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販売名（企業名）	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社) 赤十字アルブミン20%静注4g/20mL(日本赤十字社) 赤十字アルブミン20%静注10g/50mL(日本赤十字社) 赤十字アルブミン25%静注12.5g/50mL(日本赤十字社)			世界各国	

研究報告の概要	使用上の注意記載状況・その他参考事項等
○ヒトにおけるブタ由来の新型インフルエンザA型ウイルスの発現 背景：米国において、2009年4月15日と4月17日に、疫学的に無関係な患者2例の検体でブタ由来の新型インフルエンザA型(H1N1)ウイルス(S-OIV)が同定された。同一のウイルス株が、メキシコ、カナダ、その他の地域で検出された。我々は、急速に拡大しつつある米国のアウトブレイクで確定されたヒトS-OIV感染症例642例を報告する。 方法：米国でsubtype分類されていないヒトのインフルエンザA型感染の強化サーベイランスが実行された。検体は、RT-PCR法によるS-OIVの確認検査を行うために、米国疾病対策センターに送られた。 結果：4月15日から5月5日までの期間に、S-OIV感染確定例合計642症例が41の州で確認された。患者の年齢は3ヵ月齢～81歳の範囲で、60%は18歳以下であった。データのある患者のうち、18%にメキシコへの最近の渡航歴があり、16%はS-OIVアウトブレイクが発生した学校で特定された。最も好発した症状は、発熱(患者の94%)、咳(92%)、咽喉炎(66%)であった。25%の患者は下痢を呈し、25%に嘔吐があった。入院の状況が判明した患者399名のうち、36名(9%)が入院を必要とした。データを有する22名の入院患者のうち、12名は季節性インフルエンザ重症化の高いリスクを示す特徴があり、11名は肺炎をきたし、8名は集中治療室での治療を要し、4名は呼吸不全を起こし、2名は死亡した。S-OIVは、今まで同定されていない固有のゲノム組成を持つと判断された。 結論：ブタ由来の新型インフルエンザA型ウイルスは、軽症から重症疾患まで引き起こす、発熱性呼吸器感染症アウトブレイクの原因として特定された。確認された症例数は、実際の発現症例よりも少ない可能性が高い。	赤十字アルブミン20 赤十字アルブミン25 赤十字アルブミン20%静注4g/20mL 赤十字アルブミン20%静注10g/50mL 赤十字アルブミン25%静注12.5g/50mL 血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
2009年4月以降、米国において急速に拡大したブタ由来の新型インフルエンザA型(H1N1)アウトブレイクの確定症例642例の報告である。 インフルエンザウイルスは脂質膜を持つRNAウイルスである。本剤によるインフルエンザウイルス感染の報告はない。本剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれているため、本剤の安全性は確保されていると考える。	日本赤十字社では、問診で発熱などの体調不良者を献血不適としている。更に、平成21年5月18日付薬食血発第0518001号「新型インフルエンザの国内発生に係る血液製剤の安全性確保について」に基づき、新型インフルエンザの患者又は罹患の疑いのある患者と7日以内に濃厚な接触があった人の献血を制限するほか、献血後に新型インフルエンザと診断された場合には当該血漿の使用を禁止している。新型インフルエンザが流行した場合、献血者減少につながることも予想されることから、今後も引き続き情報の収集に努める。

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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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*The members of the Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team are listed in the Appendix.

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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) virus 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

