Abstract

In April 2009, a novel influenza A subtype H1N1 triple reassortant virus (novel H1N1 2009), composed of genes from swine, avian, and human influenza A viruses, emerged in humans in the United States and Mexico and spread person-to-person around the world to become the first influenza pandemic of the 21st century. The virus is believed to have emerged from a reassortment event involving a swine virus some time in the past 10 to 20 years, but pigs, pork, and pork products have not been involved with infection or spread of the virus to or among people. Because countries quickly implemented recently developed pandemic influenza plans, the disease was detected and reported and public health authorities instituted control measures in a timely fashion. But the news media’s unfortunate and inappropriate naming of the disease as the “swine flu” led to a drop in the demand for pork and several countries banned pork imports from affected countries, resulting in serious negative economic impacts on the pork industry. With the continual circulation and interspecies transmission of human, swine, and avian influenza viruses in countries around the world, there are calls for strengthening influenza surveillance in pigs, birds, and other animals to aid in monitoring and assessing the risk of future pandemic virus emergence involving different species. We identify and discuss several lessons to be learned from pandemic H1N1 2009 from a One Health perspective, as stronger collaboration among human, animal, and environmental health sectors is necessary to more effectively prevent or detect and respond to influenza pandemics and thus improve human, animal, and environmental health and well-being.

Key Words: avian influenza; H1N1; One Health; pandemic influenza; swine influenza; zoonosis

Introduction

The world experienced its first influenza pandemic of the 21st century with the emergence and global spread of novel H1N1 2009. According to the World Health Organization (WHO), pandemic influenza viruses (PIVs1) are new influenza viruses that spread easily from person to person around the world and infect people of all ages (WHO 2009a).

PIVs have emerged from either wholly avian influenza viruses (AIVs) or reassortant viruses (with genes from avian, human, and/or swine influenza viruses) that, in either case, adapted to humans and spread easily from person to person (Belshe 2005; Taubenberger et al. 2005). The interspecies transmission of animal and human influenza viruses and their relationship to pathways of PIV emergence have made influenza A one of the most serious zoonotic disease risks to public health (Van Reeth 2007; Webster et al. 1992).

Recent History of Influenza Pandemics

Influenza pandemics have occurred at 10- to 50-year intervals for hundreds of years (Kilbourne 2006; Osterholm 2005). Since the last pandemic in 1968, health authorities have been on the alert for a new PIV.

In 2003 a highly pathogenic (HP) AIV H5N1, which had infected 18 and killed 6 people in Hong Kong in 1997, began to spread among poultry and wild birds throughout Asia, Eastern Europe, the Middle East, and Africa. World attention has since focused on this virus as having the greatest potential to cause the next influenza pandemic (Osterholm 2005). As of May 6, 2009, 15 countries had reported 498 laboratory-confirmed human cases and 294 (59%) deaths attributable to HP AIV H5N1 (WHO 2009b).

Many affected countries have spent considerable time, effort, and resources to control the transmission of HP AIV H5N1 in poultry and prevent its transmission to people. Fortunately, as of May 2010 the virus had not developed the capability to spread easily from person to person. Out of concern for HP AIV H5N1, however, many countries have

1Abbreviations used in this article: AIV, avian influenza virus; HA, hemagglutinin; HP, highly pathogenic; NA, neuraminidase; PIV, pandemic influenza virus
developed pandemic influenza preparedness plans and are better prepared to detect and respond to an influenza pandemic (WHO 2009c). In addition, significant funding and attention in the United States have been targeted toward research on the development of new, improved human influenza vaccines (Fauci 2005).

**Novel H1N1 2009: Emergence, Impacts, and Responses**

In April 2009, as the world continued to monitor the spread of HP AIV H5N1, it was with surprise that a novel influenza A subtype H1N1 quadruple reassortant virus (novel H1N1 2009), comprising genes from swine, avian, and human influenza A viruses, emerged in humans in the United States and Mexico (CDC 2009a) and quickly spread person-to-person across the globe. The United States, Mexico, and other industrialized countries responded quickly and decisively to report the virus and institute evidence-based public health measures to control its spread (WHO 2009d). Even so, on June 11, 2009, WHO declared the spread of novel H1N1 2009 to be a pandemic, and by the end of December over 200 countries, territories, and communities had reported hundreds of thousands of cases and over 11,500 deaths (WHO 2009e).

As novel H1N1 2009 was first detected, network and cable television and internet news information channels that report globally on a minute-by-minute, 24-hour, 7-day-a-week basis announced the first human cases and continuously provided details on the spread of the virus, its severity of illness, and measures that countries were taking to prevent its spread.

Unfortunately, when the genetic makeup of the novel H1N1 2009 virus was reported as being similar to and having genes from influenza viruses of swine, public health authorities at first, and the media immediately thereafter, referred to it as “swine influenza” or “swine flu” (CDC 2009a; WHO 2009f). This inaccurate designation quickly led to public misperceptions of risk factors linked to infection (i.e., wrongly associating infection with pig contact or the consumption of pork), which resulted in attention diverted from effective preventive measures and significant negative economic consequences for the pork industry (Butler 2009). Moreover, at least one country took the non-evidence-based, inappropriate public health measure of depopulating its entire swine herd (CNN 2009). Pandemic H1N1 2009 has thus had significant impacts on human health, animal production, and local, national, and international economies.

**Identifying Lessons Learned**

How this novel H1N1 2009 virus emerged and was detected, and how human and animal health authorities, the swine and pork industries, and the media responded, offer several important lessons that can improve the efforts of countries, individually and collectively, to increase their capacity both to prevent the emergence of PIVs and to detect and control them earlier in animal and human populations.

Given the links between human, animal, and environmental health around the emergence of PIVs, we explore these lessons from a “One Health” perspective, defined as the collaborative efforts of multiple disciplines working locally, nationally, and globally to attain optimal health for people, animals, plants, and the environment (One Health Initiative Task Force 2008). We propose that the collaboration of public and private sectors involved in human, animal, and environmental health can contribute to greater effectiveness in the prevention, detection, and response to PIVs, thereby saving human lives, protecting animal health, and preventing significant economic losses, all of which bear on human health and well-being.

**Pandemic Influenza H1N1 2009 in Humans**

In April 2009, after identification of the novel H1N1 2009 virus as the cause of respiratory illness in two children in southern California (CDC 2009a), surveillance showed that the virus was spreading quickly around the world via person-to-person transmission. Thanks to pandemic influenza preparedness planning by many countries during the last decade, and the passage and beginning implementation of revised international health regulations (WHO 2005), the United States, Mexico, other countries, and WHO had systems in place to institute timely detection, reporting, and monitoring of this new pandemic virus in human populations (Gostin 2009; Katz 2009; WHO 2009c,d,g).

Investigators and national and international health agencies have provided details on the incidence, prevalence, and patterns of pandemic influenza H1N1 2009 in the United States and globally; the severity of clinical illness; groups at increased risk of complications; characteristics of the virus; and effectiveness of measures to prevent, treat, and/or limit infection with this virus. Clinical signs include fever, cough, sore throat, runny or stuffy nose, body aches, headache, chills and fatigue, vomiting, and diarrhea, with severity of illness ranging from mild to severe and death. Young children, children and adults with certain chronic conditions (e.g., diabetes, heart disease, asthma, and kidney disease), and pregnant women are groups at high risk of serious complications (CDC 2009b; IDSA 2009; Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team 2009; WHO 2009d,e,g).

**Emergence of Pandemic Influenza Viruses**

Influenza A viruses are single-strand, negative-sense RNA viruses composed of eight genes that encode for eleven proteins. The hemagglutinin (HA) and neuraminidase (NA) genes encode for two surface glycoproteins of the same names. The six internal genes—matrix (M), nucleoprotein (NP), nonstructural (NS)—and three polymerase segments (PB1, PB2, and PA) encode for proteins involved in virus structure

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2Based on the experience of the authors, this paper was developed from a predominantly, although not exclusively, US perspective.
and function (Webster et al. 1992). Multiple segments of the genome are believed to play important roles in infection and replication (Belshe 2005; Kawaoka et al. 1989; Neumann and Kawaoka 2006; Taubenberger et al. 2005; Yamada et al. 2006) and pathogenicity (Chen et al. 1998; Neumann and Kawaoka 2006; Subbarao and Katz 2000). Influenza A viruses are categorized into subtypes based on their HA and NA glycoprotein surface antigens; to date, 16 HA and 9 NA antigens have been identified (Fouchier et al. 2005; Webster et al. 1992). Influenza A viruses have the ability to continually change: smaller changes in circulating viruses occur through point mutations each year (i.e., “genetic drift”), and less frequent, major changes occur through mixing (i.e., reassortment) of genes from two different viruses, sometimes acquiring a new HA in coinfected cells (i.e., “genetic shift”).

