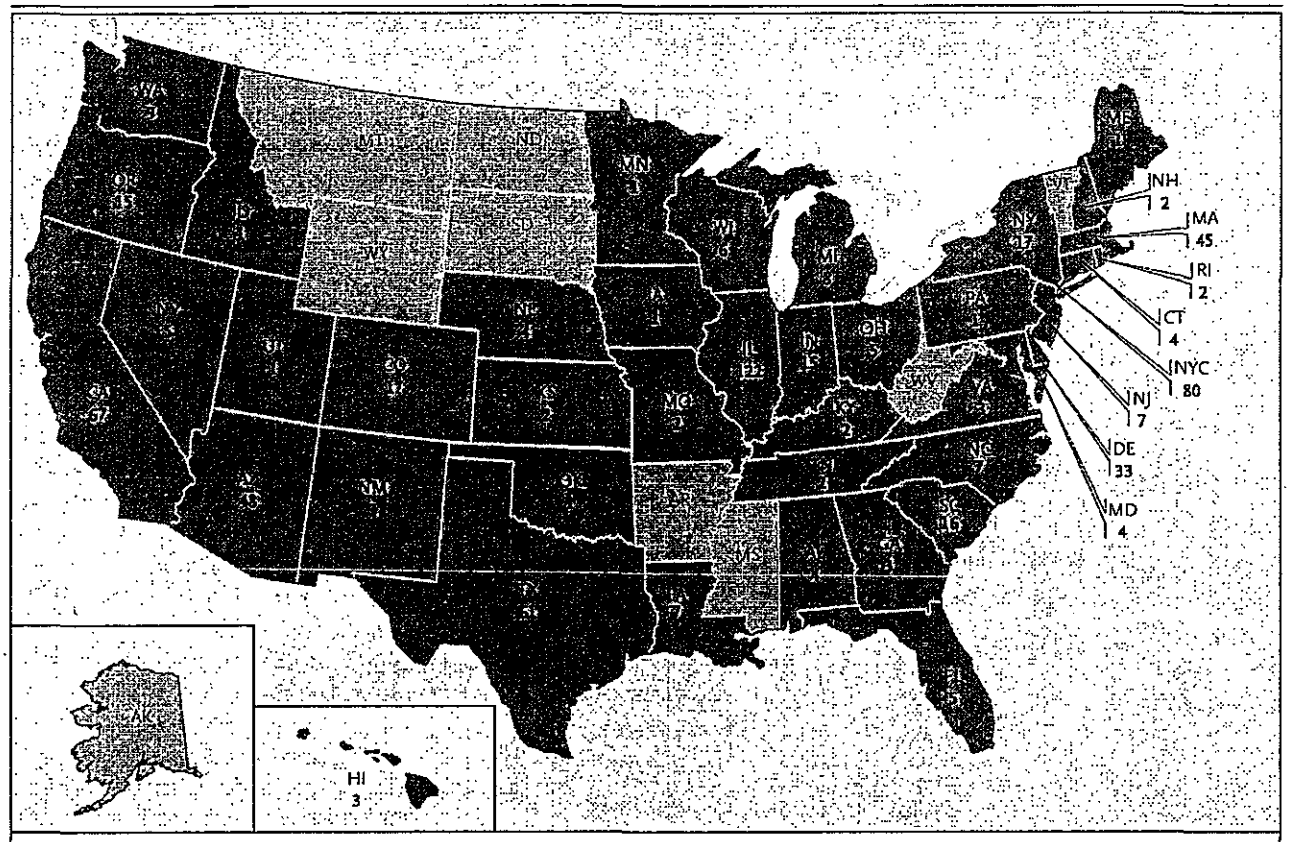

Figure 2. Distribution of 642 Confirmed Cases of Human Infection with Swine-Origin Influenza A (H1N1) Virus in the United States (May 5, 2009).

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	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).