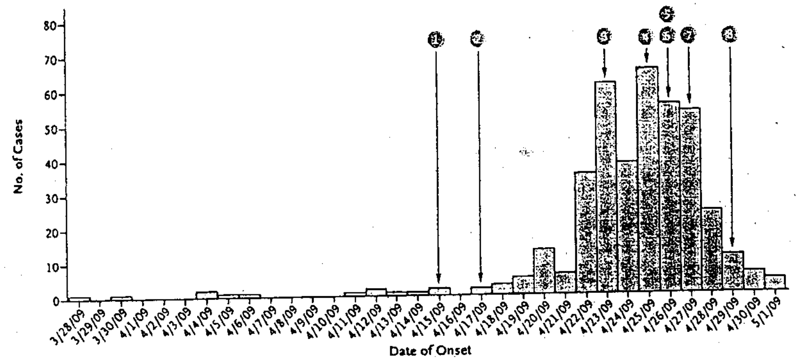
PATIENTS

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

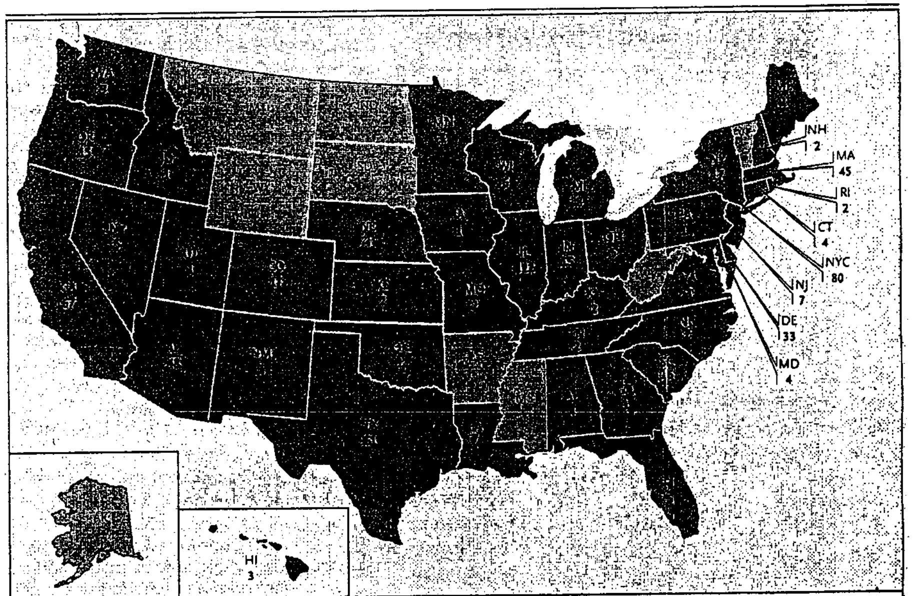


Figure 2. Distribution of 642 Confirmed Cases of Human Infection with Swine-Origin Influenza A (H1N1) Virus in the United States (May 5, 2009).

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 sequences 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.

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, 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

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 schools[7] 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 nuclei[8] 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	H1N1	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).

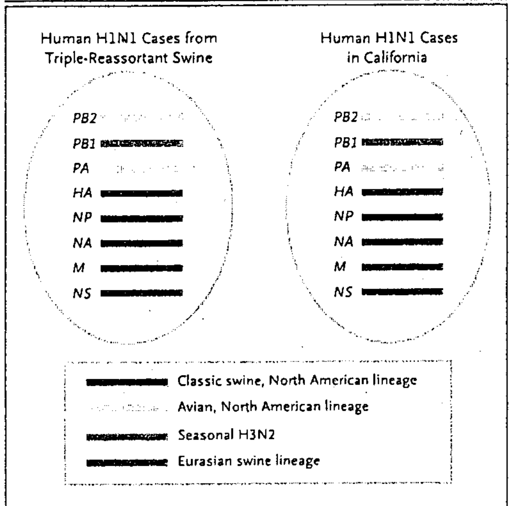


Figure 3. Comparison of H1N1 Swine Genotypes in Recent Cases in the United States.

The triple-reassortant strain was identified in specimens from patients with infection with triple-reassortant swine influenza viruses before the current epidemic of human infection with S-OIV. *HA* denotes the hemagglutinin gene, *M* the M protein gene, *NA* the neuraminidase gene, *NP* the nucleoprotein gene, *NS* the nonstructural protein gene, *PA* the polymerase PA gene, *PB1* the polymerase PB1 gene, and *PB2* the polymerase PB2 gene.

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 viruses[3] 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 influenza: 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 influenza[22] 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 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.

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
	nM		*nM*	
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). IC_{50} denotes inhibitory concentration of 50%, R resistant, and S susceptible.