The reservoir for all 16 HA and 9 NA influenza A viral subtypes is wild waterfowl. AIVs have infected a broad range of species including humans, wild aquatic and shore birds, domestic poultry and swine, horses, seals, whales, dogs, cats, and others. Interspecies transmission is considered an important step in the emergence of PIVs and occurs not infrequently (Webster et al. 1992). In the 20th century human PIVs evolved and/or incorporated genes from AIVs (Belshe 2005). Examples of the transmission of AIVs to other species in the past 10 years include subtypes H5, H7, H9, H10, and H11 viruses causing human infections (Gill et al. 2006; Koopmans et al. 2004; Lin et al. 2000; PAHO 2004; Subbarao and Katz 2000); HP AIV H5N1 infections in cats (Amonsin et al. 2006; Keawcharoen et al. 2004; Songserm et al. 2006a) and dogs (Songserm et al. 2006b); H1, H4, H5, and H9 infections in swine (Ninomiya et al. 2002; Peiris et al. 2001; Zhou et al. 1999); and H3 and H8 infections in horses and H3N8 infections in dogs (Crawford et al. 2005).

Influenza viruses of swine have been transmitted from pigs to humans (Kuntz-Simon and Madec 2009; Olsen et al. 2002; Rimmelzwaan et al. 2001; Wells et al. 1991) and to turkeys (Choi et al. 2004; USDA/APHIS 2009c), and human influenza A viruses have infected pigs (Brown 2000; Choi et al. 2005; Olsen et al. 2000). Because pigs are susceptible to coinfection with swine, avian, and human influenza viruses, they are referred to as “mixing vessels” of influenza A viruses (Ma et al. 2009a,b; Webster et al. 1992). Concern has focused on the potential for a double or triple reassortant influenza virus to emerge from pigs (coinfected with two or more of these viruses) with a high capacity for human infection, transmission, and pathogenicity—properties of a potential PIV (Ma et al. 2009a,b).

Circulating Influenza Viruses of Swine in the United States, Europe, and China

The first occurrence of influenza in US swine was documented immediately after the 1918 human influenza pandemic; it was an H1N1 subtype, thought to have resulted from transmission of the human virus to pigs. Over the next 80 years, this stable, “classical” H1N1 influenza A virus circulated in US pigs and spread to other countries (Brown 2000). In 1979 in Europe, however, a different and wholly avian H1N1 virus entered Europe’s swine population and began circulating (Brown 2000; Kuntz-Simon and Madec 2009; Marozin et al. 2002).

In 1998 in the United States, an important change occurred in influenza viruses of pigs, beginning with the detection of a reassortant H3N2 virus thought to have emerged from the mixing and reassortment of genomes of a seasonal influenza H3N2 human subtype, circulating in the human population, with the classical H1N1 influenza A virus of swine (Richt et al. 2003; Webby et al. 2000; Yoon et al. 1999; Zhou et al. 1999). This reassorted virus adapted to the US swine population, spread, and became endemic throughout North American swine. Since then, multiple new reassortants have emerged, resulting in one dominant H3N2 cluster of viruses and four cocirculating clusters of H1 influenza A viruses in swine.

The H1 clusters circulating in US swine include the classical alpha cluster, the beta cluster H1 viruses first detected in 2001–2002 (Webby et al. 2004), the gamma cluster H1 viruses that emerged in 1999–2000 (the cluster with which the 2009 novel H1N1 virus shares over 90% HA gene similarity), and the delta cluster H1 viruses that emerged in 2003 and 2005 and are most closely related to seasonal human H1 influenza viruses (Vincent et al. 2009). In addition to these antigenically and genetically diverse H1 viruses, H3N1 influenza viruses were detected in US pigs in 2004 (Lekcharoensuk et al. 2006; Ma et al. 2006), and a swine-avian reassortant H2N3 virus was detected in 2006 (Ma et al. 2007).

From May 1, 2007, to April 30, 2008, the University of Minnesota Veterinary Diagnostic Laboratory, collaborating in an informal surveillance network with other US veterinary diagnostic laboratories, used polymerase chain reaction (PCR) to subtype 422 influenza A virus–positive lung tissues or nasal swabs from pigs with respiratory disease; of these, 338 (~80%) were subtype H1N1, 79 (~19%) were H3N2, and 5 (~1%) were H1N2. In addition, 123 influenza A virus–positive materials were of mixed H1N1/H1N2/H3N2 subtypes. A cluster analysis of selected HA gene sequences obtained in early 2009 showed that 28% were beta cluster H1, 41% were of the gamma H1 cluster, 29% were of the delta cluster of H1 viruses, and only 2% were of the alpha cluster of classical swine H1N1 HA gene origin (Figure 1). The H3N2 HA gene sequences were less genetically diverse—over 90% had HA genes similar to the H3N2 virus variants called cluster IV H3s by Olsen in 2006 (Gramer 2009).

In European swine herds, subtypes H1N1 of AIV lineage, H3N2 of human lineage, and H1N2 reassortant viruses are circulating widely (European Commission Health and Consumers Directorate-General 2009; Kuntz-Simon and Madec 2009; Marozin et al. 2002; Masurel et al. 1983), and in China H1N1 (classical and avian-like), H3N2, and H1N2 influenza subtypes of swine are circulating in pigs (Guan et al. 1996; Kawaoka et al. 1998; Neumann and Kawaoka 1999; Subbarao and Katz 2000). Influenza A viruses have infected pigs (Brown 2000; Choi et al. 2005; Olsen et al. 2000). Because pigs are susceptible to coinfection with swine, avian, and human influenza viruses, they are referred to as “mixing vessels” of influenza A viruses (Ma et al. 2009a,b; Webster et al. 1992). Concern has focused on the potential for a double or triple reassortant influenza virus to emerge from pigs (coinfected with two or more of these viruses) with a high capacity for human infection, transmission, and pathogenicity—properties of a potential PIV (Ma et al. 2009a,b).
Figure 1  Evolutionary relationships predicted from a multiple sequence alignment of H1 gene segments for influenza A viruses isolated from swine during 2009 at the University of Minnesota Veterinary Diagnostic Laboratory and reference strains. There are three related clusters—alpha, beta, and gamma—and a distinct separate cluster (delta) of H1 influenza A viruses in North American swine. The length of each pair of branches represents the distance between sequence pairs, and the units at the bottom of the tree indicate the number of substitution events. Tree is nonoptimized and nonrooted.
other countries (Garten et al. 2009; Peiris et al. 2001; Webby et al. 2004; Zhou et al. 1999).

Human Infections with Influenza Viruses of Swine

A review of the literature by Myers and colleagues (2007) describes 37 civilian and 13 military human influenza cases associated with swine influenza viruses between 1958 and 2005. Most of these infections were caused by the alpha cluster of classical subtype H1N1 of swine (61% of the civilian cases identified exposure to pigs). In 2005–2007, 11 cases of human infections with triple reassortant influenza viruses of swine were reported to the Centers for Disease Control and Prevention (CDC). Shinde and colleagues (2009) described the epidemiologic and clinical features of these infections and reported that nine of the 11 cases had exposure to pigs. None of these viruses adapted to humans such that ready person-to-person transmission occurred.

Human infections with novel influenza viruses, including those from swine or other animals, became notifiable in the United States in 2007 (CDC 2009b). Several serologic studies have shown that swine workers are at increased risk of infection with influenza viruses (Gray et al. 2007; Olsen et al. 2002). In a survey in rural south-central Wisconsin during 1996–1997, 23% of 74 swine farmers were seropositive to H1 influenza A virus of swine, compared to 0.9% of 114 urban control samples. Seropositivity was associated with being a farm owner/family member, living on a farm, or entering a swine barn 4 or more days a week (Olsen et al. 2002). In an Iowa study, Gray and colleagues (2007) found that 707 swine-exposed participants were 55 times (and their 80 non-swine-exposed spouses 29 times) more likely to have elevated antibody titers to H1N1 virus of swine compared to 79 non-exposed controls.