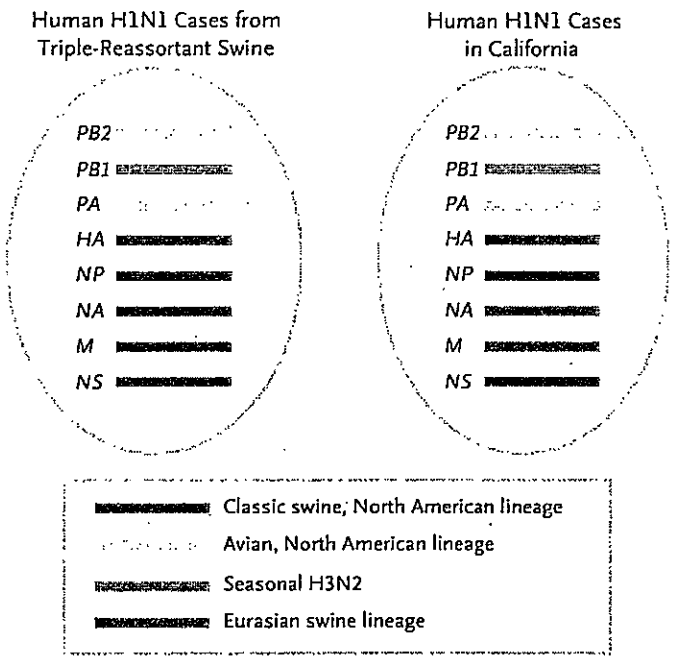

Figure 3. Comparison of H1N1 Swine Genotypes in Recent Cases in the United States.

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 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 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.

We thank all the local and state public health officials and our colleagues at the CDC for their contributions to this article.

