

Emergence of a Novel Swine-Origin Influenza A (H1N1) Virus in Humans

Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team*

ABSTRACT

BACKGROUND

On April 15 and April 17, 2009, novel swine-origin influenza A (H1N1) virus (S-OIV) was identified in specimens obtained from two epidemiologically unlinked patients in the United States. The same strain of the virus was identified in Mexico, Canada, and elsewhere. We describe 642 confirmed cases of human S-OIV infection identified from the rapidly evolving U.S. outbreak.

METHODS

Enhanced surveillance was implemented in the United States for human infection with influenza A viruses that could not be subtyped. Specimens were sent to the Centers for Disease Control and Prevention for real-time reverse-transcriptase–polymerase-chain-reaction confirmatory testing for S-OIV.

RESULTS

From April 15 through May 5, a total of 642 confirmed cases of S-OIV infection were identified in 41 states. The ages of patients ranged from 3 months to 81 years; 60% of patients were 18 years of age or younger. Of patients with available data, 18% had recently traveled to Mexico, and 16% were identified from school outbreaks of S-OIV infection. The most common presenting symptoms were fever (94% of patients), cough (92%), and sore throat (66%); 25% of patients had diarrhea, and 25% had vomiting. Of the 399 patients for whom hospitalization status was known, 36 (9%) required hospitalization. Of 22 hospitalized patients with available data, 12 had characteristics that conferred an increased risk of severe seasonal influenza, 11 had pneumonia, 8 required admission to an intensive care unit, 4 had respiratory failure, and 2 died. The S-OIV was determined to have a unique genome composition that had not been identified previously.

CONCLUSIONS

A novel swine-origin influenza A virus was identified as the cause of outbreaks of febrile respiratory infection ranging from self-limited to severe illness. It is likely that the number of confirmed cases underestimates the number of cases that have occurred.

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TRIPLE-REASSORTANT SWINE INFLUENZA viruses, which contain genes from human, swine, and avian influenza A viruses, have been identified in swine in the United States since 1998,^{1,2} and 12 cases of human infection with such viruses were identified in the United States from 2005 through 2009.³ On April 15 and April 17, 2009, the Centers for Disease Control and Prevention (CDC) identified two cases of human infection with a swine-origin influenza A (H1N1) virus (S-OIV) characterized by a unique combination of gene segments that had not been identified among human or swine influenza A viruses. As of May 5, 2009, cases of human infection with the same novel virus have also been identified in Mexico, Canada, and elsewhere. We report the first 642 confirmed cases of human infection with this virus in the United States.

METHODS

PATIENTS IN OUTBREAK

On March 30, 2009, in San Diego County, California, a 10-year-old boy with asthma (Patient 1) had an onset of fever, cough, and vomiting. On April 1, he was evaluated in an urgent care clinic, where he received treatment for his symptoms. He recovered from the illness within approximately 1 week. An influenza A virus that could not be sub-typed was identified from a nasopharyngeal specimen that was collected from Patient 1 as part of a clinical trial to evaluate an experimental diagnostic test. As specified by the study protocol, the specimen was then sent to a reference laboratory for further testing and was found to be positive for influenza A virus but negative for both human H1 and H3 subtypes, with the use of real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) testing. On April 15, the CDC received the clinical specimen and identified a novel influenza A (H1N1) virus of swine origin. On the same day, the CDC notified the California Department of Public Health, and an epidemiologic investigation was initiated by state and local health department officials and animal health officials. A viral isolate was found to contain genes from triple-reassortant swine influenza viruses that were known to circulate among swine herds in North America and two genes encoding the neuraminidase and matrix proteins that were most closely related to genes of viruses obtained from

ill pigs in Eurasia, according to results available in GenBank.

On March 28, 2009, in Imperial County, California, a 9-year-old girl (Patient 2) without an epidemiologic link to Patient 1 had an onset of cough and fever. Two days later, she was taken to an outpatient clinic that was participating in an influenza surveillance project. A nasopharyngeal swab was collected at the clinic. Patient 2 was treated with amoxicillin–clavulanate, and she had an uneventful recovery. The nasopharyngeal specimen was sent to the Naval Health Research Center in San Diego, where an influenza A virus that could not be subtyped was identified. The specimen was shipped to the CDC, where it was received on April 17, and a novel influenza A (H1N1) virus of swine origin was identified. The genotype of the virus was similar to that of the virus isolated from the sample obtained from Patient 1. On April 17, both cases were reported to the World Health Organization (WHO), according to the provisions of the International Health Regulations.