The Emergence of Pandemic H1N1 2009

Investigators have suggested that a swine population at some point in the past most likely served as the reservoir from which pandemic H1N1 2009 emerged. Results of antigenic studies of novel H1N1 2009 showed that this virus is homogeneous and contains six genes that are similar to North American triple reassortant H1N1 influenza viruses of swine but quite distinct from seasonal human A (H1N1) viruses. The time, place, and circumstance of the jump and adaptation of the virus to humans, and its emergence as a PIV in humans, remain unknown.

The origins of this virus involve genes from multiple influenza lineages of swine:

1. the HA gene segments from the currently circulating Eurasian swine H1N1 genetic lineage, which was originally derived from a wholly avian influenza virus first identified in the Eurasian swine population in 1979;
2. the HA gene segments from reassortant H1N2 lineage first detected in swine in 2000;
3. the NP and NS gene segments from the classical swine H1N1 lineage, which entered the US swine population in 1918 and continued to circulate in swine;
4. the PB2 and PA gene segments in the swine triple reassortant H3N2 lineage, which were originally of avian origin and entered North American swine herds in 1998; and
5. the PB1 gene segment, which entered swine from human influenza H3N2 infections but originated in AIVs.

The origins of the pandemic influenza H1N1 virus gene segments may thus have been circulating in swine for as many as 20 years, and segments of this new virus may have coexisted in reassorted strains of influenza for more than 10 years.

The low genetic diversity of this virus has led to suggestions that the introduction in humans was a single event or multiple events of similar viruses that occurred several months before the April 2009 detection of the first human outbreak (Garten et al. 2009; Smith et al. 2009).

Murine studies of the evolution of the 2009 pandemic H1N1 virus documented its cross reactivity with the 1918 H1N1 virus (Wei et al. 2010) due to the formation of neutralizing antibodies to conserved regions of the HA gene. This finding of a conserved region may provide insights about how pandemic viruses evolve and inform vaccine development decisions for humans. It is important to note that considerable cross reactivity within H1 subtypes has also been demonstrated in pig models (Kyriakis et al. 2010; Vincent et al. 2010), underscoring the importance of cross-species collaborative research on influenza.

Influenza in Pigs

Clinical and Epidemiologic Aspects

Swine influenza is a commonly occurring, highly contagious respiratory disease (Radostits et al. 2000) in the approximately 67 million pigs raised on 71,450 swine operations in the United States (USDA/NASS 2009). It causes considerable morbidity but mortality rates are generally under 5%.

In the United States, influenza A viruses of swine H1N1, H1N2, and H3N2 are circulating in pigs, with most viral isolates being of the subtype H1N1. In one seroprevalence study at a midwestern veterinary diagnostic laboratory during 1998–2000, approximately 23% of over 100,000 swine samples tested positive for swine influenza A antibodies, of which 67% and 34% were of H1 and H3 subtypes, respectively (Choi et al. 2002). In another serosurvey of pigs in 23 states, 20.5% of samples were positive for antibodies to H3 swine influenza viruses (Webby et al. 2000). And in a third study in the north central United
States, 26 swine influenza viruses—all of the H1N1 subtype, and 11 of the alpha cluster of classical H1—were isolated from pigs at slaughter, and 27.7% of sera from 2,375 pigs tested antibody positive for the alpha cluster of classical H1N1 (Olsen et al. 2000).

Swine influenza outbreaks occur in the United States throughout the year but often peak in colder months or during times of summer heat stress. Transmission occurs readily through aerosol droplets or direct contact, infecting pigs through their respiratory tract. After an incubation period of 2 to 7 days, most animals raised together show clinical signs (Radostits et al. 2000)—fever, coughing, nasal discharge, sneezing, labored/jerky breathing, anorexia, and lethargy. Clinical complications result from secondary bacterial or viral coinfections.

Although all ages of pigs may be infected, younger, growing pigs are most susceptible. In older boars, fevers can affect the quality and output of semen. Infections in older sows can lead to abortions or reduced lactation. Supportive therapy may include antipyretic medications to reduce fever and antibiotics to prevent or treat secondary bacterial infections (Radostits et al. 2000). Infected animals develop immunity quickly, however, generally recover, and are protected for up to several months against subsequent infections with a given subtype.

When influenza is suspected in swine, diagnosis is based on a combination of clinical signs: detection of the virus in a respiratory sample collected from a sick pig by PCR, antigen capture enzyme-linked immunosorbent assay (ELISA), or virus isolation methods; gross necropsy and histopathology lesions; and serologic assays. The latter are readily available for detecting antibodies to influenza viruses of swine, but multiple specific tests for the different HA subtypes are needed. Several assays can detect antibodies from previous infections or to vaccination, frequently making interpretation of results difficult (Erickson et al. 2005; Janke 2000).

**Human Influenza Viruses That Infect Swine**

Human influenza viruses that infect swine, with clinical illness mild or absent altogether, have been documented for decades (Brown 2000). Zhou and colleagues (1999) reported that in 1998 a seasonal human influenza H3N2 virus reassorted with a classic H1N1 influenza virus of swine and an AIV in pigs to produce a new triple reassortant H3N2 influenza virus of swine. Olsen and colleagues (2000) reported that 8% of 2,375 specimens collected from Wisconsin pigs in 1997 and 1998 tested positive for human H3 influenza viruses. Pandemic H1N1 2009 has infected swine herds in a growing number of countries, with the source of infection thought to be exposure of pigs to infected humans; clinical illness has been reported as mild and infected pigs recover (OIE 2009a). Given the susceptibility of pigs to this virus, there is potential for pandemic H1N1 2009 virus to become established in some pig populations (AASV 2009).

**Prevention and Control of Influenza Virus Infections in Swine Populations**

Preventing swine herds from infection with swine, avian, or human influenza viruses is achieved through effective biosecurity and sound management practices. Pigs are generally raised indoors in barns that house animals at different growth stages—breeding, farrowing, nursery, and growing-finish pig—in accordance with high biosecurity and sanitation standards that reduce the risk of infectious diseases (AASV 2009).

Other important management practices to reduce the potential for exposure and infection with influenza viruses include limiting herd exposure to or contact with people and vehicle traffic, properly cleaning and disinfecting trucks and vehicles that transport pigs, and quarantining any new animals that are introduced into a herd. Methods to prevent swine herds from exposure to AIVs include sealing off or screening doorways, windows, and air flow vents; providing only treated water to avoid contamination from waterfowl feces; minimizing waterfowl use of farm lagoons; not raising hogs and poultry or other domesticated birds on the same premises; preventing contamination of pig feed with feces from over-flying waterfowl by storing it in closed containers; and providing boots and clothes for workers to wear only in pig barns (Olsen 2004).

In recent decades swine production methods have changed to include raising and consolidating greater numbers of pigs per operation and by age group (Honeyman 1996). Concerns have been raised that rearing many pigs in close quarters can facilitate the introduction and transmission of swine and human influenza viruses in the herd, thereby increasing the chances for the emergence of a PIV (Saenz et al. 2006; Schmidt 2009). Furthermore, in operations with less than optimal management practices, increased dust, waste, and other airborne particulates that affect air quality can facilitate transmission through direct contact or airborne droplets (Cole et al. 2000). However, proper attention to ventilation, waste management, sanitation, and the use of personal protective clothing and equipment can minimize these risks (Olsen 2004).

Saenz and colleagues (2006) modeled the effect of percentage of agricultural workers in a community on percentage increase of human influenza cases and found that when the former exceeded 15%, the number of human influenza cases increased significantly. This effect disappeared, however, when at least 50% of the hypothetical agricultural worker population was vaccinated for seasonal influenza. These results support the view that management practices play an important role in affecting the prevalence of influenza infections in swine herds. Mathematical models may thus have some utility in research on the role of animals in the emergence of PIVs, provided they include and control for multiple epidemiologic, management, and health factors, and appropriate caution is exercised in the interpretation of findings. Mathematical models are just one tool; more multidisciplinary, integrated surveillance and research on influenza...
viruses in swine and other mammalian populations are clearly needed (AASV 2009; WHO 2006).

