.¹⁹⁰ Influenza A viruses can also be inactivated by heat of 56-60°C (133-140°F) for a minimum of 60 minutes (or higher temperatures for shorter periods), as well as by ionizing radiation or extremes of pH (pH 1-3 or pH 10-14).^{4,173,186,188,191}

Infections in Animals

Incubation Period

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

Clinical Signs

Swine influenza viruses in pigs

Swine influenza is an acute upper respiratory disease. Depending on the production system, illness may be seen only in certain age groups, while other animals remain asymptomatic.^{168,192} The clinical signs may include fever, lethargy, anorexia, weight loss, coughing, sneezing, nasal and ocular discharge, conjunctivitis and labored breathing (expiratory dyspnea or “thumping”), although all of these signs do not occur in all infected animals.^{1,3-6,159,168} The cough usually develops after a few days, at which time the fever has often started to diminish.^{6,159,168} Abortions may be seen in some herds.^{1,5,168} Secondary or concurrent bacterial or viral infections, other illnesses and stressors such as transport can exacerbate the clinical signs.^{5,6,192-194} Severe, potentially fatal bronchopneumonia is seen occasionally.⁴ Swine influenza viruses can also circulate among pigs with few or no clinical signs.^{3,6,7,8,216,192}

Other influenza viruses in pigs

Infections with the 2009 pandemic H1N1 virus have resembled swine influenza, and were mild in most cases.^{46,47,105,195-205} Diarrhea was reported in experimentally infected pigs and some infected herds, but not others.^{47,198,205-207} The clinical signs in pigs infected with avian influenza viruses vary, but respiratory illnesses and asymptomatic infections have been seen.^{90,120,123,127,128,208-210} Experimental infections and reports of infected herds suggest that pigs infected with Asian lineage H5N1 HPAI viruses do not become severely ill.^{127,128,208-210} (Additional information about these viruses is available in the ‘Avian influenza’ factsheet.)

Swine influenza viruses in turkeys

Turkeys infected with swine influenza viruses may develop respiratory disease, have decreased egg production, or produce abnormal eggs.⁴

Swine influenza viruses in mink and ferrets

Respiratory signs of varying severity have been reported in ferrets and mink. Mink infected with a Canadian triple reassortant H3N2 virus developed respiratory signs including pneumonia, with increased mortality particularly on ranches where the mink were co-infected with other pathogens.¹¹ Another swine H3N2 virus, which was a reassortant with the 2009 pandemic H1N1 virus, caused significant coughing but little mortality.²⁷ An H1N2 swine influenza virus was found in the lungs of mink during an outbreak of severe respiratory disease with hemorrhagic bronchointerstitial pneumonia.²⁶ However, the mink were co-infected with hemolytic *E. coli*, and the hemorrhagic pneumonia and high mortality rate were attributed to the secondary bacterial component.

An outbreak in ferrets was caused by a triple reassortant H1N1 swine influenza virus.¹⁰ These ferrets had respiratory signs, including severe dyspnea, and some severely affected animals died.

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

Most often, swine influenza in pigs appears as a cranioventral bronchopneumonia affecting variable amounts of lung tissue.^{5,6,168} Affected parts of the lungs are depressed and consolidated, dark red to purple-red, and sharply demarcated.^{5,6} Occasionally, a few hemorrhagic, emphysematous bullae may distend the interlobular spaces.¹⁶⁸ Concurrent bacterial infections, common in naturally infected animals, can result in more extensive lesions.¹⁶⁸ In severe, acute cases, the lungs may be diffusely edematous and congested, with large amounts of foam in the larger airways including the trachea.¹⁶⁸ Lymph nodes associated with the respiratory tract can be variably enlarged and congested.¹⁶⁸

Diagnostic Tests

Swine influenza can be diagnosed by virus isolation, the detection of viral antigens or nucleic acids, and serology.