Epidemiologic investigation of Patients 1 and 2 revealed that neither patient had a recent history of exposure to swine. According to protocol, the identification of these two epidemiologically unlinked patients with novel S-OIV infection prompted the CDC to notify state and local health departments, which initiated case investigations and implemented enhanced surveillance for influenza A viruses that could not be subtyped. The CDC issued recommendations to clinicians, asking that they consider the diagnosis of S-OIV infection in patients with an acute febrile respiratory illness who met the following criteria: residence in an area where confirmed cases of human infection with S-OIV had been identified, a history of travel to such areas, or contact with ill persons from these areas in the 7 days before the onset of illness. If S-OIV infection was suspected in a patient, clinicians were asked to obtain a nasopharyngeal swab from the patient and to contact their state and local health departments in order to facilitate initial testing of the specimen by RT-PCR assay at the state public health laboratory. State public health laboratories were asked to send all specimens identified as influenza A viruses that could not be subtyped to the CDC for further investigation. Additional cases were identified with the use of a nationally standardized case definition of confirmed swine influenza A (H1N1) vi-

rus infection, which was defined as an acute febrile respiratory illness with the presence of S-OIV confirmed by real-time RT-PCR, viral culture, or both.

This report was exempt from the requirement for institutional review, and the privacy rule of the Health Insurance Portability and Accountability Act did not apply since it was a public health investigation.

REAL-TIME RT-PCR

The CDC has developed a real-time RT-PCR assay to detect seasonal influenza A, B, H1, H3, and avian H5 serotypes. This assay has been approved by the Food and Drug Administration (FDA) and was distributed in December 2008 through U.S. Public Health laboratories and the WHO's Global Influenza Surveillance Network. Primers and probes specific for swine influenza A (H1 and H3 subtypes) were recently developed and tested for use in a modified version of this assay for the detection of human infection with swine influenza viruses. These previously developed reagents allowed the CDC to quickly modify the existing assay for specific detection of S-OIV. Technical details on this assay have been published on the WHO Global Influenza Programme Web site at www.who.int/csr/resources/publications/swineflu/CDCrealtimeRTPCRprotocol_20090428.pdf.

NUCLEOTIDE SEQUENCING AND PHYLOGENETIC ANALYSIS

A total of 49 viral isolates from specimens obtained from patients with confirmed S-OIV infection in 13 states in the United States were grown in MDCK cell cultures. Amplicons for sequencing were generated by reverse transcription, followed by PCR amplification to generate overlapping double-stranded DNA amplicons covering each of eight segments of the influenza virus genome. Primers were designed to bind approximately every 200 to 250 nucleotides along the genome with degenerate bases to allow for sequence variation (for details, see the Supplementary Appendix, available with the full text of this article at NEJM.org).

Sequencing reactions were performed on a standard high-throughput sequencing system with the use of BigDye Terminator, version 3.1 (Applied Biosystems) with 1 mm³ of template double-stranded DNA. Sequence data were assembled and contiguous sequences were generated with the

Sequencher software package, version 4.7 (Gene Codes). All sequence data that were used in this study are available from GenBank (see the Supplementary Appendix for details).

PHYLOGENETIC ANALYSIS

Phylogenetic trees were inferred with the use of the maximum-likelihood method in the GARLI 0.96b7 package. All phylogenetic analyses were visualized in TreeView, version 1.6.6.

RESULTS

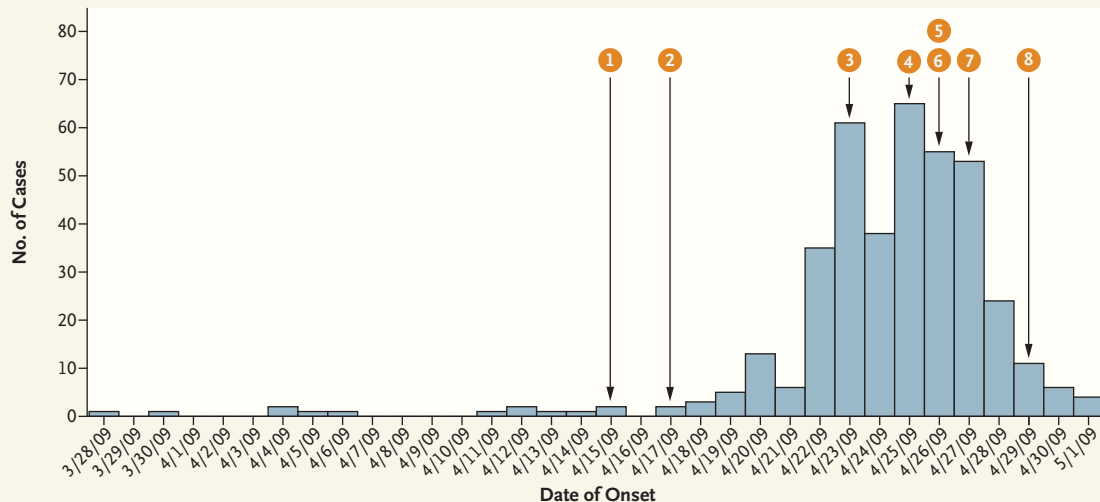
PATIENTS

From April 15 through May 5, 2009, a total of 642 confirmed cases of human infection with the outbreak strain of S-OIV were identified in 41 states (Fig. 1 and 2). Cases of human infection with the outbreak strain of S-OIV were also reported in Mexico, Canada, and other countries.⁴ Among 381 U.S. patients for whom data were available, 18% reported having traveled to Mexico within 7 days before the onset of illness; of these patients, 7 were subsequently hospitalized.

