

## ORIGINAL ARTICLE

# Triple-Reassortant Swine Influenza A (H1) in Humans in the United States, 2005–2009

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## ABSTRACT

**BACKGROUND**

Triple-reassortant swine influenza A (H1) viruses — containing genes from avian, human, and swine influenza viruses — emerged and became enzootic among pig herds in North America during the late 1990s.

**METHODS**

We report the clinical features of the first 11 sporadic cases of infection of humans with triple-reassortant swine influenza A (H1) viruses reported to the Centers for Disease Control and Prevention, occurring from December 2005 through February 2009, until just before the current epidemic of swine-origin influenza A (H1N1) among humans. These data were obtained from routine national influenza surveillance reports and from joint case investigations by public and animal health agencies.

**RESULTS**

The median age of the 11 patients was 10 years (range, 16 months to 48 years), and 4 had underlying health conditions. Nine of the patients had had exposure to pigs, five through direct contact and four through visits to a location where pigs were present but without contact. In another patient, human-to-human transmission was suspected. The range of the incubation period, from the last known exposure to the onset of symptoms, was 3 to 9 days. Among the 10 patients with known clinical symptoms, symptoms included fever (in 90%), cough (in 100%), headache (in 60%), and diarrhea (in 30%). Complete blood counts were available for four patients, revealing leukopenia in two, lymphopenia in one, and thrombocytopenia in another. Four patients were hospitalized, two of whom underwent invasive mechanical ventilation. Four patients received oseltamivir, and all 11 recovered from their illness.

**CONCLUSIONS**

From December 2005 until just before the current human epidemic of swine-origin influenza viruses, there was sporadic infection with triple-reassortant swine influenza A (H1) viruses in persons with exposure to pigs in the United States. Although all the patients recovered, severe illness of the lower respiratory tract and unusual influenza signs such as diarrhea were observed in some patients, including those who had been previously healthy.

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**P**IGS HAVE BEEN HYPOTHESIZED TO ACT AS a mixing vessel for the reassortment of avian, swine, and human influenza viruses and might play an important role in the emergence of novel influenza viruses capable of causing a human pandemic.<sup>1-3</sup> Recent reports of widespread transmission of swine-origin influenza A (H1N1) viruses in humans in Mexico, the United States, and elsewhere highlight this ever-present threat to global public health.<sup>4,5</sup> Between the 1930s and the 1990s, the most commonly circulating swine influenza virus among pigs — classic swine influenza A (H1N1) — underwent little change. However, by the late 1990s, multiple strains and subtypes (H1N1, H3N2, and H1N2) of triple-reassortant swine influenza A (H1) viruses — whose genomes included combinations of avian, human, and swine influenza virus gene segments — had emerged and became predominant among North American pig herds.<sup>6,7</sup>

Influenza virus infection was identified as a cause of febrile respiratory illness in pigs as early as 1931, 3 years before influenza viruses were identified as a cause of illness in people.<sup>8</sup> Swine influenza viruses are enzootic among pigs in North America.<sup>9,10</sup> Cases and clusters of human infections with swine influenza viruses have been reported sporadically in the United States since the 1970s.<sup>4,10-28</sup> Worldwide, more than 50 cases of swine influenza virus infection in humans, most due to classic swine influenza virus, have been documented in the past 35 years,<sup>4,23,25,28-30</sup> and serologic studies suggest that people with occupational swine exposure are at highest risk for infection.<sup>22,24,31,32</sup>

Before the current epidemic of swine-origin influenza A (H1N1) viruses, illness from classic swine influenza viruses, including seven deaths, had been reported in both previously healthy persons and those with preexisting medical conditions (including pregnancy).<sup>13,16,17,20,21,27,29</sup> Signs and symptoms of infection with classic swine influenza virus in humans are often indistinguishable from those of infection with human influenza viruses.<sup>29</sup> Until April 2009, only limited, nonsustained human-to-human transmission of swine influenza virus had been reported.<sup>19,33,34</sup>

There have been at least four published case reports of human infection with triple-reassortant swine influenza A viruses (two of subtype H3N2 from Canada and two of subtype H1N1 from the United States).<sup>23,25,31,35</sup> Before 2005, the Centers

for Disease Control and Prevention (CDC) had been receiving approximately one or two case reports of human infection with classic swine influenza viruses per year. The first human infection with triple-reassortant swine influenza A (H1) virus reported to the CDC occurred in December 2005.<sup>23</sup> In June 2007, human infection with a novel influenza A virus (including influenza viruses of animal origin) was classified as a nationally notifiable infectious disease in the United States.<sup>36</sup> From December 2005 through February 2009, the CDC received 11 notifications of human infection with triple-reassortant swine influenza A (H1) viruses, 8 of which occurred after June 2007. In this article, we characterize the epidemiologic and clinical features of the first 11 cases in humans reported to the CDC in the United States between December 2005 and February 2009. An additional human case of infection with triple-reassortant swine influenza A (H1) viruses was detected in South Dakota in January 2009 but is not described here, because serologic studies for the patient and the patient's contacts are pending finalization of the serologic assay for infection with triple-reassortant swine influenza A (H1) viruses.