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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CLINICAL TRIAL REGISTRATION

The *Journal* requires investigators to register their clinical trials in a public trials registry. The members of the International Committee of Medical Journal Editors (ICMJE) will consider most clinical trials for publication only if they have been registered (see N Engl J Med 2004;351:1250-1). Current information on requirements and appropriate registries is available at www.icmje.org/faq.pdf.

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研究報告の概要

オーストラリアの研究者は、ブタインフルエンザに感染する人々の一部が生命を脅かす疾患にかかる理由について手掛かりを発見した可能性がある。それが正しい場合、パンデミックの死亡者を減らす助けになる治療の武器が存在する。グループは、新型 H1N1 ウイルスで重症になった妊婦がウイルスを退けて、身体がワクチンに反応するのを助けることが知られている特定の抗体が低レベルにあることを発見した。

このチームは、Dr. Claire Gordon が抗体レベル（クラスだけではなくサブクラスまで見る検査）をオーダーした時に発見を実現した。サブタイプの低下が特に急速だった重症患者が現れた際にチームが召集され、免疫グロブリン（提供された血液から得られる抗体含有血液製剤）が役に立つかどうか検討した。試験は入院患者が IgG2 抗体レベルが低いことを示した。彼らは ICU の全てのブタインフルエンザ患者の検査を指示し始めた。「ICU が必要な全ての患者で IgG2 が不十分であることを発見した」と、彼はサンフランシスコからのインタビューで言った。データは ICAAC（米国微生物学会年次会議）で示された。

重症例は、軽症だった人々で検出される約 3 分の 1 の IgG2 濃度であった。

2～20%の人々がいくつかの抗体欠損があるが、それらの人々全員が IgG2 欠損であるわけではないことが知られている。危篤状態であった患者の４人のうち、３人が免疫グロブリン治療で生存した。

グループの仕事はまだ仮説を証明していないものの、ブタインフルエンザ患者を看護している北半球の医師は IgG2 レベルを確認して、細菌感染症でしばしば重病の人々に与えられる免疫グロブリンを使用することを考慮すべきであるとチームリーダーの Dr. Grayson は語った。

使用上の注意記載状況・その他参考事項等

2. 重要な基本的注意

(1) 本剤の原材料となる献血者の血液については、HBs 抗原、抗 HCV 抗体、抗 HIV-1 抗体、抗 HIV-2 抗体、抗 HTLV-I 抗体陰性で、かつ ALT(GPT) 値でスクリーニングを実施している。更に、プールした試験血漿については、HIV-1、HBV 及び HCV について核酸増幅検査（NAT）を実施し、適合した血漿を本剤の製造に使用しているが、当該 NAT の検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した血漿を原料として、Cohn の低温エタノール分画で得た画分から人フィブリノゲンを濃縮・精製した製剤であり、ウイルス不活化を目的として、製造工程においてリン酸トリ-n-ブチル(TNBP)／ポリソルベート 80 処理、ウイルス除去膜によるろ過処理、凍結乾燥の後、60℃、72 時間の加熱処理を施しているが、投与に際しては、次の点に十分注意すること。

報告企業の意見

新聞情報ではあるが、オーストラリアの研究者がブタインフルエンザに感染する人々の IgG2 抗体レベル低いと重篤になる可能性があり、治療に免疫グロブリンが有用である可能性があることを示唆する報告である。
インフルエンザA(H1N1)はオルソミクソウイルス科に属し、ビリオンは球形で、直径80～120nmの脂質エンベロープを有する比較的大きなRNAウイルスである。万一、インフルエンザA(H1N1)が原料血漿に混入したとしてもBVDをモデルウイルスとしたウイルスバリデーション試験成績から、本剤の製造工程にて十分に不活化・除去されると考えている。

今後の対応

本報告は本剤の安全性に影響を与えるものではないと考えるので、特段の措置はとらない。

(20)

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THE CANADIAN PRESS

Low levels of key antibodies may lead to severe disease, study suggests

Wed Sep 16, 6:09 PM

By Helen Branswell, Medical Reporter, The Canadian Press

TORONTO - Australian researchers may have uncovered a clue as to why some people who catch swine flu suff life-threatening illness.