Four clusters of confirmed S-OIV infection were identified early in the investigation in schools and universities in South Carolina (7 students), Delaware (22 students), Texas (5 students), and New York (70 students, school staff, and contacts of students). Some students attending the school in New York where the cluster of confirmed cases occurred and who did not have confirmed infection were reported to have traveled to Mexico during the week preceding the cluster of illnesses. In addition to the confirmed cases that were identified in the four school outbreaks, respiratory illnesses for which samples were not obtained occurred among household and school contacts of patients with confirmed S-OIV infection.

DEMOGRAPHIC AND CLINICAL FEATURES

The age of patients with confirmed S-OIV infection ranged from 3 months to 81 years (Table 1). A total of 40% of patients were between the ages of 10 and 18 years, and only 5% of patients were 51 years of age or older. Among the patients for whom clinical information was available, the most common symptoms were fever (94%), cough (92%), and sore throat (66%). In addition, 25% of patients had diarrhea, and 25% had vomiting.



- 1 April 15, 2009 — CDC identifies S-OIV from specimen taken from Patient 1.
- 2 April 17, 2009 — CDC identifies S-OIV from specimen taken from Patient 2 and the U.S. government notifies World Health Organization (WHO) of Patients 1 and 2 per International Health Regulations.
- 3 April 23, 2009 — CDC conducts first press briefing related to outbreak.
- 4 April 25, 2009 — WHO declares public health emergency of international concern.
- 5 April 26, 2009 — WHO raises global pandemic alert to phase 3, characterized by sporadic cases or small clusters of disease caused by human–animal transmission of an influenza reassortant virus.
- 6 April 26, 2009 — United States declares public health emergency.
- 7 April 27, 2009 — WHO raises global pandemic alert to phase 4, characterized by human-to-human transmission of an animal or human–animal influenza reassortant virus able to cause “community-level outbreaks.”
- 8 April 29, 2009 — WHO raises global pandemic alert to phase 5, characterized by human-to-human transmission of the virus in at least two countries in one WHO region.

Figure 1. Epidemiologic Curve of Confirmed Cases of Human Infection with Swine-Origin Influenza A (H1N1) Virus with Known Date of Illness Onset in the United States (March 28–May 5, 2009).

Data regarding the date of onset of illness were available for 394 patients. This epidemiologic curve does not reflect all cases of infection with S-OIV from March 28 through May 5, 2009, because of the lag in case reporting and laboratory confirmation.

Of the 399 patients with confirmed S-OIV infection for whom hospitalization status was known, 36 (9%) required hospitalization. The age of hospitalized patients ranged from 19 months to 51 years. Of the 22 hospitalized patients for whom data were available, 4 (18%) were children under the age of 5 years, and 1 patient (4%) was pregnant. Nine patients (41%) had chronic medical conditions: a 41-year-old woman with autoimmune disease treated with multiple immunosuppressive agents; a 35-year-old man with Down's syndrome and a history of congenital heart disease; a 33-year-old woman who was 35 weeks pregnant and who had been in relatively good health with a history of mild asthma and psoriasis

that were not being treated with medications; a 22-month-old child with a history of neonatal myasthenia gravis, a ventriculoseptal defect, swallowing dysfunction, and chronic hypoxia; and five patients with asthma alone. Seven patients (32%) reported having traveled to Mexico within 7 days before the onset of illness. Eleven patients (50%) had radiologically confirmed pneumonia, including one patient who had pneumomediastinum, one patient who had necrotizing pneumonia, and one patient who had an empyema that was surgically drained, with no growth from culture of empyema fluid. Eight patients (36%) required admission to an intensive care unit, and four patients (18%) had respiratory failure requiring