Virus isolation is useful for the characterization of influenza viruses, and can be used in diagnosis, although faster and simpler techniques such as RT-PCR tend to be employed in most clinical cases. Swine influenza viruses can be isolated in embryonated chicken eggs or cell cultures (e.g., Madin–Darby canine kidney cells).^{1,211} These viruses can be isolated from lung tissues at necropsy, and from nasal swabs (and some other respiratory or oral fluid samples) collected from acutely ill pigs.^{1,4,5,211,212} Virus shedding can be brief, and samples should ideally be collected from a pig within 24-72 hours after the onset of clinical signs.^{1,211} Isolated viruses can be subtyped with hemagglutination inhibition and neuraminidase inhibition tests or RT-PCR, as well as by sequence analysis of the viral HA and NA genes.^{1,6,66,211}

RT-PCR assays, which can detect viral RNA in tissue samples and respiratory or oral fluids, are often used in influenza diagnosis.^{1,6,211,212} Immunohistochemistry or immunofluorescence can identify antigens in lung tissue samples, nasal epithelial cells or bronchoalveolar lavage fluids.^{1,6,211} Antigens can also be detected with ELISAs.^{1,6,211}

Serology on paired samples can diagnose swine influenza retrospectively.^{1,5} The hemagglutination inhibition test, which is subtype specific, is used most often.^{1,5,6} It may not detect new viruses.⁶ ELISA kits are also available.^{1,211} Other serological assays (e.g., virus neutralization, indirect fluorescent antibody test, agar gel immunodiffusion) have been described in swine, but are not commonly used in diagnosis.^{1,211} Cross-reactivity can be an issue with serological tests, although the extent of its interference can differ with the viruses present in an area, as well as the test.²¹¹

Treatment

Animals with influenza are usually treated with supportive care.⁵ Antibiotics may be used to control secondary infections. Antiviral drugs used to treat human influenza are not generally administered to swine.

Control

Disease reporting

Although swine influenza viruses are common and widespread among pigs in most locations, veterinarians should remain aware of any requirement to report this disease in their area.

Prevention

A number of swine influenza vaccines are made commercially; however, vaccines may not be available for all viruses, or combinations of viruses, present in an area. Influenza vaccines eliminate or reduce clinical signs, but they do not always prevent infections or virus shedding, although the amount of virus shed may be decreased. A poor match between the HA component of the vaccine and field virus can compromise protection.¹⁰⁴ Some combinations of swine influenza vaccines and poorly matched challenge viruses were also reported to exacerbate disease in pigs, at least in a laboratory setting.^{87,213-215} Influenza vaccines are changed periodically to reflect the current subtypes and strains in an area. Historically, swine influenza viruses did not change rapidly or frequently.^{4,6,159} This allowed vaccines to be updated less often than in humans, where vaccines may be modified yearly based on worldwide influenza virus surveillance. However, swine influenza virus diversity has increased greatly in some areas, such as the U.S.^{7,61,87,88,103,104,106} In addition, selection pressures from increased vaccination might encourage more rapid changes. At present, there is no systematic worldwide surveillance program for swine influenza viruses.^{32,211} However, local, regional or national surveillance has increased in some areas, including Europe, North America (e.g., a voluntary surveillance program in the U.S.) and parts of Asia.²¹¹

Management measures such as all-in/all-out production help prevent the introduction of viruses.^{4,6,20,58,82} Isolating newly acquired pigs (or animals returning to a facility) and testing before release also reduces the risk of transmission to the rest of the herd.^{4,6,20,58,82} Additional sources of infection to consider in biosecurity plans include contact with wild and feral pigs, wild birds (especially waterfowl and other birds from aquatic habitats), poultry, people, unsafe water sources that may contain viruses, and possibly even other species such as horses.^{3,4,6,58,82,110,132,173,174,216-220} Sanitation and routine hygiene help prevent transmission on fomites and mechanical vectors.^{58,221-223} To prevent human influenza viruses (including 2009 pandemic H1N1 virus) from entering a herd, swine workers and others who have influenza-like illnesses should avoid contact with pigs, and the public should be restricted from entering swine operations.²²¹ The use of human seasonal influenza vaccines may decrease the risk of introducing these viruses to pigs, as well as the risk of recombination between human and swine influenza viruses.^{58,63,221}

Isolating infected animals (as soon as possible after the onset of illness) may help reduce transmission within a

facility during an outbreak,²²² and quarantines (including voluntary self-quarantine) reduce transmission between premises. Once a herd of swine has been infected, the virus may persist and periodically cause outbreaks in young animals and other susceptible pigs; however, good management can decrease the severity of disease.^{3,5,6,20,82} Infected swine herds can be cleared of influenza viruses by depopulation, and management measures can also be successful.^{20,58,82}

Measures to prevent transmission to other susceptible species, such as turkeys, ferrets and mink, depend on avoiding contact with pigs (or swine influenza virus-infected turkeys), their tissues and contaminated environmental sources.