Use of Influenza Vaccines in Swine

Sows are frequently vaccinated against influenza to promote transfer of maternally derived antibodies to young pigs, the group most susceptible to infection, and to minimize severity of clinical illness. Vaccines do not prevent infection completely, but their use can reduce the severity of illness, decrease both viral multiplication and shedding, and thus limit viral transmission.

Vaccines are available commercially or prepared autogenously using isolates obtained during outbreaks from affected pigs; most are made from inactivated whole viruses (propagated in either tissue culture cell lines or embryonated chicken eggs) and prepared with an adjuvant. Their effectiveness depends on how closely the vaccine strains match those causing illness in the herd. Cross protection against antigenic variants of influenza A viruses appears broader for swine than for people.

One challenge to successful swine influenza vaccination programs in US pigs is a historically inflexible system for licensing new vaccines that slows the availability of new vaccines that protect against circulating viruses that are continually changing from antigenic drift and shift. A second challenge is variability of waning maternal antibodies among populations of young pigs; this waning leaves young pigs susceptible to infection, which facilitates continued circulation of the virus in the herd (Thacker and Janke 2008).

In November 2009, the Office International des Epizooties (OIE; also called the World Organization for Animal Health) suggested that vaccination for pandemic H1N1 2009 may not be worthwhile until the virus becomes more prevalent in swine herds (OIE 2009a,b). The American Association of Swine Veterinarians (AASV 2009) has recommended use of such a vaccine in affected herds if it is proven to reduce virus shedding and the risk of viral transmission to other swine or workers. To assist US swine farmers in protecting their herds from pandemic H1N1 2009 infection, the US Department of Agriculture (USDA) issued a 1-year conditional license to a veterinary biologics company for a pandemic H1N1 2009 swine vaccine (USDA/APHIS 2009c).

Virologic and Epidemiologic Surveillance for Influenza A Viruses of Swine

Given the high prevalence and low mortality caused by endemic influenza virus infections of swine, the OIE and, in the United States, the USDA have not classified it as a reportable or regulated disease (OIE 2009a; USDA/APHIS 2009a). Also in the United States, with modest and finite resources available for disease surveillance and control of other diseases of much higher consequence to animal health and international trade, significant investments for sustained, virologic surveillance by government programs have not been possible. Such surveillance is labor intensive and quite costly, and limited budgets of animal health authorities at national and state levels have precluded assigning it a higher priority for funding.

Challenges in the Conduct of Influenza Surveillance in Swine

Laboratory confirmation of infection and genomic sequencing of viruses require the restraint and handling of clinically ill pigs to obtain nasal swabs or the collection of fresh tissues at necropsy. Serologic monitoring for influenza infections is also labor intensive because of the multiple antigenic strains of H1N1, H1N2, and H3N2 viruses cocirculating in swine herds, variable vaccination status, different HA inhibition test methods, and different types of viral antigens used by different laboratories (Erickson et al. 2005). More recently laboratories have used antigen detection by immunohasays and molecular-based assays, such as reverse transcriptase PCR, with partial or full genomic sequencing, for surveillance purposes. Virus isolation and full genomic sequencing are necessary to detect subtle changes in the influenza A virus genome. All of these laboratory tests and assays are useful but expensive.

Furthermore, several large food production companies, important in the rearing of swine globally for trade and consumption, have been reluctant to share isolates from their herds due to fears of interruption to business and trade (AASV 2009). Concerns about human health risks of influenza viruses in swine, and the economic impact of endemic influenza on US swine producers, however, have prompted the consideration and testing of various approaches to virologic surveillance.

Given the challenges, the efficient and effective surveillance of influenza viruses in swine operations will require a strategic approach. University, state, and private diagnostic laboratories have collaborated to maintain an extensive database of influenza viruses isolated from swine, including genomic sequences (USDA/APHIS 2009a). One informal virologic surveillance effort comprising an informal network of US veterinary diagnostic laboratories has identified the numerous reassortant influenza viruses circulating in US pigs. This system has been supported primarily by client-user fees and, less frequently, by investigators using research funds for studies of endemic respiratory disease in pigs. A critical factor in the success of these virologic surveillance efforts has been the assurance of anonymity and thus the prevention of penalties for clients submitting specimens. The National Institute of Allergy and Infectious Diseases has funded special surveillance efforts for influenza A viruses in animal populations to detect different subtypes and strains for studies of immunity and pathogenesis, and for development of human influenza vaccines effective against all subtypes. These efforts in pigs have focused on testing specimens collected from clinically ill animals that may have been exposed to bird feces (e.g., in contaminated water systems) (NIAID 2009).
International Measures

In Europe, influenza surveillance in pig populations has been carried out for several years (European Commission Health and Consumers Directorate-General 2009). In China extensive serologic surveys have been conducted in pigs to detect and identify influenza viruses (Guan et al. 1996; Li et al. 2003; Ninomiya et al. 2002; Peiris et al. 2001; Yu et al. 2008). In November 2009, the OIE advised its members to notify it of H1N1 2009 infections in swine, noting that information from reports would be critical for transparency and for evidence-based policies and decision making as the global situation evolves (OIE 2009b). The United Nations Food and Agriculture Organization (FAO) has published guidelines for surveillance of pandemic H1N1 2009 and other influenza viruses in swine populations (Ferrari et al. 2009).

Since the introduction of these measures, an increasing number of countries—including the United States, Canada, Germany, Indonesia, Italy, Norway, and Thailand, among others—have reported swine infections with pandemic H1N1 2009. The source of infection in these reports is cited as inconclusive or unknown, with human-to-animal transmission sometimes mentioned (OIE 2010). There is no evidence, however, that pigs are playing a role in the global spread of the virus in the human population (OIE 2009a,b).

US Efforts

In August 2009, USDA/APHIS Veterinary Services, in collaboration with the CDC and other stakeholders, launched a surveillance program for influenza viruses in US swine, including novel H1N1 2009, and published guidelines for diagnosing, managing, and reporting potential cases (USDA/APHIS 2009a,b). The goals of the program are to detect the novel H1N1 2009 virus, ensure the timely detection of any new strains, determine the distribution of new strains in swine to inform policy decisions, and identify the genetic characteristics of viruses necessary for vaccine and diagnostics development. The strategy calls for both voluntary surveillance of (1) swine populations epidemiologically linked to a human infected with an influenza virus from pigs, and (2) sick swine at first points of concentration at commingling events such as auctions, markets, fairs, or other swine exhibition events; and testing of case-compatible swine accessions submitted to veterinary diagnostic laboratories.

As of March 2010, the program had reported several species infected with pandemic H1N1 2009 in the United States: clinically healthy swine sampled at the Minnesota and South Dakota state fairs; pigs with respiratory disease on swine farms in Illinois, Indiana, and North Carolina; clinically ill pet ferrets exposed to humans with influenza-like illness in Oregon and Nebraska; clinically ill domestic cats exposed to humans with influenza-like illness in Oregon, and Pennsylvania; a clinically ill cheetah in California; and clinically ill turkeys with possible exposure to humans with influenza-like illness in Virginia and California (USDA/APHIS 2010). In December 2009 a pet dog, with coughing, anorexia, and lethargy, tested positive for pandemic H1N1 2009 (IDEXX 2009).

In general, however, the support for and scope of surveillance for swine, avian, and human influenza viruses in pigs have been limited when compared to those for influenza in humans, precluding a comprehensive understanding of the national prevalence and patterns of influenza viruses in the United States and other countries.

Impacts of Pandemic Influenza H1N1 Reporting by the News Media

As the first human cases of novel H1N1 2009 emerged in the United States and Mexico and the genetic makeup of the virus was determined to be similar to influenza viruses of swine, avian, and human genetic lineages, public health officials, including prominent influenza virologists, immediately referred to the new disease as “swine flu” even though the virus was not spread through contact with pigs. With cable and internet news channels broadcasting “breaking news” minute by minute, many in the public and numerous policymakers jumped to the wrong conclusion that pigs and pork products were involved in transmitting pandemic H1N1 2009 infection to humans.