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## METHODS

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### **SURVEILLANCE, REPORTING, AND DATA COLLECTION**

A confirmed case of human infection with triple-reassortant swine influenza A (H1) viruses was defined as any case with laboratory confirmation at the CDC (see the Laboratory Confirmation section below). Clinical and demographic information about the first three patients identified (Patients 1, 2, and 3) were obtained before 2007, the year when human infection with a novel influenza A virus became a nationally notifiable disease and systematic data collection was initiated. The infection in Patient 1 was jointly investigated by the Wisconsin State Division of Public Health and the CDC and has been reported previously.<sup>23</sup> Epidemiologic data for Patient 2 were limited, since the family declined to participate in a case investigation. The Iowa State Department of Public Health and the CDC collaborated to conduct an investigation of the illness in Patient 3.

Cases of human infection with a novel influenza A virus are reported to the CDC by state public health laboratories in conjunction with state public health departments through the Nation-

ally Notifiable Diseases Surveillance System (see the Supplementary Appendix, available with the full text of this article at NEJM.org). All cases are reported in the CDC's weekly surveillance reports ([www.cdc.gov/flu](http://www.cdc.gov/flu)). As part of the reporting process, a standardized surveillance reporting form is submitted, including the following information: demographic characteristics, chronic medical conditions, status with respect to seasonal influenza vaccination, clinical signs and symptoms, results of diagnostic testing for influenza, antiviral treatment, laboratory abnormalities, clinical complications, outcome, and exposures to swine and other animals. All cases of laboratory-confirmed human infection with triple-reassortant swine influenza A (H1) viruses identified in the United States since 2007 (i.e., the cases in Patients 4 through 11) (Table 1) were formally reported to the CDC in this way. Besides reports of human infection with triple-reassortant swine influenza A (H1) viruses, no human infections with other novel animal influenza viruses (e.g.,

avian influenza viruses) have been reported since national reporting of novel influenza A virus infections was instituted in 2007.

Descriptive data were analyzed with the use of Stata statistical software (version 8). The analysis of data presented in this report was not subject to review by the institutional review board, and the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA) did not apply because the collection, analysis, and dissemination of data for human cases of novel influenza virus infection is considered a public health surveillance activity.

#### LABORATORY CONFIRMATION

All patients in this series had respiratory samples collected during their illness, which were submitted to their state public health laboratories for microbiologic testing. All but one patient (Patient 7) initially received a diagnosis of infection with an influenza A virus that could not be subtyped, on the basis of reverse-transcriptase-polymerase-

**Table 1. Demographic and Exposure Characteristics of 11 Patients Infected with Triple-Reassortant Swine Influenza A (H1) Viruses.**

Patient No.	Age	Sex	State of Residence	Date of Illness Onset	Estimated Incubation Period	Exposure*	Ill Swine Present
1	17 yr	M	WI	Dec. 2005	3 days	Butchered a pig (direct contact)	Not known
2	7 yr	M	MO	Jan. 2006	Not known	Reported no contact with a pig (unknown contact)	Not known
3	4 yr	F	IA	Nov. 2006	7–10 days	Had contact with patient with suspected case of swine influenza (epidemiologically linked contact)	Yes
4	10 yr	F	OH	Aug. 2007	3–4 days	Exhibited swine at fair, handled pigs (direct contact)	Yes
5	36 yr	M	OH	Aug. 2007	3–4 days	Exhibited swine at fair, handled pigs (direct contact)	Yes
6	48 yr	F	IL	Aug. 2007	7 days	Visited fair, did not stop at pigpen (near vicinity)	Yes
7	16 mo	M	MI	Aug. 2007	7 days	Visited fair, came within 1 m of pigs (close proximity)	Yes
8	2 yr	M	IA	Nov. 2007	1–10 days	Lived on swine farm, came within 1 m of pigs (close proximity)	Yes
9	26 yr	F	MN	Jan. 2008	9 days	Visited live-animal market, came within 1 m of pigpen (close proximity)	Not known
10	14 yr	M	TX	Oct. 2008	3 days	Visited a swine farm, brought home and handled a pig (direct contact)	Yes
11	3 yr	M	IA	Feb. 2009	1–10 days	Visited swine farm owned by his family, touched pigs (direct contact)	Yes

\* Direct contact refers to touching or handling a pig; close proximity refers to standing within 1.83 m (6 ft) of a pig, without known direct contact; near vicinity refers to presence of pigs on the premises but not in close proximity; epidemiologically linked refers to a person who is epidemiologically linked to another person with a confirmed or suspected infection; and unknown refers to unknown contact or unavailable contact information.

chain-reaction (RT-PCR) testing. (Influenza A viruses that cannot be subtyped are defined as those for which the subtype cannot be determined with the use of standard laboratory methods and reagents for circulating human influenza A virus strains — subtype H1N1 or H3N2.) The clinical specimen obtained from Patient 7 was found to be positive for influenza A (H1N2) on viral culture performed at the Michigan State Public Health Laboratory and was then sent to the CDC for further testing.