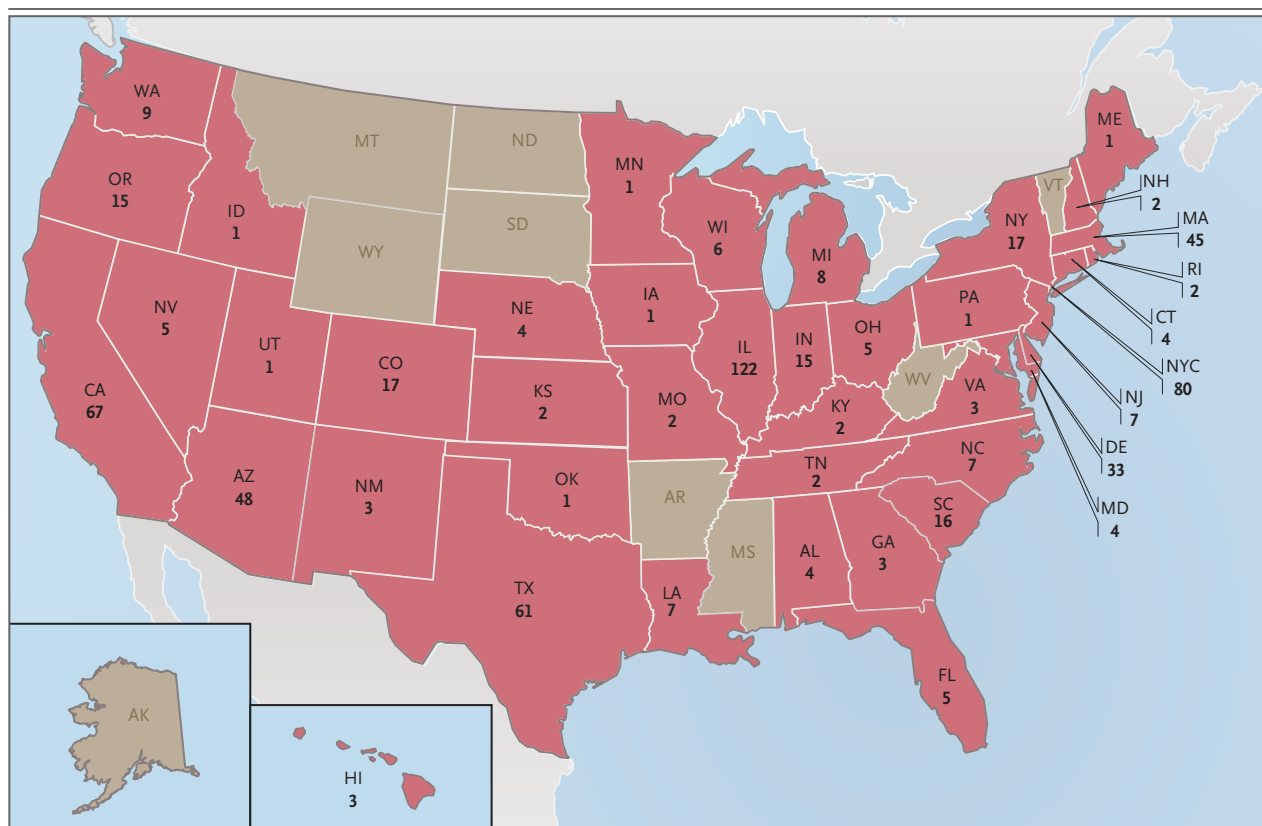


Figure 2. Distribution of 642 Confirmed Cases of Human Infection with Swine-Origin Influenza A (H1N1) Virus in the United States (May 5, 2009).

There were no cases in the District of Columbia. One case involving a resident of Kentucky occurred in Georgia.

mechanical ventilation. Fourteen patients (74%) were treated with oseltamivir after admission to the hospital. As of May 5, 18 of the 22 patients (82%) had recovered from the acute illness; 2 patients — a previously healthy 23-month-old child and a previously healthy 30-year-old woman — remained critically ill with respiratory failure, and the 22-month-old child with neonatal myasthenia gravis and the 33-year-old woman who was pregnant when she became ill died.

LABORATORY ANALYSES

Original clinical samples that were obtained from all 642 patients with confirmed infection and that were received by the CDC were tested with the use of real-time RT-PCR assays for swine influenza, and all the samples were confirmed to be positive for S-OIV. Among the 49 S-OIV isolates from 13 states in the United States that were sequenced at the CDC as of May 5, 2009, all were 99 to 100% identical in all genes. Phylogenetic analysis of se-

quences of all genes of A/California/04/2009, the virus isolated from Patient 1, showed that its genome contained six gene segments (PB2, PB1, PA, HA, NP, and NS) that were similar to ones previously found in triple-reassortant swine influenza viruses circulating in pigs in North America (Table 2). The genes encoding neuraminidase (NA) and M protein (M) were most closely related to those in influenza A viruses circulating in swine populations in Eurasia (Fig. 3). This particular genetic combination of influenza virus segments had not been seen before in the United States or elsewhere. Previous North American triple-reassortant swine influenza A (H1) viruses were known to be composed of the hemagglutinin (HA), nucleoprotein (NP), NA, M, and nonstructural protein (NS) genes, originating from classic swine influenza A viruses; the polymerase PB2 (PB2) and polymerase (PA) genes from avian influenza viruses from the North American lineage; and the polymerase PB1 (PB1) gene from human influenza A viruses.

Table 1. Characteristics and Symptoms of the 642 Patients with Confirmed Swine-Origin Influenza A (H1N1).