The media’s repeated reference to the human PIV as “swine flu” not only caused public health confusion but also led to the stigmatization of swine farmers, which, when added to economic stresses already affecting the industry, contributed to even larger economic losses for them, especially smaller operations. Unwarranted concerns based on the inappropriate designation also led to official and unofficial bans by at least 17 countries on imports of US pork or pork products (American Meat Institute 2009)—China maintained its ban until mid-December 2009 (Reuters 2009). US consumer demand for pork decreased significantly as well. After the first report of novel H1N1 2009 on April 24, 2009, there was an estimated decrease in cash revenue of approximately $20 per head, a huge drop in a business where, at best, there are only marginal profits over the cost of production. Overall, the economic loss to the US hog industry between April 24 and the end of 2009 from pandemic H1N1 2009 has been estimated to approach $1.3 billion (Butler 2009).

In addition to economic losses to the pork industry, another unfortunate consequence of the misnaming of the disease was the draconian, non-evidence-based decision of Egyptian policymakers to depopulate their country’s 300,000-head swine herd (CNN 2009). Not only were many animals killed unnecessarily, but the action led to another public health crisis: a buildup of garbage and vermin in the streets. Pigs, being omnivores and scavengers, play an important role in keeping garbage levels under relative control in developing countries (Slackman 2009).

Although the public health community was responsive to pleas to change the name of the disease and immediately began to call it novel H1N1 2009, and later pandemic H1N1 2009 (CDC 2009c; WHO 2009f), the news media persisted in using
the term “swine flu.” In September, US Secretary of Agriculture Tom Vilsack called on the media to cease using this inappropriate, damaging term (USDA 2009), but with little effect.

Morens and colleagues (2009) discuss several challenges in arriving at consensus definitions of scientific terms and note how difficult it is to change the use of a term once adopted. They emphasize the formidable challenge of finding the vocabulary to convey complicated, scientific concepts that are understandable to a scientifically illiterate public.

The media’s failure to heed requests by human and animal health authorities and the pork industry to stop using the term “swine flu” serves as an unfortunate example of actions that led to unnecessary negative economic repercussions for the food industry. These and other negative impacts discourage participation in surveillance programs, the sharing of viral isolates, and the prompt reporting of unusual disease events—all critical for the early detection and response to emerging zoonotic diseases.

**One Health Approach to Disease Prevention, Detection, and Control**

Visionary health professionals have long stressed the importance of multidisciplinary and multisectoral collaboration to confront health challenges posed by zoonotic diseases (Carter 2009; Monath et al. 2010; Schwabe 1983). Beginning in the late 1990s, a “One Health” movement emerged (www.onehealthinitiative.com), drawing on multidisciplinary expertise and experience to define its concepts and approaches (Kaplan et al. 2009; One Health Initiative Task Force 2007; WCS 2009). The One Health Initiative Task Force defined One Health as “the collaborative effort of multiple disciplines—working locally, nationally, and globally—to attain optimal health for people, animals and our environment.” Multiple studies and reports (IOM 2005; IOM/NRC 2009; NRC 2001) and textbooks (Dvorak et al. 2008; Rabinowitz and Conti 2010) have incorporated the One Health perspective in emphasizing the need for human and animal health professionals to work together to address the growing number of emerging zoonotic disease outbreaks in humans and animals and achieve better outcomes of health and well-being for all species.

**Lessons Learned for Preventing, Detecting, and Responding to Pandemic Influenza from a One Health Perspective**

Since the late 1990s, significant human illness caused by AIV infections has brought global attention both to the occurrence and epidemiology of influenza A viruses in animal populations and to the risks they pose to human health. Outbreaks of zoonotic avian and swine viruses in animal populations have devastated household, industry, regional, national, and global economies due to the following factors:

- decreased consumer demand for chicken and pork products;
- international trade bans on animals, meat, eggs, milk, and other animal products;
- large-scale depopulation of animals as part of disease prevention and control efforts;
- negative impacts on the livelihoods of food animal producers in all countries, at farm, district, regional, and national levels;
- increases in household poverty and loss of income for food, health, education, and important development goals at household and national levels; and
- reduction in the availability of animal protein and thus greater risk of protein-energy malnutrition in people (UN 2009) and increased susceptibility to infectious diseases.

Unfortunately, these impacts have resulted in less participation in and support for surveillance and early reporting in animal populations.

There are several lessons to be learned from pandemic H1N1 2009 taking a One Health perspective, which we believe can improve global influenza pandemic preparedness and response.

(1) As highlighted in the Report on Sustaining Global Surveillance and Response to Emerging Zoonotic Diseases (IOM/NRC 2009), an effective global, strategic, integrated surveillance and response system is needed, and will require human, animal, and environmental health professionals to work together to achieve earlier detection and disease control in animal populations to minimize threats to human and animal health. The report also emphasized the importance of timely and effective prevention and disease control efforts by all concerned to save human and animal lives and promote well-being. The report’s 12 recommendations encompass technical, economic, and political considerations, and stress the need for capacity building as well as closer and more effective and coordinated communication between human and animal health authorities locally, nationally, and internationally for more effective and appropriate outbreak investigations. The report also cited the need for communication platforms (e.g., joint committees, task forces, virtual meetings, executive dashboards) and protocols that support multiple disciplines and sectors coming together to share information and participate in joint planning, investigation, analysis, and decision making on response.

Although public health authorities have called for better and greater surveillance of influenza viruses in pigs and other animals, policymakers and public health officials frequently are unaware of the sizable difference in the level of resources available to human health authorities for influenza surveillance and disease control in human populations compared to those for the animal health sector.

In short, new approaches to overcome jurisdictional funding, regular communication, and decision making among those in the agriculture, public health, environment, and public and private sectors are needed for a successful, strategic, One Health approach that prevents the emergence of pandemic influenza or enables detection and response at the earliest point possible. In addition, for successful surveillance of influenza
viruses in swine populations, ensuring the anonymity of the source of specimens has proven effective in encouraging agricultural industries to submit specimens, resulting in the availability of more information about the evolution and changes in influenza viruses in swine populations.

(2) More comprehensive surveillance for infection and disease in occupational groups that work most closely with animals (i.e., poultry and swine workers, live market workers and vendors, abattoir workers, veterinarians and animal health technicians) is a must for earliest detection of new influenza virus infections in humans. Individuals in these groups are most likely to become infected first and spread infection to others. Early detection and disease control in these groups could greatly reduce human-to-human transmission. Surveillance in these groups can also play an important role in the detection and early reporting of unusual diseases in animal populations (Gray et al. 2007; IOM/NRC 2009).

(3) To avoid both public confusion about risk factors of exposure and unnecessary negative economic impacts on food animal producers and the food industry, it is essential to identify a different, standard way of naming influenza viruses and disease in humans when the virus may have originated in an animal population that is not in fact involved in transmission. Protecting against unfounded economic losses to food production and processing industries, as well as the unnecessary depopulation of animal herds, is critically important to establish trust with human and animal health authorities. Such trust is a prerequisite for encouraging the early reporting of unusual disease occurrences in food animal populations, the sharing of influenza isolates with the public sector, and greater participation in coordinated and integrated disease control efforts.

(4) Greater efforts and resources are necessary for the prevention and transmission of influenza viruses between pigs and people. These would include greater support for and adoption of biosecurity, sound management, and vaccination practices on swine operations to reduce the prevalence and shedding of influenza viruses among animals, and more timely development and licensure of swine influenza vaccines to address newly identified viral subtypes.

Public health and animal health groups have recommended measures to reduce the potential for transmission of influenza viruses between pigs and humans and prevent opportunities for coinfection of human, avian, and swine influenza viruses (CDC 2009d; Olsen 2006). These measures include:

- vaccinating pigs for influenza viruses,
- vaccinating swine workers with human seasonal influenza vaccines,
- providing sick leave to ill farm workers and encouraging those with influenza-like illness or acute respiratory infections to stay away from work during the 3 to 7 days they are likely shedding virus,
- installing ventilation systems in containment swine production facilities to minimize recirculation of air in swine barns and reduce the exposure of workers and animals to influenza viruses, and
- promoting basic hygiene practices.

Hygiene practices should include a routine change of clothing for swine workers before they leave swine barns and farm premises, installation and use of hand washing stations throughout animal housing areas, and minimization of hand-to-face contact. Personal protective equipment should be provided and its use encouraged as appropriate.