Samples testing positive for influenza A viruses that cannot be subtyped are routinely forwarded to the Influenza Division laboratories at the CDC for further characterization and sequencing. At the CDC, all 11 cases of swine influenza virus infection were confirmed and viruses subtyped with the use of real-time RT-PCR and the hemagglutination-inhibition assay.<sup>37,38</sup> For swine influenza virus detected in respiratory-fluid samples from patients, complete genome-sequence analysis was performed on amplified RNA to determine the constellation of genes and whether the identified swine influenza virus was a triple-reassortant virus containing gene segments from swine, avian, and human influenza viruses. The GenBank accession numbers of five triple-reassortant swine influenza A (H1) viral isolates are listed in the Supplementary Appendix. The internal gene components of a triple-reassortant swine influenza A (H1) virus isolated from ill pigs associated with both patients in Ohio (Patients 4 and 5) have recently been reported.<sup>28</sup>

Susceptibility to antiviral drugs, the adamantanes (amantadine and rimantadine), was assessed by means of the pyrosequencing assay<sup>39</sup> with the use of viral RNA extracted from the original clinical specimens, viral isolates, or both. Susceptibility of the viral isolates to the neuraminidase inhibitors oseltamivir and zanamivir was assessed by means of the chemiluminescent neuraminidase-inhibition assay, with the use of the NASTar Kit, as previously described.<sup>40</sup>

## RESULTS

The demographic and epidemiologic characteristics of the patients and their illnesses, including the incubation period and source of swine exposure, are listed in Table 1. The median age of the patients was 10 years (range, 16 months to 48 years); eight patients were younger than 18 years

of age. Seven of the 11 patients (64%) were male. Patients 4 and 5 were a father–daughter pair. Patient 3 was part of a family with three other members who had suspected, but not laboratory-confirmed, cases of infection with swine influenza virus. All patients resided in either the midwestern or southern United States.<sup>41</sup> Four of the 11 cases (36%) were reported in August, 1 (9%) in October, 2 (18%) in November, 1 (9%) in December, 2 (18%) in January, and 1 (9%) in February.

Exposures to pigs occurred on pig farms (for three patients), at agricultural fairs (for four patients), at a live-animal market (for one patient), and in a custom slaughterhouse (for one patient). In 8 of the 11 cases (73%), pigs were reported to have shown signs of respiratory illness. Five of the 11 patients (45%) touched pigs, 3 patients (27%) came within 1.83 m (6 ft) of pigs but had no known direct contact, and 1 patient (9%) attended a fair but did not visit areas where pigs were exhibited. The exposure was unknown for one patient (9%), and another patient (9%) was epidemiologically linked to a person with a suspected case of infection who had had direct contact with ill pigs — suggesting limited human-to-human transmission of a triple-reassortant swine influenza A (H1) virus. Among the seven patients with exposure to pigs or venues with pigs at a discrete time (known within 1 day), the median incubation period (the interval between the most recent exposure and the onset of illness) was 3.5 days (range, 3 to 9).

The clinical characteristics of the patients are shown in Table 2. Four of the 11 patients (36%) had a preexisting medical condition: asthma (Patients 6 and 10), an uncharacterized immunodeficiency (Patient 2), or eczema (Patient 11). At least three patients had received current-season influenza vaccine in the season when the triple-reassortant swine influenza A (H1) virus infection was diagnosed; two of the three did not require hospitalization. Among the 10 patients for whom clinical information was available, symptoms included fever (9 patients), cough (10 patients), headache (6 patients), sore throat (6 patients), and diarrhea (3 patients). Myalgia, vomiting, and shortness of breath were reported in two patients each; one patient had conjunctivitis. Among the six patients whose temperature had been reported, the median was 39.7°C (103.5°F) (range, 38.5 to 40.4 [101.3 to 104.8]).