Characteristic	Value
Male sex — no./total no. (%)	302/592 (51)
Age	
Median — yr	20
Range — yr	3 mo to 81 yr
Age group — no./total no. (%)	
0–23 mo	14/532 (3)
2–4 yr	27/532 (5)
5–9 yr	65/532 (12)
10–18 yr	212/532 (40)
19–50 yr	187/532 (35)
≥51 yr	27/532 (5)
Student in school outbreak — no./total no. (%)	104/642 (16)
Recent history of travel to Mexico — no./total no. (%)*	68/381 (18)
Clinical symptoms — no./total no. (%)	
Fever	371/394 (94)
Cough	365/397 (92)
Sore throat	242/367 (66)
Diarrhea	82/323 (25)
Vomiting	74/295 (25)
Hospitalization — no./total no. (%)	
Total	36/399 (9)
Had infiltrate on chest radiograph	11/22 (50)
Admitted to intensive care unit	8/22 (36)
Had respiratory failure requiring mechanical ventilation	4/22 (18)
Treated with oseltamivir	14/19 (74)
Had full recovery	18/22 (82)
Vaccinated with influenza vaccine during 2008–2009 season	3/19 (16)
Died	2/36 (6)

* A recent history was defined as travel to Mexico no more than 7 days before the onset of illness.

such as A/swine/Belgium/1/83 H1N1 (Fig. 2 in the Supplementary Appendix). In contrast, the H1N1 triple-reassortant swine influenza virus in the recent human infections contains NA from the North American swine lineage.³ The NA genes from the Eurasian and North American swine influenza virus lineages are highly divergent, with more than 77 differences in amino acids between these lineages. There are two differences in nucleotides and one difference in amino acids between the viruses isolated from specimens taken from Patients 1 and 2. Data from both genetic sequencing and functional neuraminidase-inhibition assays indicate that all S-OIVs that have been examined are susceptible to both oseltamivir and zanamivir, two antiviral medications approved for the prevention and treatment of influenza in the United States (Table 3).

Like NA, the M gene of A/California/04/2009 has the closest homology to the M gene in the Eurasian lineage of swine influenza viruses (Fig. 3 in the Supplementary Appendix). Analyses of the M gene from all samples from the current epidemic showed a serine 31-to-asparagine mutation that confers resistance to M2 blockers (adamantanes), including amantadine and rimantadine. This phenotype is typical for recent Eurasian lineage swine influenza viruses but has not previously been seen in American swine viruses.

Sequences of the PB1, PB2, PA, NP (replication complex), and NS genes obtained from samples from the current epidemic have the closest homology to the genes in the swine influenza viruses that have been recently isolated in the United States from the North American swine lineage. These sequences were 99 to 100% identical at the amino acid level (data not shown; sequences are available from GenBank).

DISCUSSION

Although the HA of S-OIV belongs to the same lineage as the gene found in recent human cases of triple-reassortant influenza A (H1) virus infection, the two genes differ by approximately 20 to 30 amino acids in the HA1 regions alone (Fig. 1 in the Supplementary Appendix). Among viral isolates from the current epidemic, there were up to five nucleotide changes resulting in four amino acid changes in HA.

The NA of S-OIV has the closest homology to the Eurasian lineage of swine influenza viruses,

As of May 5, 2009, a total of 642 cases of human infection with a novel swine-origin influenza A (H1N1) virus have been identified in the United States, and additional cases have been identified in Mexico, Canada, and elsewhere.⁴ On April 25, the WHO declared a public health emergency of international concern, and on April 26, the United States declared a public health emergency. On April 29, the WHO raised the pandemic influenza phase from 4 to 5, indicating that human-to-human transmission of the virus was occurring

in at least two countries in one WHO region. The emergence of S-OIV infection among humans presents the greatest pandemic threat since the emergence of influenza A (H3N2) virus in 1968.

In the United States to date, most confirmed cases of S-OIV infection have been characterized by self-limited, uncomplicated febrile respiratory illness and symptoms similar to those of seasonal influenza (cough, sore throat, rhinorrhea, headache, and myalgia), but approximately 38% of cases have also involved vomiting or diarrhea, neither of which is typical of seasonal influenza. However, some patients have been hospitalized with more severe disease, and two patients have died. The observation that 60% of patients were 18 years of age or younger suggests that children and young adults may be more susceptible to S-OIV infection than are older persons or that because of differences in social networks, transmission to older persons has been delayed. It is also possible that elderly persons may have some level of cross-protection against S-OIV infection from preexisting antibodies against other influenza A (H1N1) viruses, as suggested by serologic studies of the 1976 swine influenza vaccine.^{5,6} A potential case-ascertainment bias may also exist, with more young people being tested as part of outbreaks of S-OIV infection in schools⁷ and fewer older persons being tested for influenza. However, the epidemic is evolving rapidly, and the number of confirmed cases is an underestimate of the number of cases that have occurred.