Morbidity and Mortality

Swine influenza viruses

Swine influenza viruses are common in pig populations, and many farms worldwide have been infected with at least one virus. A number of studies report seroprevalence rates of approximately 20-60%, with some studies reporting higher or lower values.^{3,6,54,58,82,125,143,211} In Europe, virus prevalence is generally higher in intensive swine-raising regions.⁵⁴ Studies of feral swine in North America and wild boars in Europe and Asia have found antibodies to swine influenza viruses in 0% to $\geq 40\%$ of the animal tested, but fewer animals seem to be infected than in domesticated herds.^{58,110,224,225}

The patterns of disease vary with the type of production system, and with immunity in breeding pigs and other members of the herd.^{167,168,226} Maternal antibodies decrease the severity of the illness in young animals, but can also impair the development of immunity.^{6,192,227,228} In the classical picture of influenza, up to 100% of the animals in a naive herd may become ill, and if the virus infects a population without immunity (e.g., as in 1918), it may cause an epizootic with rapid transmission in pigs of all ages.^{1,3,5,20,82} In other cases, the virus can persist in a herd,^{3,6,20,82} typically by infecting susceptible populations of young animals.⁵⁸ In these herds, recurrent outbreaks may be seen in nursery piglets and/or in older, fattening pigs.^{58,168,192} Seasonality varies with the climate and type of production system. Under traditional production systems, annual outbreaks occur mainly during the colder months in temperate regions, but may be seen year-round in tropical and subtropical climates.^{2,3,5,6,20,52,82} Outbreaks can occur at any time of the year under intensive (confinement rearing) farming practices, although there may be seasonal peaks when rapidly changing outside temperatures make it more difficult to control climatic conditions in the barn (e.g., in autumn).^{2,110,168} The main economic impact is usually from reduced weight gain and a longer time to reach market weight.^{1,2} Mortality rates are generally low; in uncomplicated cases, the case fatality rate varies from $< 1\%$ to 4%, and most animals recover within 3-7 days.^{1,3-6} However, outbreaks can differ in severity, depending on management factors, co-infections with other pathogens and other stressors.^{3-6,20,82}

Other influenza viruses in pigs

The 2009 pandemic H1N1 virus appears to cause mild disease in pigs.^{46,47,105,195-205,229} Morbidity rates ranging from < 1% to as high as 90% have been reported, but little or no mortality has been seen.^{46,47,105,197-199,201-206,229-233}

Seroprevalence rates for Asian lineage H5N1 HPAI viruses range from <1% to 5% in some Asian and Middle Eastern countries, although these viruses do not seem to cause severe illness in pigs.^{127,128,209,210,234} H5N1 viruses were also detected in 7.5% of nasal swabs collected from asymptomatic Indonesian pigs in 2005-2007.¹²⁷ Antibodies to H3, H4 and H6 avian influenza viruses were reported in up to 1-2% of pigs sampled in southern China,¹²⁵ while antibodies to H9 viruses were found in 4-5% of pigs in one study, and > 15% of pigs in a more recent report.^{129,235}

Swine influenza viruses in mink and ferrets

Morbidity and mortality rates in influenza outbreaks among mink vary greatly, and appear to be influenced by factors such as co-infections with other pathogens.^{3,11,26,27,236,237} 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%.¹⁰

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. Clinical signs seem to appear in approximately 2-3 days in cases caused by triple reassortant H3N2 swine influenza viruses in the U.S.³⁹

Clinical Signs

Most laboratory-confirmed, symptomatic swine influenza virus infections have been characterized by upper respiratory signs that resemble human influenza, including gastrointestinal signs in some patients, although acute parotitis was reported in a 6-year-old with H3N2 influenza, and one young patient had only fever and vomiting.^{2,3,6,9,12,13,17,21,22,24,35-41,155} In a recent series of infections caused by North American triple reassortant H3N2 viruses, redness of the eyes or eye irritation appeared to be more common than with seasonal influenza viruses.³⁹ Illnesses caused by swine influenza viruses have been mild in most healthy people and some immunocompromised individuals, although young children were sometimes hospitalized for dehydration.^{9,12,13,17,21,22,24,35-37,39,40} Pneumonia, serious illnesses and deaths have also been seen, generally though not always in people who had underlying health conditions or were immunocompromised by illnesses or pregnancy.^{14,16-19,24,34,35,37,39,42} Serological evidence suggests mild or asymptomatic cases might occur among people who are occupationally exposed.^{3,6,8,184,185,238-242}