Four patients (Patients 3, 6, 7, and 9) were hos-

**Table 2. Clinical Characteristics of 11 Patients Infected with Triple-Reassortant Swine Influenza A (H1N1) Viruses.\***

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11
Chronic condition	No	Yes (immuno-deficiency)	No	No	No	Yes (asthma)	No	No	No	Yes (asthma)	Yes (eczema)
Received influenza vaccine in season of infection	Yes	Not known	Yes	Not known	Not known	No	No	No	No	No	Yes
Fever	No	Not known	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Maximum temperature (°C) †			39.9				38.5	40.0	40.4	39.4	38.8
Cough	Yes	Not known	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sore throat	No	Not known	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Headache	Yes	Not known	Yes	Yes	Yes	Yes	No	No	No	Yes	No
Dyspnea	No	Not known	No	No	No	Yes	No	No	Yes	No	No
Diarrhea	No	Not known	Yes	No	No	No	No	No	Yes	Yes	No
Conjunctivitis	No	Not known	No	No	No	No	No	No	No	Yes	No
Other signs and symptoms	Rhinorrhea, back pain	Upper respiratory infection	Vomiting, dehydration	Myalgia	Myalgia	Vomiting, cyanosis	Rhinorrhea, anorexia, dehydration	Malaise			Rhinorrhea, lethargy
Findings on chest radiograph	Normal	ND	ND	ND	ND	Pneumonia	Normal	Not known	Pneumonia	ND	ND
Oseltamivir treatment	No	Not known	No	Yes	Yes	Yes	No	No	Yes	No	No
Hospitalization	No	No	Yes	No	No	Yes	Yes	No	Yes	No	No
Mechanical ventilation	No	No	No	No	No	Yes	No	No	Yes	No	No
Outcome	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered

\* ND denotes test not done.

† To convert values for temperature to degrees Fahrenheit, subtract 32 and multiply by 5/9.

pitalized because of the severity of their illness. In Patients 3 and 7, the disease was self-limited. Patient 3, a 4-year-old, previously healthy girl, was hospitalized because of dehydration and a need for medical monitoring after a 3-day history of fever (temperature, 39.2 to 39.9°C [102.5 to 103.9°F]), vomiting, cough, headache, and congestion; a rapid influenza test was positive for influenza A virus (see the Supplementary Appendix) on day 2 of hospitalization, but she was not treated with oseltamivir. She was discharged from the hospital, fully recovered, after 3 days. Patient 7, a 16-month-old, previously healthy boy, was hospitalized for 1 day for dehydration; he presented with fever (38.5°C [101.3°F]), cough, sore throat, rhinorrhea, and anorexia. A rapid influenza test was positive for influenza A virus, but he was not treated with oseltamivir.

In Patients 6 and 9, the disease was severe and prolonged. Patient 6, a 48-year-old woman with a history of smoking, gastroesophageal reflux disease, and asthma controlled with inhaled corticosteroids, was hospitalized after a 2-day history of fever, chills, cough, and subsequent cyanosis. She underwent intubation and mechanical ventilation for pneumonia and respiratory failure on admission. Specimens from bronchoscopy and bronchoalveolar lavage, initially performed 7 days after admission, yielded influenza A virus on viral culture and *Pseudomonas aeruginosa* on bacterial culture. The patient was treated with multiple broad-spectrum antibiotics and oseltamivir (starting on day 11 of hospitalization) and was discharged, in improved condition, on day 19.

Patient 9, a 26-year-old, previously healthy woman, was hospitalized with pneumonia and sepsis after presenting with a 3-day history of fever (a temperature as high as 40.4°C [104.8°F]), cough, vomiting, diarrhea, shortness of breath, and evidence of hypoxia (oxygen saturation, 86%). Initial laboratory testing showed leukopenia (white-cell count, 2100 per cubic millimeter) and thrombocytopenia (platelet count, 135,000 per cubic millimeter). Both viral culture and RT-PCR testing performed on a nasopharyngeal-wash specimen collected on day 2 of hospitalization were positive for influenza A virus. The hospital course was complicated by respiratory failure requiring invasive mechanical ventilation, hypotension requiring a brief course of inotropic medication, and progression to multilobar pneumonia. The patient was treated with multiple broad-spec-

trum antibiotics and oseltamivir (beginning on day 19 of hospitalization). She was discharged in improved condition approximately 30 days after admission and eventually had a full recovery.

Of the four patients who underwent chest radiography, the two who were critically ill (Patients 6 and 9) had abnormal findings that were consistent with pneumonia. In addition to these two critically ill patients, two outpatients were treated with oseltamivir (Patient 5, who was treated within 1 day after the onset of symptoms, and Patient 4, who was treated within 3 days). All patients, including the four with severe disease requiring hospitalization, recovered from their illness. Three of four patients with complete blood counts performed during the course of their disease had abnormal findings; two had leukopenia (a white-cell count of <5000 per cubic millimeter), one had lymphopenia (a total lymphocyte count of <800 per cubic millimeter or a total white-cell count with <15% lymphocytes), and one had thrombocytopenia (a total platelet count of <150,000 per cubic millimeter).

Results of laboratory and virologic testing performed by hospital laboratories and state public health laboratories are listed in Table 3. The results of rapid influenza point-of-care tests were positive in seven of the eight patients who underwent testing by this method. The presence of influenza A virus was initially detected by means of rapid influenza point-of-care testing in 64% of patients, viral culture in 18%, and RT-PCR testing in 9%; one patient (9% of the total) was negative for the virus on rapid testing but was positive on viral culture. Of the five patients who underwent both rapid influenza point-of-care testing and viral culture, three had positive results for both tests.