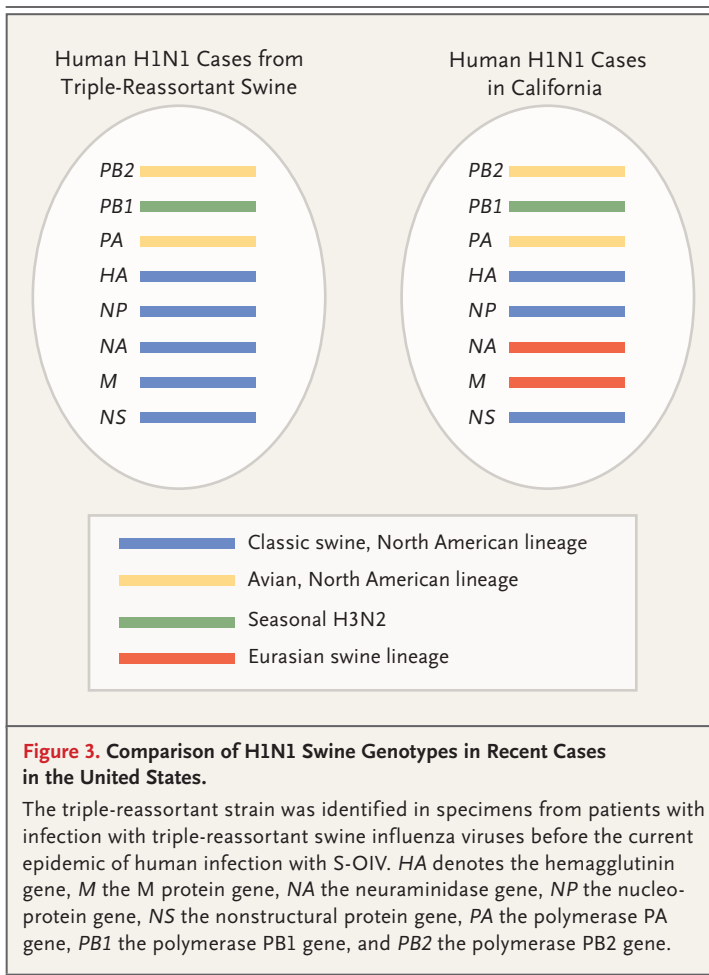
Continued identification of new cases in the United States and elsewhere indicates sustained human-to-human transmission of this novel influenza A virus. The modes of transmission of influenza viruses in humans, including S-OIV, are not known but are thought to occur mainly through the dissemination of large droplets and possibly small-particle droplet nuclei⁸ expelled when an infected person coughs. There is also potential for transmission through contact with fomites that are contaminated with respiratory or gastrointestinal material.^{9,10} Since many patients with S-OIV infection have had diarrhea, the potential for fecal viral shedding and subsequent fecal-oral transmission should be considered and investigated. Until further data are available, all potential routes of transmission and sources of viral shedding should be considered.

The incubation period for S-OIV infection appears to range from 2 to 7 days; however, addi-

Table 2. Phylogenetic Analysis of Sequences of all Genes Identified in A/California/04/2009.*

Gene	Nucleotide Length	NCBI Number	Strain	Lineage	Subtype	Identities	Additional Information
HA	1701	AF455600.1	A/Swine/Indiana/P12439/00	North American swine	H1N2	1621/1701 (95%)	
NA	1410	AJ412690.1	A/Swine/Belgium/1/83	Eurasian swine	H1N1	1302/1410 (92%)	
M	972	AJ293925.1	A/Hong Kong/1774/99	Eurasian swine	H3N2	945/972 (97%)	Human case of H3N2 Eurasian swine influenza
PB2	2264	EU301177.2	A/swine/Korea/JNS06/2004	North American swine	H3N2	2186/2264 (96%)	
PB1	2274	AF342823.1	A/Wisconsin/10/98	North American swine	H1N1	2203/2274 (96%)	
PA	925	AF455717.1	A/Swine/North Carolina/93523/01	North American swine	H1N2	877/925 (94%)	
NP	1497	AF251415.2	A/Swine/Iowa/533/99	North American swine	H3N2	1449/1497 (96%)	
NS	838	AF153262.1	A/Swine/Minnesota/9088-2/98	North American swine	H3N2	809/838 (96%)	

* Data were derived from the Human Genome Project with the use of the Basic Local Alignment Search Tool (BLAST) algorithm (www.ncbi.nlm.nih.gov).



tional information is needed. On the basis of data regarding viral shedding from studies of seasonal influenza, most patients with S-OIV infection might shed virus from 1 day before the onset of symptoms through 5 to 7 days after the onset of symptoms or until symptoms resolve; in young children and in immunocompromised or severely ill patients, the infectious period might be longer.¹¹ Studies of viral shedding to define the infectious period are under way. The potential for persons with asymptomatic infection to be the source of infection to others is unknown but should be investigated.