And if they are right, there is an existing weapon in the treatment arsenal that could help reduce the pandemic death toll. The group found that pregnant women who became severely ill with the new H1N1 virus had low leve of a particular antibody that is known to fight off viruses and help the body respond to vaccine.

Moderately ill women were much less likely to have significantly suppressed levels of the antibody, the researchers reported. "We all believe we may have stumbled onto something very interesting," said Dr. Lindsay Grayson, director of infectious disease at Austin Health, a network of three hospitals in Melbourne.

"To our knowledge it's the first time that a correlation or an association is being noted between severe influenza o any sort and a subtle but potentially important immune deficiency."

The team made the discovery when Grayson's colleague, Dr. Claire Gordon, ordered a test that looked at antibody levels - not just by class, but looking at individual subtypes within those classes. The call was made in the case of a very sick patient whose decline was particularly rapid, and the team was debating whether immune globulin - a blood product containing antibodies harvested from donated blood - might help.

The testing showed the patient had low levels of an antibody called IgG2, which Grayson admitted came as a surprise. They started ordering tests on all their swine flu patients in ICU.

"What we found was almost everyone, all the patients who needed ICU were IgG2 deficient," he said in an interview from San Francisco, where the data were presented at ICAAC, the annual meeting of the American Society for Microbiology. Severe cases had IgG2 levels that were about one-third of those detected in people who were moderately ill.

While the work was only done in pregnant women, Grayson and others said it would be useful to look to see if this deficiency might explain why a small subset of swine flu cases become gravely ill while most people only suffer through a bout of the flu.

It's known that between two and 20 per cent of people have some antibody deficiency, he said, though not all of those people would be IgG2 deficient.

Three of four critically ill patients treated with immune globulin survived, defying predictions of those caring for them.

Dr. Donald Low, chief microbiologist at Toronto's Mount Sinai, said the findings are exciting, if preliminary, and might explain why aboriginals seem to be at greater risk of developing severe disease if they contract swine flu. He suggested the hypothesis should be studied further.

"It would be a fishing expedition, but obviously worthwhile." "I think the bottom line is that this is obviously something that has to be looked into.

And it may have therapeutic implication. ... It could be a marker for women at higher risk if they get infected to get more severe disease."

But Dr. Anand Kumar, an intensive care specialist from Winnipeg who treated a lot of severely ill swine flu patients in the spring and early summer, was not as optimistic.

"The results are just what I'd expect in any group of critically ill," he said by email. Kumar, who is also an infectious diseases specialist, said it is not uncommon for all antibody levels to drop with critical illness and the more severe the sickness, the steeper the drop.

But he does think the notion of treating pandemic flu patients with antibodies harvested from other people makes sense, though he believes the immune globulin should be from people who've recovered from swine flu and have antibodies specific to the virus.

Grayson admitted they can't say at this point whether there is a cause-and-effect relationship at work here, meaning low IgG2 levels in the patients predisposed them to suffering from more severe disease once they caught the virus.

But he doesn't believe the reverse is at play, that the infection caused the low IgG2 levels.

"We don't think that influenza is causing this deficiency. We think that instead the influenza is picking out those people who have the deficiency," he said.

The numbers are admittedly small and will require further study, likely in the Northern Hemisphere. Swine flu rates are dropping in Melbourne, Grayson said.

Still, 16 of 19 severely ill patients had very low IgG2 levels, compared to three of 20 with moderate illness.

The team looked at healthy pregnant women and found that about 60 per cent of them were mildly deficient in IgG2 levels, which leads them to believe this may be one of the immune system changes that occurs to allow a pregnant woman to carry a foreign body - a fetus - without rejecting it. But Grayson said the group needs to follow women after they deliver to see if their IgG2 levels rise to normal levels.

Grayson said while the group's work hasn't proven their hypothesis, Northern Hemisphere doctors caring for the sickest of swine flu patients in the weeks and months to come should consider checking IgG2 levels and using immune globulin, which is often given to people seriously ill with some bacterial infections.

"In many ways, this is applying a general principle that we apply to bacteria diseases to now say well, 'Gee, we've made this interesting observation. This might work for influenza,'" he said.

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