The CDC confirmed that all 11 patients had infection with triple-reassortant swine influenza A (H1) viruses. The eight individual gene segments found in all 11 viral isolates are shown in Figure 1. With regard to the triple-reassortant swine influenza A subtype, 10 of the 11 patients (91%) were infected with viral subtype H1N1, and 1 patient (9%) was infected with H1N2.

The hemagglutinin (HA) genes of the triple-reassortant swine influenza A (H1) viruses isolated from five patients in this series were found to come from two different phylogenetic lineages currently circulating in North American swine: swH1-beta and swH1-gamma<sup>28</sup> (see Figure 1 in the Supplementary Appendix). Although each lin-

**Table 3. Results of Laboratory and Virologic Testing of 11 Patients Infected with Triple-Reassortant Swine Influenza A (H1) Viruses.\***

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11
Leukopenia†	NA	NA	NA	NA	NA	No	Yes	No	Yes	NA	NA
Lymphopenia‡	NA	NA	NA	NA	NA	Yes	No	No	NA	NA	NA
Thrombocytopenia§	NA	NA	NA	NA	NA	No	No	No	Yes	NA	NA
Rapid influenza point-of-care testing											
Test performed	Yes	No	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Test positive for influenza A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Viral culture											
Test performed	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	No
Test positive for influenza A	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	No	No
RT-PCR testing¶											
Test performed	Yes	No	No	Yes	Yes	No	No	Yes	Yes	No	Yes
Test positive for influenza A	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Swine influenza subtype	H1N1	H1N1	H1N1	H1N1	H1N1	H1N1	H1N2	H1N1	H1N1	H1N1	H1N1

\* NA denotes test not performed or results not available.

† Leukopenia was defined as a white-cell count of less than 5000 per cubic millimeter.

‡ Lymphopenia was defined as a total lymphocyte count of less than 800 cells per cubic millimeter or less than 15% lymphocytes in the total white-cell count.

§ Thrombocytopenia was defined as a total platelet count of less than 150,000 per cubic millimeter.

¶ Reverse-transcriptase–polymerase-chain-reaction (RT-PCR) testing was performed at a local, state, or hospital laboratory.

age has 98 to 100% identical amino acids within itself, the two lineages have diverged from one another by approximately 50 amino acids in the HA gene since their establishment and differ from circulating human seasonal influenza (H1) viruses by more than 100 amino acids. Preliminary data suggest that there is no cross-reactivity between ferret antiserum raised against triple-reassortant swine influenza A (H1) viral isolates and contemporary seasonal human influenza A (H1) viruses. All viral isolates from the 11 patients in this series were susceptible to both adamantanes (amantadine and rimantadine) and neuraminidase inhibitors (oseltamivir and zanamivir).

### DISCUSSION

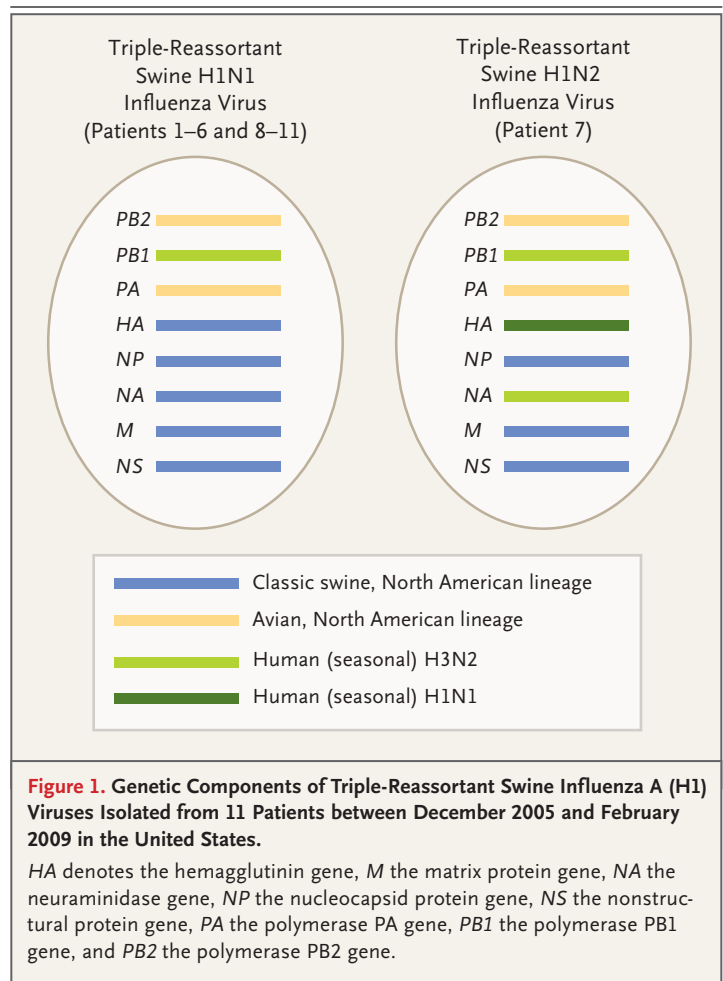
In this report, we describe the clinical and epidemiologic characteristics of 11 cases of laboratory-confirmed infection with triple-reassortant swine influenza A (H1) viruses, which were identified and reported in the United States before the current epidemic of swine-origin influenza A (H1N1) viruses in humans. The patients' exposures to pigs or their environments varied widely in setting and degree, and almost half the patients had not directly touched pigs. The median incubation period was 3.5 days (range, 3 to 9) from the most recent exposure to pigs or their environment, but in general it appeared to be longer than the incubation period for seasonal influenza.<sup>42</sup> However, exposure to a human with a triple-reassortant swine influenza A (H1) virus as the source of infection could not be ruled out as a possible explanation for the apparently longer incubation period. The most frequent signs and symptoms in the patients were nonspecific and indistinguishable from those of human influenza. However, some of the patients with triple-reassortant swine influenza A (H1) virus infection had evidence of severe lower respiratory tract illness and signs that are unusual for influenza, such as diarrhea. Although all patients recovered, a wide spectrum of clinical severity was seen, including two cases of critical illness, one of which occurred in a previously healthy woman.