The clinical spectrum of novel S-OIV infection is still being defined, but both self-limited illness and severe outcomes, including respiratory failure and death, have been observed among identified patients — a wide clinical spectrum similar to that seen among persons infected with earlier strains of swine-origin influenza viruses³

and seasonal influenza viruses.¹² The severe illness and deaths associated with seasonal influenza epidemics are in large part the result of secondary complications, including primary viral pneumonia, secondary bacterial pneumonia (particularly with group A streptococcus, *Staphylococcus aureus*, and *Streptococcus pneumoniae*),¹³⁻¹⁵ and exacerbations of underlying chronic conditions.¹⁶ These same complications may occur with S-OIV infection. Patients who are at highest risk for severe complications of S-OIV infection are likely to include but may not be limited to groups at highest risk for severe seasonal influenza: children under the age of 5 years, adults 65 years of age or older, children and adults of any age with underlying chronic medical conditions, and pregnant women.^{17,18} Of the 22 hospitalized patients with confirmed S-OIV infection who have been identified thus far and for whom data are available, 12 had characteristics (pregnancy, chronic medical conditions, or an age of less than 5 years) that conferred an increased risk of severe seasonal influenza, although none of the patients were 65 years of age or older.

Human infection with novel S-OIV emerged in the United States at a time when seasonal influenza A and B virus activity was decreasing. The cocirculation of human influenza A (H1N1) virus, influenza A (H3N2) virus, or influenza B virus in areas where human cases of S-OIV infection are being identified presents diagnostic and treatment challenges for clinicians. Clinicians should consider the diagnosis of S-OIV infection in patients with febrile respiratory illness seeking care in affected areas or in those who have traveled to affected areas. The CDC has developed a Swine Influenza Virus Real-Time RT-PCR Detection Panel. Under the Project Bioshield Act of 2004, the FDA has issued an emergency-use authorization, allowing for the use of this assay by state public health laboratories to respond to the current outbreak.¹⁹ If S-OIV infection is suspected and diagnostic testing is indicated, clinicians should obtain a nasopharyngeal specimen, notify their local public health department, and arrange for specimens to be tested for S-OIV by Swine Influenza Virus Real-Time RT-PCR Detection Panel, according to local and state public health guidance and after consideration of local laboratory capacity for diagnostic testing.

Two classes of antiviral medication are available for the treatment of seasonal human influ-

enza: neuraminidase inhibitors (oseltamivir and zanamivir) and adamantanes (rimantadine and amantadine). During the 2008–2009 influenza season, almost all circulating human influenza A (H1N1) viruses in the United States were resistant to oseltamivir.²⁰ However, genetic and phenotypic analyses indicate that S-OIV is susceptible to oseltamivir and zanamivir but resistant to the adamantanes.²¹ At this time, the clinical effectiveness of antiviral treatment for S-OIV infection is unknown. As of May 5, 2009, the CDC has recommended that given the severity of illness observed among some patients with S-OIV infection, therapy with neuraminidase inhibitors should be prioritized for hospitalized patients with suspected or confirmed S-OIV infection and for patients who are at high risk for complications from seasonal influenza. As recommendations are updated, they will be posted on the CDC's Web site at www.cdc.gov/h1n1flu/recommendations.htm. The FDA has issued an emergency-use authorization that approves the use of oseltamivir to treat influenza in infants under the age of 1 year (treatment that is normally approved for those 1 year of age or older) and for chemoprophylaxis in infants older than 3 months of age (chemoprophylaxis that is normally approved for children 1 year of age or older).¹⁹

Prevention and control measures for S-OIV are based on our understanding of seasonal human influenza²² and consideration of potential modes of transmission. As of May 5, 2009, the CDC has recommended that health care workers who provide direct care for patients with known or suspected S-OIV infection should observe contact and droplet precautions, including the use of gowns, gloves, eye protection, face masks, and fit-tested, disposable N95 respirators. In addition, patients with confirmed or suspected S-OIV infection should be placed in a single-patient room with the door kept closed, and airborne-infection isolation rooms with negative-pressure handling should be used whenever an aerosol-generating procedure is being performed. Frequent hand washing with soap and water may reduce the risk of infection and transmission.²³ As recommendations are updated, they will be posted at www.cdc.gov/h1n1flu/guidelines_infection_control.htm. Because the novel S-OIV strain is antigenically distinct from the influenza A (H1N1) strain represented in the 2008–2009 influenza vaccine, seasonal influenza

Table 3. Susceptibility of 37 Isolates of Swine-Origin Influenza A (H1N1) Virus to Neuraminidase Inhibitors.*

Variable	Oseltamivir		Zanamivir	
	IC ₅₀	R/S	IC ₅₀	R/S
	<i>nM</i>		<i>nM</i>	
Mean	0.57	S	0.59	S
Median	0.54		0.59	
Seasonal control				
Known susceptibility	0.63	S	0.60	S
Known resistance	265.27	R	1.27	S

* Susceptibility was analyzed with the use of chemiluminescent neuraminidase inhibition assay with the NASTar Kit (Applied Biosystems). IC₅₀ denotes inhibitory concentration of 50%, R resistant, and S susceptible.

vaccination during the 2008–2009 influenza season is not anticipated to provide protection against novel S-OIV infection. A strain of S-OIV has been identified as a potential egg-derived candidate strain for S-OIV vaccine development and has been sent to partner laboratories for evaluation and further development.

