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, 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 na-
tional 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, re-
vealing leukopenia in two, lymphopenia in one, and thrombocytopenia in another.
Four patients were hospitalized, two of whom underwent invasive mechanical venti-
lation. 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 influ-
enz 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.
PIGS 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. 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. Viruses in humans in Mexico, the United States, and other countries have been documented in the past 35 years, 4, 10–28 and 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 become predominant among North American pig herds. 6, 7

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. Classic swine influenza viruses are enzootic among pigs in North America. 8, 10 Cases and clusters of human infections with swine influenza viruses have been reported sporadically in the United States since the 1970s. 4, 10–28 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, 4, 23, 25, 28–30 and serologic studies suggest that people with occupational swine exposure are at highest risk for infection. 22, 24, 31, 32

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

Outside the United States, there have been two published case reports of human infection with triple-reassortant swine influenza A (H1) viruses (both subtype H3N2). 25, 35 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 CDC identified the first human infection with triple-reassortant swine influenza A (H1) viruses in the United States in December 2005. 23

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. 36 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 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.

METHODS

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. 23 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 Nationally 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). 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 though 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

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

* 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.
the basis of reverse-transcriptase–polymerase-
chain-reaction (RT-PCR) testing. (Influenza A vi-
ruses 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 cul-
ture performed at the Michigan State Public Health
Laboratory and was then sent to the CDC for fur-
ther testing.

Samples of influenza A viruses that cannot be
subtyped are routinely forwarded to the Influe-
enza 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-inhi-
bition assay. For swine influenza virus detected
in respiratory-fluid samples from patients, com-
plete genome-sequence analysis was performed
on amplified RNA to determine the constellation
of genes and whether the identified swine influ-
enza virus was a triple-reassortant virus contain-
ing gene segments from swine, avian, and human
influenza viruses. The GenBank accession num-
ers of five triple-reassortant swine influenza A
(H1) viral isolates are listed in the Supplemen-
tary Appendix. The internal gene components of
a triple-reassortant swine influenza A (H1) virus
isolated from ill pigs associated with both pa-
ients in Ohio (Patients 4 and 5) have recently been
reported.

Susceptibility to antiviral drugs, the adaman-
tanes (amantadine and rimantadine), was assessed
by means of the pyrosequencing assay with the
use of viral RNA extracted from the original clinical
specimens, viral isolates, or both. Susceptibility
of the viral isolates to the neuraminidase inhi-
bitors oseltamivir and zanamivir was assessed
by means of the chemiluminescent neuramini-
dase-inhibition assay, with the use of the NAStar
Kit, as previously described.

**RESULTS**

The demographic and epidemiologic characteris-
tics of the patients and their illnesses, including
the incubation period and source of swine expo-
sure, 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. Pa-
tient 3 was part of a family with three other mem-
bers who had suspected, but not laboratory-con-
ﬁrmed, cases of infection with swine inﬂuenza
virus. All patients resided in either the midwest-
ern or southern United States. Four of the 11
cases (36%) were reported in August, 1 (9%) in
October, 2 (18%) in November, 1 (9%) in Decem-
ber, 2 (18%) in January, and 1 (9%) in February.

Exposures to pigs occurred on pig farms (for
three patients), at agricultural fairs (for four pa-
ients), 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 ex-
hibited. The exposure was unknown for one pa-
tient (9%), and another patient (9%) was epide-
miologically 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 in-
ﬂuenza 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 incuba-
tion 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 (Pa-
tients 6 and 10), an uncharacterized immunode-
ﬁciency (Patient 2), or eczema (Patient 11). At least
three patients had received current-season influ-
enza vaccine in the season when the triple-reas-
sortant swine inﬂuenza A (H1) virus infection was
diagnosed; two of the three did not require hos-
pitalization. Among the 10 patients for whom
clinical information was available, symptoms in-
cluded fever (9 patients), cough (10 patients), head-
ache (6 patients), sore throat (6 patients), and diar-
rhea (3 patients). Myalgia, vomiting, and short-
ness 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]).
**Table 2. Clinical Characteristics of 11 Patients Infected with Triple-Reassortant Swine Influenza A (H1) Viruses.**

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

* ND denotes test not done.
† To convert values for temperature to degrees Fahrenheit, subtract 32 and multiply by 5/9.
Four patients (Patients 3, 6, 7, and 9) were hospitalized 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, 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-spectrum 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 (H1N1) 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-gamma28 (see Figure 1 in
the Supplementary Appendix). Although each lineage 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. 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 of the patients were nonspecific and indistinguishable from those of human influenza. However, some of the patients with triple-reassortant swine influenza A (H1) viruses had evidence of severe lower respiratory tract illness and signs that are unusual for influenza, such as diarrhea. All patients recovered, but a wide spectrum of clinical severity was seen, including two cases of critical illness. Although all patients recovered, a wide spectrum of clinical severity was seen, including two cases of critical illness and signs that are unusual for influenza.

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

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

* 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.
tively, recent increases in case reporting might reflect 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.\textsuperscript{22,24,32}

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),\textsuperscript{43} 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 (\url{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.\textsuperscript{4}

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\textsuperscript{4,5} 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

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Genetic Components of Triple-Reassortant Swine Influenza A (H1) Viruses Isolated from 11 Patients between December 2005 and February 2009 in the United States.}
\end{figure}
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. 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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