Although the causes of the increased case reports since December 2005 are unclear, improved virologic surveillance and testing capacity in state public health laboratories and heightened awareness of reporting requirements for cases of novel influenza A may be contributing factors. Alternatively, recent increases in case reporting might re-

flect a true increase in human infections due to changes in zoonotic transmission arising from recent genetic evolution in circulating triple-reassortant swine influenza A (H1) viruses. The phylogenetic data indicate that more than one currently circulating lineage of North American triple-reassortant swine influenza A (H1) viruses has been responsible for recent human infections, with no evidence of adaptive changes shared among them to explain the increase in detected cases.

Few, if any, patients in this series were initially suspected of having swine influenza virus infection. Most cases were discovered through virologic testing of respiratory specimens as part of routine seasonal influenza surveillance, highlighting the importance of routine influenza surveillance in the detection of human infections with either seasonal influenza virus or novel influenza virus of animal origin. Although the incidence of infections with triple-reassortant swine influenza A (H1) viruses in the general population is unknown, the number of cases in our series is most likely an underestimate of the true incidence of swine influenza virus infections in the United States. Several seroepidemiologic studies have consistently shown a higher risk of infection with classic swine influenza virus in occupationally exposed populations than in the general population.<sup>22,24,32</sup>

Given the zoonotic potential of influenza viruses, clinicians should consider animal influenza virus infections in the differential diagnosis for patients presenting with febrile respiratory illness and a recent history of exposure (direct, close, distant, or epidemiologically linked) to swine, poultry, or wild birds (e.g., at agricultural fairs or on farms),<sup>43</sup> especially when human influenza viruses are not circulating in the community. However, during periods when there is evidence of efficient human-to-human transmission of a novel influenza A virus in the community, clinicians should have a low threshold for suspecting, diagnosing, and treating infection appropriately on the basis of the most current recommendations ([www.cdc.gov/flu](http://www.cdc.gov/flu)). Clinicians who suspect swine or other zoonotic influenza virus infections in patients with acute respiratory illness should contact their state or local health department to facilitate appropriate specimen collection and timely diagnostic testing at a state public health laboratory.<sup>4</sup>



Our findings underscore the need for close communication and collaboration between human and animal health agencies for ongoing surveillance, investigation, research, prevention, and control efforts. In the context of current reports of epidemic swine-origin influenza A (H1N1) viruses in the United States and Mexico<sup>4,5</sup> and global concern regarding the emergence of a human influenza pandemic of animal-influenza origin, epidemiologic and laboratory surveillance of interspecies transmission of influenza viruses should be increased, especially in environments in which humans and swine are routinely exposed to each other. Cases of infection in persons who have been exposed to pigs may be sentinels for early zoonotic transmission of novel triple-reassortant swine influenza A (H1) viruses to humans. Consequently, surveillance in settings involving pigs might facilitate early identification and joint responses of public health and animal health agencies to

contain potential outbreaks before widespread community transmission occurs. The mechanism and relative efficiency of indirect and remote exposures to swine influenza (through close proximity, fomites, aerosols, or person-to-person transmission) in the acquisition of human infection with triple-reassortant swine influenza A (H1) viruses require further study. Although uncommon, such cases are likely to continue to occur sporadically, since the triple-reassortant swine influenza A (H1) viruses are endemic in North American swine herds. Clinical and epidemiologic features of human illness, including the usefulness of rapid influenza point-of-care testing and any determinants of antiviral resistance, should continue to be assessed.