(5) Invest in One Health research to enhance understanding of the emergence, prevention, detection, and control of PIVs. For example, multidisciplinary research is needed to address questions in the following and other areas:

- better methods to prevent, predict, and detect the emergence of PIVs in animal populations;
- the relationship between animal production management practices, risk of infection, the spread of influenza viruses from animals to humans, and food safety;
- the risk and potential outcomes of coinfection in humans or pigs with both pandemic H1N1 2009 and HP AIV H5N1; and
- the development and delivery of better vaccines (AASV 2009; Fauci 2005; WHO 2006).

Animal models have been and will continue to be an indispensable component of biomedical research efforts to address these and other questions. Investigations in this area will also require both sufficient numbers of researchers and educators from different disciplines and interdisciplinary training (NRC 2004, 2005).

In summary, the first influenza pandemic of the 21st century offers important lessons in helping human and animal health authorities understand how better to prevent future influenza pandemics, or to detect and respond to their emergence earlier and more effectively. Enhanced collaboration and integration of efforts across multiple professions and sectors will be essential for achieving success.

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References

AASV [American Association of Swine Veterinarians]. 2009. American Association of Swine Veterinarians position statement on pandemic (H1N1) 2009 influenza. Available online (www.aasv.org/aasv/position-pH1N1.pdf); accessed December 28, 2009.

American Meat Institute. 2009. H1N1 Trade Updates. Trade update 9/12. Available online (www.meatami.com/ht/d/sp/i/49332/pid/49332); accessed December 28, 2009.
Amonsin A, Payungporn S, Theamboonlers A, Thanawongnuwech R, Suradhat S, Pariyothorn N, Tantiltcharoen R, Damrongwananapokin S, Buranathai C, Chaisingh A, Songserm T, Povorawan Y. 2006. Genetic characterization of H5N1 influenza A viruses isolated from zoo tigers in Thailand. Virology 344:480-491.

Belsha RB. 2005. The origins of pandemic influenza: Lessons from the 1918 virus. N Engl J Med 353:2209-2211.

Brown IH. 2000. The epidemiology and evolution of influenza viruses in pigs. Vet Microbiol 74:29-46.

Butler D. 2009. Testimony of the National Pork Producers Council on the US Pork Industry Economic Crisis before the US House Committee on Agriculture Subcommittee on Livestock, Dairy, and Poultry, October 22. Available online (http://agriculture.house.gov/testimony/111/h102209/Butler.pdf); accessed December 28, 2009.

Carter CN. 2009. One man, one medicine, one health: The James H. Steele Story. New York: BookSurge Publishing.

CDC. 2009a. Swine influenza A (H1N1) infection in two children—Southern California. MMWR 58:400-402.

CDC. 2009b. Novel influenza A virus infections—2010 case definition. Available online (www.cdc.gov/ncphi/disss/nndss/casedef/novel_influenzaA.htm); accessed December 20, 2009.

CDC. 2009c. Novel influenza A (H1N1) virus infections in three pregnant women: United States, April-May 2009. MMWR 58:497-500.

CDC. 2009d. Interim Guidance for Workers Who Are Employed at Commercial Swine Farms: Preventing the Spread of Influenza A Viruses, Including the 2009 H1N1 Virus. Available online (www.cdc.gov/h1n1-flu/guidelines_commercial_settings_with_pigs.htm); accessed December 21, 2009.

Chen J, Lee KH, Steinhauser DA, Stevens DJ, Skelhel JJ, Wiley DC. 1998. Structure of the hemagglutinin precursor cleavage site, a determinant of influenza pathogenicity and the origin of the labile conformation. Cell 95:409-417.

Choi YK, Goyal SM, Joo HS. 2002. Prevalence of swine influenza virus subtypes on swine farms in the United States. Arch Virol 147:1209-1220.

Choi YK, Lee JH, Erickson G, Goyal SM, Joo HS, Webster RG, Webbry R. 2004. H3N2 influenza virus transmission from swine to turkeys, United States. Emerg Infect Dis 10:2156-2160.

Choi YK, Nguyen TD, Ozaki H, Webbry RJ, Puthavathana P, Buranathai C, Chaisingh A, Auewarakul P, Hanh NT, Ma SK, Hui PY, Guan Y, Peiris M, Garten RJ, Davis CT, Russell CA, Linstrom S, Balish A, Sessions WM, Xu S, Skeper E, Deyde V, Okomo-Adhiambo M, Gubareva L, Barnes J, Smith CB, Emery SL, Millman MJ, Rivailler P, Smagula J, de Graaf M, Burke DF, Fouchier RAM, Puppas C, Alpuche-Arandam C, López-Gatell H, Olvera H, López I, Myers CA, Faix D, Blair PJ, Yu C, Keene KM, Dotson PD Jr, Boxrud D, Sambol AR, Abid SH, St George G, Bannerman T, Moore AL, Stringer DJ, Blevins P, Demmler-Harrison GJ, Ginsberg M, Kriner B, Waterman S, Smole S, Guevara HF, Belongia EA, Clark PA, Beatrice ST, Donis R, Katz J, Finelli L, Bridges CB, Shaw M, Jernigan DB, Uyeki TM, Smith DJ, Klimov AI, Cox NJ. 2009. Antigenic and genetic characteristics of swine-origin 2009 A(H1N1) influenza viruses circulating in humans. Science 325:197-201.

Gill JS, Webbry R, Gilchrist MJR, Gray GC. 2006. Avian influenza among waterfowl hunters and wildlife professionals. Emerg Infect Dis 12:1284-1286.

Gostin LO. 2009. Influenza A (H1N1) and pandemic preparedness under the rule of international law. JAMA 301:2376-2378.

Gramer MR. 2009. Swine influenza virus: Epidemiology, diagnostics, and research updates. Proc AAVS 471-473.

Gray GC, McCarthy T, Capuano AW, Setterquist SF, Olsen CW, Alavanja MC, Lynch CF. 2007. Swine workers and swine influenza virus infections. Emerg Infect Dis 13:1871-1878.

Guan Y, Shottridge KF, Krauss S, Li PH, Kawaoka Y, Webster RG. 1996. Emergence of avian H5N1 influenza viruses in pigs in China. J Virol 70:8041-8046.

Honeyman MS. 1996. Sustainability issues of US swine production. J Anim Sci 74:1410-1417.

IDEXX Laboratories. 2009. H1N1 influenza virus infection confirmed in household pets (Industry Alert). Available online (www.idexx.com/view/xhtml/en/us/smallanimal/2009/h1n1-alert.jsf?SSOTOKEN=0); accessed December 22, 2009.

IOM [Institute of Medicine]. 2005. Microbial Threats to Health: Emergence, Detection, and Response. Washington: National Academies Press.

IOM/NRC [National Research Council]. 2009. Sustaining Global Surveillance and Response to Emerging Zoonotic Diseases. Washington: National Academies Press.

Janke BH. 2000. Diagnosis of swine influenza. Swine health prod 87:79-84.

Kaplan B, Kahn LH, Monath TP, eds. 2009. “One Health, One Medicine”: Linking human, animal and environmental health. Vet Ital 45(1), January-March. Teramo, Italy: Istituto Zooprofilattico Sperimentale dell’Abruzzo e del Molise G. Caporale.

Katz R. 2009. Use of revised international health regulations during influenza A (H1N1) epidemic. Emerg Infect Dis 15:1165-1170.

Kawaoka Y, Krauss S, Webster RG. 1989. Avian-to-human transmission of the P1b gene of influenza A viruses in the 1957 and 1968 pandemics. J Virol 63:4603-4608.

Keawcharoen J, Oraveerakul K, Kuiken T, Fouchier RAM, Amonsin A, Payungporn S, Noppornpanth S, Wattanodorn S, Thamboonlers A, Tantiltcharoen R, Pattarangasan R, Arty N, Ratanakorn P, Osterhaus ADME, Povorawan Y. 2004. Avian influenza H5N1 in tigers and leopards. Emerg Infect Dis 10:2189-2191.

Kilbourne ED. 2006. Influenza pandemics of the 20th century. Emerg Infect Dis 12:9-14.

Koopmans M, Wilbrink B, Conyn M, Natrop G, van der Nat H, Vennema H, Meijer A, van Steenbergen J, Fouchier R, Osterhaus A, Bosman A. 2004. Transmission of H7N7 avian influenza A virus to human beings.
during a large outbreak in commercial poultry farms in the Netherlands. Lancet 363:587-593.