Given the rapidly evolving nature of this outbreak, the CDC's recommendations are likely to change as more information becomes available. Clinicians are advised to monitor the H1N1 Influenza Center (NEJM.org) and the CDC Web site (www.cdc.gov/h1n1flu/) for changes in guidance for testing, treatment, and infection control.

In conclusion, we report an outbreak of human infection with a novel influenza A (H1N1) virus of swine origin in the United States, which is spreading through sustained human-to-human transmission in multiple countries. The identification of human S-OIV infection in geographically dispersed countries and across continents demonstrates the ease with which infection can be spread and facilitated by air and land travel and community networks and gatherings. As enhanced surveillance for S-OIV infection is implemented globally, additional cases are expected to be identified. The cases of infection with S-OIV described in this report may provide guidance for clinicians with respect to presenting symptoms and outcomes of infection with this novel virus.

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

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

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APPENDIX

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REFERENCES

- Olsen CW. The emergence of novel swine influenza viruses in North America. *Virus Res* 2002;85:199-210.
- Vincent AL, Ma W, Lager KM, Janke BH, Richt JA. Swine influenza viruses: a North American perspective. *Adv Virus Res* 2008;72:127-54.
- Shinde V, Bridges CB, Uyeki TM, et al. Triple-reassortant swine influenza A (H1) in humans in the United States, 2005–2009. *N Engl J Med* 2009;360:2616-25.
- Influenza A. (H1N1) — update 12. Geneva: World Health Organization, 2009. (Accessed May 26, 2009, at http://www.who.int/csr/don/2009_05_03a/en/index.html.)
- Cate TR, Kasel JA, Couch RB, Six HR, Knight V. Clinical trials of bivalent influenza A/New Jersey/76-A/Victoria/75 vaccines in the elderly. *J Infect Dis* 1977;136:Suppl:S518-S525.
- Dolin R, Wise TG, Mazur MH, Tuazon CU, Ennis FA. Immunogenicity and reactivity of influenza A/New Jersey/76 virus vaccines in normal adults. *J Infect Dis* 1977;136:Suppl:S435-S442.
- Jordan H, Mosquera M, Nair H, France A. Swine-origin influenza A (H1N1) virus infections in a school — New York City, April 2009. *MMWR Morb Mortal Wkly Rep* 2009;58(Dispatch):1-3. (Also available at <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm58d0430a1.htm>.)
- Blachere FM, Lindsley WG, Pearce TA, et al. Measurement of airborne influenza virus in a hospital emergency department. *Clin Infect Dis* 2009 January 9 (Epub ahead of print).
- Bean B, Moore B, Sterner B, Petersen L, Gerding DN, Balfour HH Jr. Survival of influenza viruses on environmental surfaces. *J Infect Dis* 1982;146:47-51.
- Boone SA, Gerba CP. The occurrence of influenza A virus on household and day care center fomites. *J Infect Dis* 2005;191:103-9.
- Carrat F, Vergu E, Ferguson NM, et al. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. *Am J Epidemiol* 2008;167:775-85.

12. Myers KP, Olsen CW, Gray GC. Cases of swine influenza in humans: a review of the literature. *Clin Infect Dis* 2007;44: 1084-8.
13. Hageman JC, Uyeki TM, Francis JS, et al. Severe community-acquired pneumonia due to *Staphylococcus aureus*, 2003-04 influenza season. *Emerg Infect Dis* 2006;12: 894-9.
14. McCullers JA. Insights into the interaction between influenza virus and pneumococcus. *Clin Microbiol Rev* 2006;19: 571-82.
15. O'Brien KL, Walters MI, Sellman J, et al. Severe pneumococcal pneumonia in previously healthy children: the role of preceding influenza infection. *Clin Infect Dis* 2000;30:784-9.
16. Fiore A, Shay D, Broder K, et al. Prevention and control, recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2008;57:1-60.
17. Centers for Disease Control and Prevention. 2008-09 Influenza prevention & control recommendations: influenza vaccination coverage levels. (Accessed May 26, 2009, at <http://www.cdc.gov/flu/professionals/acip/coveragelevels.htm>.)
18. Influenza vaccines. *Wkly Epidemiol Rec* 2005;80:279-87.
19. Update: infections with a swine-origin influenza A (H1N1) virus — United States and other countries, April 28, 2009. *MMWR Morb Mortal Wkly Rep* 2009;58: 431-3.
20. Update: influenza activity — United States, September 28, 2008–April 4, 2009, and composition of the 2009–10 influenza vaccine. *MMWR Morb Mortal Wkly Rep* 2009;58:369-74.
21. Update: drug susceptibility of swine-origin influenza A (H1N1) viruses, April 2009. *MMWR Morb Mortal Wkly Rep* 2009;58:433-5.
22. Bridges CB, Kuehnert MJ, Hall CB. Transmission of influenza: implications for control in health care settings. *Clin Infect Dis* 2003;37:1094-101.
23. Ryan MA, Christian RS, Wohlrahe J. Handwashing and respiratory illness among young adults in military training. *Am J Prev Med* 2001;21:79-83.

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