Our data are subject to several limitations. Cases of infection with triple-reassortant swine influenza A (H1) viruses were reported through passive influenza surveillance systems; therefore additional cases might have occurred that were not identified. Overall, few patients with influenza-like symptoms are tested for influenza, and even fewer would undergo specific testing that would lead to a diagnosis of infection with triple-reassortant swine influenza A (H1) virus (with severe infections perhaps more likely to be diagnosed).

Complete clinical and epidemiologic data were not available for some cases, especially those identified before the start of systematic data collection.

As recent events suggest, the generation of novel influenza viruses through the reassortment of swine influenza viruses with other human and animal influenza viruses may be inevitable.<sup>7</sup> In this context, the possibility of novel influenza viruses causing epidemic and pandemic disease in large populations of immunologically susceptible humans remains a major ongoing public health threat. Consequently, during interpandemic periods, all human infections with influenza viruses of animal origin, even those that appear to be clinically mild, warrant a thorough public health investigation to assess the epidemiologic and clinical risk to humans.

No potential conflict of interest relevant to this article was reported.

The views expressed in this article are those of the authors and do not necessarily represent the views of the CDC.

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#### REFERENCES

1. Ma W, Kahn RE, Richt JA. The pig as a mixing vessel for influenza viruses: human and veterinary implications. *J Mol Genet Med* 2009;3:158-66.
2. Scholtissek C. Pigs as 'mixing vessels' for the creation of new pandemic influenza A viruses. *Med Princ Pract* 1990;2:65-71.
3. Ito T, Couceiro JN, Kelm S, et al. Molecular basis for the generation in pigs of influenza A viruses with pandemic potential. *J Virol* 1998;72:7367-73.
4. Swine influenza A (H1N1) infection in two children — southern California, March–April 2009. *MMWR Morb Mortal Wkly Rep* 2009;58:400-2.
5. Update: swine influenza A (H1N1) infections — California and Texas, April 2009. *MMWR Morb Mortal Wkly Rep* 2009;58(Dispatch):1-3.
6. Olsen CW. The emergence of novel swine influenza viruses in North America. *Virus Res* 2002;85:199-210.
7. Vincent AL, Ma W, Lager KM, Janke BH, Richt JA. Swine influenza viruses: a North American perspective. *Adv Virus Res* 2008;72:127-54.
8. Shope RE. Swine influenza. III. Filtration experiments and etiology. *J Exp Med* 1931;54:373-85.
9. Olsen CW, Easterday BC, Van Reeth K. Swine influenza. In: Straw BE, Zimmerman JJ, D'Allaire S, Taylor DJ, eds. *Diseases of swine*. 9th ed. Ames, IA: Blackwell Publishing, 2006:469-82.
10. Hinshaw VS, Bean WJ Jr, Webster RG, Easterday BC. The prevalence of influenza viruses in swine and the antigenic and genetic relatedness of influenza viruses from man and swine. *Virology* 1978;84:51-62.
11. Dacso CC, Couch RB, Six HR, Young JF, Quarles JM, Kasel JA. Sporadic occurrence of zoonotic swine influenza virus infections. *J Clin Microbiol* 1984;20:833-5.
12. Gaydos JC, Hodder RA, Top FH Jr, et al. Swine influenza A at Fort Dix, New Jersey (January-February 1976). II. Transmission and morbidity in units with cases. *J Infect Dis* 1977;136:Suppl:S363-S368.
13. Gaydos JC, Hodder RA, Top FH Jr, et al. Swine influenza A at Fort Dix, New Jersey (January-February 1976). I. Case finding and clinical study of cases. *J Infect Dis* 1977;136:Suppl:S356-S362.
14. Hodder RA, Gaydos JC, Allen RG, Top FH Jr, Nowosiwsky T, Russell PK. Swine influenza A at Fort Dix, New Jersey (January-February 1976). III. Extent of spread and duration of the outbreak. *J Infect Dis* 1977;136:Suppl:S369-S375.
15. O'Brien RJ, Noble GR, Easterday BC, et al. Swine-like influenza virus infection in a Wisconsin farm family. *J Infect Dis* 1977;136:Suppl:S390-S396.
16. Patriarca PA, Kendal AP, Zakowski PC, et al. Lack of significant person-to-person spread of swine influenza-like virus following fatal infection in an immunocompromised child. *Am J Epidemiol* 1984;119:152-8.
17. Smith TF, Burgert EO Jr, Dowdle WR, Noble GR, Campbell RJ, Van Scoy RE. Isolation of swine influenza virus from autopsy lung tissue of man. *N Engl J Med* 1976;294:708-10.
18. Thompson RL, Sande MA, Wenzel RP, Hoke CH Jr, Gwaltney JM Jr. Swine-influenza infection in civilians: report of two cases. *N Engl J Med* 1976;295:714-5.
19. Top FH Jr, Russell PK. Swine influenza A at Fort Dix, New Jersey (January-February 1976). IV. Summary and speculation. *J Infect Dis* 1977;136:Suppl:S376-S380.
20. Kimura K, Adlakha A, Simon PM. Fatal case of swine influenza virus in an immunocompetent host. *Mayo Clin Proc* 1998;73:243-5.
21. McKinney WP, Volkert P, Kaufman J. Fatal swine influenza pneumonia during late pregnancy. *Arch Intern Med* 1990;150:213-5.
22. Myers KP, Olsen CW, Setterquist SE, et