Kuntz-Simon G, Madey F. 2009. Genetic and antigenic evolution of swine influenza viruses in Europe and evaluation of their zoonotic potential. Zoonoses Publ Health 56:310-325.

Kyrkias CS, Gramer MR, Barfe F, Van Doorselaere V, Van Reeth K. 2010. Efficacy of commercial swine influenza vaccines against challenge with a recent European H1N1 field isolate. Vet Microbiol (in press).

Lekcharoenaks P, Lager KM, Venuvalapalli R, Woodruff M, Vincent AL, Richt J. 2006. Novel swine influenza virus subtype H3N1, United States. Emerg Infect Dis 12:787-794.

Li H, Xin X, Yang H, Li Y, Qin Y, Xuexui C, Chen H, Yu K, Bi Y, Tong G. 2003. Serological and virologic surveillance for swine influenza virus infections among pigs over large areas in China in 1998-2002. 4th International Symposium on Emerging and Re-emerging Pig Diseases. Rome, June 29-July 2. Available online www.unipir.it/arpa/facvet/dip/dipsa/ric/prs2003/260-261.pdf; accessed December 21, 2009.

Lin YP, Shaw M, Gregory V, Cameron K, Lim W, Klimov A, Subbarao K, Guan Y, Krauss S, Shortridge K, Webster R, Cox N, Hay A. 2000. Avian-to-human transmission of H9N2 subtype influenza A viruses: Relationship between H9N2 and H5N1 human isolates. Proc Natl Acad Sci U S A 97:9654-9658.

Ma W, Gramer M, Rossow K, Yoon KJ. 2006. Isolation and genetic characterization of new reassortant H3N2 swine influenza virus from pigs in the Midwestern United States. J Virol 80:5092-5096.

Ma W, Vincent AL, Gramer MR, Brockwell CB, Lager KM, Janke BH, Gafter PC, Patnakay DP, Webbly RJ, Richt J. 2007. Identification of H2N3 influenza A viruses from swine in the United States. Proc Natl Acad Sci U S A 104:20949-20954.

Ma W, Lager KM, Vincent AL, Janke BH, Gramer MR, Richt JA. 2009a. The role of swine in the generation of novel influenza viruses. Zoonosis Publ Health 56:236-337.

Ma W, Kahn RE, Richt JA. 2009b. Pigs as a mixing vessel for influenza viruses: Human and veterinary implications. J Mol Gen Med 3:158-166.

Marozin S, Gregory V, Cameron K, Bennett M, Valette M, Aymard M, Foni E, Barigazzi G, Lin Y, Hay A. 2002. Antigenic and genetic diversity among swine influenza A H1N1 and H1N2 viruses in Europe. J Gen Virol 83:735-745.

Masurdl N, deBoer GF, Anker WJ, Huffels AD. Prevalence of influenza viruses A-H1N1 and A-H3N2 in swine in the Netherlands. Comp Immunol Microbiol Infect Dis 1983:141-149.

Mauk J, Kohn N, Kaplan B. 2010. Introduction: One Health Perspective. ILAR J 51:163-198.

Morens DM, Folkers GK, Fauci AS. What is a pandemic? J Infect Dis 2009;200:1018-1021.

Myers KP, Olsen CW, Gray GC. 2007. Cases of swine influenza in humans: A review of the literature. Clin Infect Dis 44:1084-1088.

Neumann G, Kawaoka Y. 2006. Host range restriction and pathogenicity in the context of influenza pandemic. Emerg Infect Dis 12:881-886.

NIAID [National Institute of Allergy and Infectious Diseases]. Centers of Excellence for Influenza Research and Surveillance (CEIRS). 2009 H1N1 Outbreak: University of Minnesota related to 2009 H1N1 outbreak. Available online (www3.niaid.nih.gov/LabsAndResources/resources/ceirs/h1n1outbreak.htm); accessed December 22, 2009.

Ninnomiya A, Takada A, Okazaki K, Shortridge KF, Kida H. 2002. Seroepidemiology of avian H4, H5, and H9 influenza A virus transmission to pigs in southeastern China. Vet Microbiol 88:107-114.

Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team. 2009. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med 360:2605-2615.

NRC [National Research Council]. 2001. Animal Health at the Crossroads: Preventing, Detecting, and Diagnosing Animal Diseases. Washington: National Academies Press.

NRC. 2004. National Need and Priorities for Veterinarians in Biomedical Research. Washington: National Academies Press.

NRC. 2005. Critical Needs for Research in Veterinary Science. Washington: National Academies Press.

OIE [Office International des Epizooties]. 2009a. Pandemic H1N1: Questions and Answers. Available online (www.oie.int/eng/press/h1n1/en_h1_n1_faq.asp); accessed May 29, 2010.

OIE. 2009b. OIE’s role in the pandemic influenza H1N1: Editorials from the Director General. Available online (www.oie.int/eng/edito/en_lastedito.htm); accessed May 29, 2010.

OIE. Weekly Disease Information. WAHID Interface. 2010. Available online (www.oie.int/wahis/public.php?page=weekly_report_index&admin=0); accessed May 29, 2010.

Olsen CW. 2002. The emergence of novel swine influenza viruses in North America. Vir Res 85:199-210.

Olsen CW. 2004. Influenza: Pigs, people and public health. Public Health Fact Sheet, National Pork Board 2:1-4. Available online (www.pork.org/PorkScience/Documents/PUBLICHEALTH%20influenza.pdf); accessed December 21, 2009.

Olsen CW, Carey S, Hinshaw L, Karasai A. 2000. Virologic and serologic surveillance for human, swine and avian influenza virus infections among pigs in the north-central United States. Arch Virol 145:1399-1419.

Olsen CW, Brammer L, Easterday BC, Arden N, Delay E, Baker I, Cox NJ. 2002. Serologic evidence of H1 swine influenza virus infection in swine farm residents and employees. Emerg Infec Dis 8:814-819.

Olsen CW, Karasai A, Carman S, Li Y, Bastien N, Ojkic D, Alves D, Charbonneau G, Henning BM, Low DE, Burton L, Broukhanski G. 2006. Triple reassortant H3N2 influenza A viruses, Canada 2005. Emerg Infect Dis 12:1132-1135.

One Health Initiative Task Force. 2008. One Health: A New Professional Imperative. Final Report. American Veterinary Medical Assciation. Available online www.avma.org/onehealth/onehealth_final.pdf; accessed December 28, 2009.

Osterholm M. 2005. Preparing for the Next Pandemic. Foreign Affairs, July/August 2005.

PAHO [Pan American Health Organization]. 2004. Avian Influenza Virus A (H10 N7) Circulating among Humans in Egypt. EID Weekly updates. Available online (www.paho.org/English/AD/DPC/IDD/eid-eer-07-may-2004.html); accessed December 28, 2009.

Peiris JSM, Guan Y, Markwell D, Ghose P, Webster RG, Shortridge KF. 2001. Cocirculation of avian H9N2 and contemporary “human” H3N2 influenza A viruses in pigs in southeastern China: Potential for genetic reassortment? J Virol 75:9679-9686.

Rabinowitz PM, Conti LA. 2010. Human-Animal Medicine: Clinical Approaches to Zoonoses, Toxins and Other Shared Health Risks. New York: Elsevier.

Radootsi OM, Gay CC, Blood DC, Hinchliff KW. 2000. Veterinary Medicine: A Textbook of the Diseases of Cattle, Sheep, Pigs, Goats, and Horses, 9th ed. New York: WB Saunders Co. p 1157-1159.

Reuters. 2009. China lifts import ban on US, Canada, Mexico pork, Beijing, November 30. Available online (www.reuters.com/article/idUS-TRE5B001W20091201); accessed December 28, 2009.

Richt JA, Lager KM, Janke BH, Woods RD, Webster RG, Webby RJ. 2003. Pathogenic and antigenic properties of phylogenetically distinct reassortant H3N2 swine influenza viruses cocirculating in the United States. J Clin Microbiol 41:3198-3205.

Rimmelzwaan GF, de Jong JC, Bestebroer TM, van Loon AM, Claas ECJ, Fouchier RAM, Osterhaus ADME. 2001. Antigenic and genetic characterization of swine influenza A (H1N1) viruses isolated from pneumonia patients in the Netherlands. Virology 282:301-306.