Diagnostic Tests

Tests used to detect influenza virus infections in humans can include RT-PCR, virus isolation and assays to detect influenza virus antigens.^{161,243-248} Many recent swine influenza cases were diagnosed by genetic methods, particularly RT-PCR.³⁹ Routine diagnostic tests used to detect human influenza viruses, including commercial rapid test kits, do not necessarily detect zoonotic viruses.^{161,243,244,249,250} One indication that a novel, possibly zoonotic influenza, virus might be present is the detection of an influenza A virus, but not the hemagglutinins in seasonal human influenza viruses.¹⁶¹ Zoonotic influenza virus infections are occasionally diagnosed retrospectively by serology,^{251,252} however, serological diagnosis can be complicated by cross-reactivity with human influenza viruses. A further difficulty is that the HA and NA of some swine influenza viruses (the main targets of antibody responses) originally came from human influenza viruses. Testing for novel influenza viruses is generally performed by state, regional or national public health laboratories.^{161,245}

Treatment

Supportive care for uncomplicated influenza in humans includes fluids and rest. Additional adjunct and supportive treatments for more severe cases vary, and can include various drugs, including antibiotics to treat or prevent secondary bacterial pneumonia, and mechanical ventilation.²⁵³

Two groups of antiviral drugs – the adamantanes (amantadine, rimantadine), and neuraminidase inhibitors (zanamivir, oseltamivir, peramivir and laninamivir) – are used to treat some cases of influenza, although some of these drugs (peramivir and laninamivir) are not licensed in all countries.^{78,160,161,187,250,254,255} Both groups of drugs are effective against some influenza A viruses (depending on antiviral resistance patterns), although they may have some side effects.^{78,161,187,250,254-256} Antiviral drugs are most effective if they are started within the first 48 hours after the clinical signs begin, but they may also be used in severe or high risk cases first seen after this time.^{161,187,250,254-256}

Antiviral resistance can develop rapidly, and may emerge during treatment.^{3,78,160,161} A recent study reported resistance to neuraminidase inhibitors in 9% of influenza viruses from pigs that contained the N2 neuraminidase (H1N2 and H3N2 viruses and H9N2 avian influenza viruses).²⁵⁷ Published reports suggest that neuraminidase resistance is uncommon among swine influenza viruses in the U.S. and Germany.^{258,259} However, amantadine-resistant isolates are currently prevalent in some swine influenza lineages in the U.S.,²⁵⁸ and the U.S. Centers for Disease Control and Prevention (CDC) recommends that neuraminidase inhibitors be chosen.⁶³

Prevention

Protective measures for zoonotic influenza viruses include sanitation and hygiene (e.g., frequent hand washing), avoidance of contact with sick animals or animals known to be infected, and the use of personal protective equipment (PPE) when working with infected pigs.⁶³ Depending on the circumstances, recommended PPE may include masks to reduce droplet transmission or respirators, as well as other barriers such as protective clothing and gloves.⁶³

Although swine influenza viruses are not likely to be present in retail meat,¹⁵⁹ any viruses that survived long enough to reach consumers could be inactivated by cooking pork (e.g., to the internal temperature of 160°F/ 71.1°C recommended to destroy other pathogens found in this meat).^{63,188,223,260} In addition, ordinary food safety precautions include 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.^{190,223} Influenza viruses are killed if cutting boards are sanitized with 1 tbsp bleach in a gallon of water.²²³

More detailed recommendations have been published by some national agencies, including the CDC in the U.S.⁶³ With the increased number of human infections associated with agricultural fairs in North America, the CDC has issued guidelines for people attending fairs and for fair planners.⁶³ Currently, it recommends that people at increased risk for serious infection with human seasonal influenza viruses (including young children) stay away from swine and pig barns at fairs. The CDC also recommends that people with no risk factors avoid close contact with sick pigs, use good hand hygiene, and not eat or drink around pigs. They should also avoid bringing objects that may contact the mouth, especially those used by infants and young children, (e.g., cups and bottles, or children's toys) into the area. Pigs suspected to be ill should be isolated (or sent home, if appropriate) and seen by a veterinarian. Guidelines for fair organizers have been published on the CDC Web site.⁶³ When visiting a physician for an illness that began soon after contact with animals, the potential for zoonotic exposure should be mentioned.