- al. Are swine workers in the United States at increased risk of infection with zoonotic influenza virus? *Clin Infect Dis* 2006;42:14-20.
23. Newman AP, Reisdorf E, Beinemann J, et al. Human case of swine influenza A (H1N1) triple reassortant virus infection, Wisconsin. *Emerg Infect Dis* 2008;14:1470-2.
24. Olsen CW, Brammer L, Easterday BC, et al. Serologic evidence of H1 swine influenza virus infection in swine farm residents and employees. *Emerg Infect Dis* 2002;8:814-9.
25. Olsen CW, Karasin AI, Carman S, et al. Triple reassortant H3N2 influenza A viruses, Canada, 2005. *Emerg Infect Dis* 2006;12:1132-5.
26. Wentworth DE, McGregor MW, Macklin MD, Neumann V, Hinshaw VS. Transmission of swine influenza virus to humans after exposure to experimentally infected pigs. *J Infect Dis* 1997;175:7-15.
27. Wentworth DE, Thompson BL, Xu X, et al. An influenza A (H1N1) virus, closely related to swine influenza virus, responsible for a fatal case of human influenza. *J Virol* 1994;68:2051-8.
28. Vincent AL, Swenson S, Lager KM, Gauger PC, Loiacono C, Zhang Y. Characterization of an influenza A virus isolated from pigs during an outbreak of respiratory disease in swine and people during a county fair in the United States. *Vet Microbiol* 2009 January 6 (Epub ahead of print).
29. Myers KP, Olsen CW, Gray GC. Cases of swine influenza in humans: a review of the literature. *Clin Infect Dis* 2007;44:1084-8.
30. Adiego Sancho B, Omenaca Teres M, Martinez Cuenca S, et al. Human case of swine influenza A (H1N1), Aragon, Spain, November 2008. *Euro Surveill* 2009;14(7):pii=19120.
31. Gray GC, McCarthy T, Capuano AW, Setterquist SF, Olsen CW, Alavanja MC. Swine workers and swine influenza virus infections. *Emerg Infect Dis* 2007;13:1871-8.
32. Ramirez A, Capuano AW, Wellman DA, Leshner KA, Setterquist SF, Gray GC. Preventing zoonotic influenza virus infection. *Emerg Infect Dis* 2006;12:996-1000.
33. Robinson JL, Lee BE, Patel J, et al. Swine influenza (H3N2) infection in a child and possible community transmission, Canada. *Emerg Infect Dis* 2007;13:1865-70.
34. Wells DL, Hopfensperger DJ, Arden NH, et al. Swine influenza virus infections: transmission from ill pigs to humans at a Wisconsin agricultural fair and subsequent probable person-to-person transmission. *JAMA* 1991;265:478-81.
35. Bastien N, Bowness D, Burton L, et al. Parotitis in a child infected with triple reassortant influenza A, Canada. *J Clin Microbiol* 2009 April 1 (Epub ahead of print).
36. Council of State and Territorial Epidemiologists position statement: national reporting for initial detections of novel influenza A viruses. Atlanta: CSTE, 2007. (Accessed May 26, 2009, at <http://www.cste.org/PS/2007ps/2007psfinal/ID/07-ID-01.pdf>).
37. Kendal AP, Pereira MS, Skehel JJ, eds. Concepts and procedures for laboratory-based influenza surveillance. Atlanta: Centers for Disease Control and Prevention, 1982.
38. Kendal AP, Cate TR. Increased sensitivity and reduced specificity of hemagglutination inhibition tests with ether-treated influenza B/Singapore/222/79. *J Clin Microbiol* 1983;18:930-4.
39. Bright RA, Medina MJ, Xu X, et al. Incidence of adamantane resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern. *Lancet* 2005;366:1175-81.
40. Sheu TG, Deyde VM, Okomo-Adhiambo M, et al. Surveillance for neuraminidase inhibitor resistance among human influenza A and B viruses circulating worldwide from 2004 to 2008. *Antimicrob Agents Chemother* 2008;52:3284-92.
41. USDA quarterly hogs and pigs report. Washington, DC: National Agricultural Statistics Service, Dec. 2008.
42. Gregg MB. The epidemiology of influenza in humans. *Ann N Y Acad Sci* 1980;353:45-53.
43. Fiore AE, Shay DK, Broder K, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008. *MMWR Recomm Rep* 2008;57:RR-7:1-60.

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