Saenz RA, Hethcote HW, Gray GC. 2006. Confined animal feeding operations as amplifiers of influenza. Vector-borne zoonotis dis 6:338-346.

Schmidt CW. 2009. Swine CAFOs and novel H1N1 flu: Separating facts from fears. Env Health Persec 117:A394-A401.

Schwabe CW. 1983. Veterinary Medicine and Human Health. Baltimore: Williams and Wilkins.

Shinde V, Bridges C, Uyeiki T, Shu B, Balish A, Xu X, Linstrom S, Sugareva LV, Deyde V, Garten RJ, Harris M, Gerber S, Vasagys S, Smith F, Pacseo N, Martin K, Dufcicy D, Riger K, Conover C, Quinlisk P, Klimov A, Bressey JS, Finelli L. 2009. Triple-reassortant swine influenza A (H1) in humans in the United States 2005-2009. N Engl J Med 360:2616-2625.
Slackman M. 2009. Belatedly, Egypt spots flaws in wiping out pigs. New York Times, September 20.

Smith GJD, Vijaykrishna D, Bahl J, Lyckett SJ, Worobey M, Pybus OG, Ma SK, Cheung CL, Raghwani J, Bhatt S, Peiris JS, Gnan Y, Ramboura A. 2009. Origins and evolutionary genomics of the 2009 swine origin H1N1 influenza A pandemic. Nature 459:1122-1125.

Songtorn T, Amornsin A, Jam-on R, Sue-Heng N, Meemak N, Pariyorothorn N, Payungporn S, Theamboonlers A, Pooworawan Y. 2006a. Avian influenza H5N1 in naturally infected domestic cat. Emerg Infect Dis 12:681-683.

Songtorn T, Amornsin A, Jam-on R, Sue-Heng N, Pariyorothorn N, Payungporn S, Theamboonlers A, Chutinimitkul S, Thawongmuwech R, Pooworawan Y. 2006b. Fatal avian influenza A H5N1 in a dog. Emerg Infect Dis 12:1744-1747.

Subbarao K, Katz J. 2000. Avian influenza viruses infecting humans. Cell Mol Life Sci 57:1770-1784.

Taubenberger JK, Reid AH, Lourens RM, Wang R, Jin G, Fanning TG. 2005. Characterization of the 1918 influenza virus polymerase genes. Nature 437:889-893.

Thacker E, Janke B. 2008. Swine influenza virus: Zoonotic potential and vaccination strategies for the control of avian and swine influenza. J Infect Dis 197 (Suppl 1):S19-S23.

UN [United Nations]. 2009. The Millennium Development Goals Report 2009. New York: United Nations.

USDA [US Department of Agriculture]. 2009. Statement from Agriculture Secretary Vilsack regarding animal health and 2009 pandemic H1N1 influenza. Office of Communication, Release. No. 0433.09. Available online (www.usda.gov/wps/portal/ut/p/_s.7_0_A/7_0_1OB?contentidonly=true&contentid=2009/09/0433.xml); accessed December 28, 2009.

USDA/APHIS [Animal and Plant Health Inspection Service]. 2009a. National Surveillance Plan for Swine Influenza Virus: Including Novel H1N1 2009 Virus. August 7, v 2.0. Available online (www.aphis.usda.gov/newsroom/hot_issues/h1n1/downloads/H1N1_Surveillance_Plan_2009.pdf); accessed December 21, 2009.

USDA/APHIS. 2009b. Guidelines for Novel H1N1 2009 Virus in Swine in the United States. August 7, v 2.0. Available online (www.aphis.usda.gov/newsroom/hot_issues/h1n1/downloads/Novel_H1N1_2009_Guidelines.pdf); accessed December 21, 2009.

USDA/APHIS. 2009c. USDA issues conditional license for pandemic H1N1 vaccine for swine. December 11. Available online (www.aphis.usda.gov/newsroom/content/2009/12/h1n1_vaccine.shtml); accessed December 28, 2009.

USDA/APHIS. 2010. 2009 Pandemic H1N1 influenza presumptive and confirmed results. March 25. Available online (www.usda.gov/wps/portal/ut/p/_s.7_0_A/7_0_1OB?contentidonly=true&contentid=2009/03/0433.xml); accessed December 28, 2009.

WHO [World Health Organization]. 2008. International Health Regulations (2005), 2nd ed. Geneva: World Health Organization.

WHO. 2006. Influenza research at the human and animal interface. Report of a WHO Working Group. WHO/CDS/EP/06.3. Geneva, September 21-22.

WHO. 2009a. Pandemic preparedness: What is an influenza pandemic? Available online (www.who.int/csr/disease/influenza/pandemic/en/); accessed December 29, 2009.

WHO. 2009b. Cumulative number of confirmed human cases of avian influenza A(H5N1) reported to WHO. Available online (www.who.int/csr/disease/avian_influenza/country/cases_table_2009_12_30/en/index.html); accessed January 4, 2010.

WHO. 2009c. Pandemic influenza preparedness and response: A WHO guidance document. Available online (www.who.int/csr/disease/influenza/PIPGuidance09.pdf); accessed December 28, 2009.

WHO. 2009d. Global influenza surveillance network: Laboratory surveillance and response to pandemic H1N1 2009. Weekly Epidemiol Rec 84:361-365.

WHO. 2009e. Pandemic (H1N1) 2009: Update 80. Available online (www.who.int/csr/don/2009_12_23/en/index.html); accessed December 28, 2009.

WHO. 2009f. Swine influenza—update 2. Available online (www.who.int/csr/don/2009_04_27/en/index.html); accessed December 28, 2009.

WHO. 2009g. Swine influenza—update 2. Available online (www.who.int/csr/don/2009_04_27/en/index.html); accessed December 28, 2009.

WHO. 2009h. Interim WHO guidance for the surveillance of human infection with swine influenza A (H1N1) virus. 2009g. Available online (www.who.int/csr/disease/swineflu/WHO_case_definitions.pdf); accessed December 28, 2009.

Yamada S, Suzuki Y, Suzuki T, Le MQ, Nidom CA, Sakai-Tagaya Y, Muramoto Y, Ito M, Kiso M, Horimoto T, Shinya K, Sawada T, Kiso M, Usui T, Murata T, Lin Y, Hay A, Haire LF, Stevens DJ, Russell RJ, Gamblin SJ, Skelch JJ, Kawaoka Y. 2006. Haemagglutinin mutations responsible for the binding of H5N1 influenza A viruses to human-type receptors. Nature 444:378-382.

Yoon KJ, Harmon K, Schneider JD. 1999. Characterization of H3N2 swine influenza viruses in Iowa swine. Iowa State University, Health. ASL-R689. p 189-190. Available online (www.ipic.iastate.edu/reports/00swinereports/asl-689.pdf); accessed December 21, 2009.

Yu H, Hua RH, Zhang Q, Liu TQ, Liu HL, Li GX, Tong GZ. 2008. Genetic evolution of swine influenza A (H3N2) viruses in China from 1970 to 2006. J Clin Microbiol 46:1067-1075.

Zhou NN, Senne DA, Landgraf JS, Swenson SL, Erickson G, Rossov K, Liu L, Yoon K, Krauss S, Webster RG. 1999. Genetic reassortment of avian, swine, and human influenza A viruses in American pigs. J Virol 73:8851-8856.

Webby RJ, Swenson SL, Krauss SL, Goyals J, Goyal SM, Webster RG. 2000. Evolution of swine H3N2 influenza viruses in the United States. J Virol 74:8243-8251.

Webby RJ, Rossow K, Erickson G, Sims G, Webster R. 2004. Multiple lineages of antigenically and genetically diverse influenza A virus co-circulate in the United States swine population. Vir Res 103:67-73.

Wei CJ, Boyington JC, Dai K, Houser KV, Pearce MB, Kong WP, Yang ZY, Tunpey TM, Nabel GJ. 2010. Cross-neutralization of 1918 and 2009 influenza viruses: Role of glycans in viral evolution and vaccine design. Sci Transl Med 2:24ra21.

Wells DL, Hofepensperger DJ, Arden NH, Harmon MW, Davis JP, Tipple MA, Schonberger LB. 1991. Swine influenza virus infections: Transmission from ill pigs to humans at a Wisconsin agricultural fair and subsequent probable person-to-person transmission. JAMA 265:478-481.