Morbidity and Mortality

The overall prevalence of swine influenza virus infections in humans is uncertain. While interpreting serological studies is complicated by cross-reactivity with past and present human influenza viruses, these studies suggest that exposure might be relatively common among people who work with pigs.^{3,6,8,55,184,185,238-242,261-266} If most infections resemble human influenza, they may not be investigated and recognized as zoonoses. More than 350 serologically or virologically confirmed clinical cases caused by H1N1, H1N2 and H3N2 viruses have been reported sporadically since the 1950s (with one localized outbreak at the Fort Dix military base in 1976), with cases being documented more frequently in recent years.^{3,6,8,9,12-25,34-}

^{42,63,155} These cases have occurred in people who had occupational contact with pigs, as well as in others who had more casual contact, such as visitors at agricultural fairs or livestock shows.^{17,35,36,39,155} There have also been a few cases with no apparent swine contact, including some where the virus was probably transmitted on fomites or acquired from another person.^{12,17,24} Several cases occurred in young children and infants who lived on pig farms and/or whose family members were occupationally exposed to swine.^{17,19,21,37,42}

While zoonotic cases have been seen in Europe and Asia, most recent cases were documented in the U.S., where this disease has been reportable in humans since 2005, and where the number of reported cases has increased dramatically in the last few years.^{3,6,8,9,12-25,34-42,63} Approximately one swine influenza case was documented every 1-2 years in the U.S. before 2005, while 21 cases caused by various subtypes were reported to the CDC between December 2005 and June 2011.^{35,36,63} Thirteen infections with swine H3N2 viruses, all containing the TRIG cassette, were reported between August 2011 and April 2012.^{35,36} Respiratory illnesses were also noted in 169 people who had shared exposure to these cases or to pigs, although the cause of the illness could not be definitively identified in most (and some cases were shown to be caused by other respiratory pathogens).³⁵ An additional 306 virologically confirmed triple reassortant human H3N2 cases, associated with exposure to pigs at fairs, were found in 2012.^{36,39} Whether this increase in case numbers is related to genetic changes in the viruses circulating in North America, increased surveillance, the new reporting requirements or a combination of factors is still uncertain.^{35,36,39,61,63,64}

Many cases of swine influenza, including most of the recent H3N2 cases in the U.S., affected children; however, clinical cases also occur in adults.^{9,12-14,16-19,21,22,24,34-37,39,40,42} Adults might have some immunity due to previous exposures to human influenza viruses, which contributed HA and NA gene segments to many viruses now circulating in swine. People who are at higher risk of severe illness after exposure to human influenza viruses are expected to also be at greater risk from swine influenza viruses.⁶³ Some known risk groups for human influenza include young children, the elderly, people who are immunosuppressed including pregnant women, and those with chronic respiratory, cardiovascular or other health conditions.⁶³

Nine of the swine influenza cases reported between 1950 and 2014 (< 3%) were fatal.^{36,37,39,42,267} The diagnoses in fatal cases included primary viral pneumonia or secondary bacterial infection, and one patient was described as having extensive involvement of the abdominal organs.¹⁷ Three patients who died were previously healthy (two were young, while one was 37 years of age), one was pregnant, three were immunosuppressed (two had cancer, while the third was a 3-year-old child receiving long-term steroids for chronic kidney disease), and one was elderly and had congestive heart failure and diabetes.^{3,6,12,14,16,16-18,37,39,42,267,268} The health status of one person was not known. Severe or fatal

cases involved various viruses including the classical H1N1 swine influenza virus, Eurasian H1N1 viruses and a North American H3N2 virus.^{3,6,12,18,19,37,39,268} but there is no reason to believe that other viruses could not cause serious disease. However, most clinical cases (including at least two cases in immunocompromised individuals) have been mild and resembled human influenza.^{9,12-14,16-19,21,22,24,34-37,39,40,42,155}

Internet Resources

Centers for Disease Control and Prevention (CDC).
Information on Swine Influenza
<http://www.cdc.gov/flu/swineflu/index.htm>

Public Health Agency of Canada (PHAC). Influenza
<http://healthycanadians.gc.ca/diseases-conditions-maladies-affections/disease-maladie/flu-grippe/index-eng.php>

PHAC. Pathogen Safety Data Sheets
<http://www.phac-aspc.gc.ca/lab-bio/res/psds-ftss/index-eng.php>

The Merck Manual
<http://www.merckmanuals.com/professional>

The Merck Veterinary Manual
<http://www.merckvetmanual.com/>

United States Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS).
<https://www.aphis.usda.gov/aphis/home/>

World Health Organization. Zoonotic Influenza
http://www.who.int/influenza/human_animal_interface/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/en/international-standard-setting/terrestrial-manual/access-online/>

OIE Terrestrial Animal Health Code
<http://www.oie.int/en/international-standard-setting/terrestrial-code/access-online/>

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