APPENDIX

The members of the Novel Swine-Origin Influenza A (H1N1) Investigation Team are as follows (asterisks indicate members of the Epidemic Intelligence Service, Office of Workforce and Career Development, Centers for Disease Control and Prevention): *Alabama Department of Public Health:* S. Massingale, T. Pippin, S. Davidson; *Alaska Department of Health and Social Services:* J. Butler, J. McLaughlin, E. Funk; *Arizona Department of Health Services:* S.M. Anderson, L. Erhart, K.K. Komatsu; *American Samoa Government Department of Health:* S. Lemusu, S. Mageo, I. Tuliau; *California Department of Public Health:* M. Acosta, O. Anderson, G. Chavez, S. Chen, D. Cottam, C. Fritz, D. Gilliss, C. Glaser, J. Glover, H. Guevara, K. Hansen, K. Harriman, R. Harrison, D. Hatch, H. Kayman, J. Kim, A. Kimura, A. Kjemtrup, R. Kreutzer, J. Louie, B. Lyman, B. Maryas, S. Messenger, E. Moyer, R. Neiman, H. Rosen, J. Rosenberg, L. Rudolph, K. Salibay, M. Samuels, R. Schechter, D. Schnurr, R. Shaikh-Lesko, C. Sheets, C. Starling, B. Sun, J. Talarico, D. Vugia, C. Wheeler, K. Winter, D. Wohlfeiler, E. Yamada; *Colorado Department of Public Health and Environment:* J. Kenfield, K. Gershman, N. Calonge; *Connecticut Department of Public Health:* M. Carter, J. Fontana, P. Mshar; *Dickinson County Health Department:* L. Davies, B.L. Holmes; *District of Columbia Department of Health:* C. Glymph, G. Lum, R. Diggs; *Florida Department of Health:* L. Ball, J. Hamilton, R. Hopkins; *Guam Department of Public Health and Social Services:* L. Duguies, A. Mathew, J.T. O'Mallan; *Georgia Department of Public Health:* D. Cole, C.L. Drenzek, T. Parrott; *Hawaii Department of Health:* J.L. Elm, M. Nakata, S.Y. Park; *Houston Department of Health and Human Services:* D. Awosika-Olumo; *Illinois Department of Public Health:* C. Finley, K. Hunt, K. McMahon; *Imperial County Public Health Department:* P. Kriner, K. Lopez, M. Rios; *Indiana State Department of Health:* M. Glazier, J. Monroe, S. Richards; *Iowa Department of Public Health:* A. Garvey, M. Harris, P. Quinlisk; *Kansas Department of Health and Environment:* M.C. Bañez Ocfemia, D.C. Hunt, D. Neises, I.C. Trevino-Garrison; *Kentucky Department of Public Health:* K.E. Humbaugh, E.C. Lutterloh, T.J. Sugg; *Louisiana Department of Health and Hospitals:* J. Guidry, S. Martin, R. Ratard; *Maine Department of Health and Human Services:* K. Gensheimer, A. Pelletier, S. Robinson; *Maryland Department of Health and Mental Hygiene:* D. Blythe; *Massachusetts Department of Public Health:* N.M. Cocoros, S.M. Lett, S. Smole; *Michigan Department of Community Health:* J. Collins, S. Vagasky, E. Wells; *Mississippi State Department of Health:* M. Currier, P. Byers, R. James; *Minnesota Department of Health:* A. DeVries, R. Lynfield, S. Magnan; *Missouri Department of Health and Senior Services:* K. Oo, S. Patrick, G. Turabelidze; *Montana Department of Health and Human Services:* B. Barnard, A. Weber, J. Mason; *Naval Health Research Center:* D. Faix, P. Blair; *Navy Medical Center, San Diego, CA:* S. Sherman, J. Tueller; *Nebraska Department of Health and Human Services:* T. Safranek, J. Schaeffer, R. Williams; *New Hampshire Department of Health and Human Services:* C. Adamski, E. Talbot, S. Mcrae-Stern; *New Jersey Department of Health and Human Services:* C. Genese, M. Malavet, L. McHugh; *New York City Department of Health and Mental Hygiene:* Swine Flu Investigation Team; *New York State Department of Health:* K. St. George, K. Noyes, P.F. Smith; *North Carolina Department of Health and Human Services:* J. Casani, J. Engel, Z. Moore; *North Dakota Department of Health:* D. Dwelle, M. Feist, T. Wiedrich; *Ohio Department of Health:* J. O'Quin, K. Boyland, B. Bradley, F. Smith, K. Smith, K. Winpisinger; *Oklahoma State Department of Health:* K. Bradley, M. McDermott, K. Rayno; *Oregon Department of Health:* P. Cieslak, K. Hedberg, M. Kohn; *Pennsylvania Department of Health:* J. Lute, M. Moll, S. Ostroff; *Randolph Air Force Base 12th Medical Group:* S.Y. Green; *Rhode Island Department of Health:* U. Bandy, T. Cooper, E. King; *San Antonio Metropolitan Health District:* B.J. Alsip, F.A. Blevins, F.A. Guerra, R. Sanchez; *San Diego County Health and Human Services:* M. Ginsberg, J. Johnson, A. Maroufi, D. Sunega; *South Carolina Department of Health and Environmental Control:* D. Drociuk, J. Gibson, G. Potter; *South Dakota Department of Health:* V. Horan, B. Jameson, L. Kightlinger; *Tennessee Department of Health:* T. Jones, D. Kirschke, K. Moore; *Texas Department of State Health Services:* C. Alaniz, C. Davis, R. Espinoza, V.P. Fonseca, S. Guerra, B. Hannemann, G. Heseltine, R. Jones, C. Morgan, *N. Pascoe, S. Penfield, C. Rohr-Allegrini, T. Shim,* J. Taylor, R. Taylor, N. Walea, D. Zane; *US Air Force School of Aerospace Medicine:* L.E. Sinclair, M.J. Shim, P.M. Lucas, T.F. Gibbons; *Utah Department of Health:* T. Garrett, R. Herlihy, R. Rolfs; *Vermont Department of Health:* M. Celotti, P. Kelso, S. Schoenfeld; *Virginia Department of Health:* D. Helentjaris, J.L. Pearson, K. Remley; *Washington State Department of Health:* R. Gautom, M. Goldoft, A. Marfin; *Wisconsin Department of Health Services:* J. Davis, S. Foldy, R. Heffernan; *Wyoming Department of Health:* A. Erickson, R. McClinton, C. Van Houten; *Centers for Disease Control and Prevention:* G. Armstrong, A. Ades, A. Balish, J. Barnes, E. Barzilay, L. Berman, R. Beato, M. Bell, M. Biggerstaff, D.M. Blau,* C. Braden, L. Brammer, J. Bresee, D. Callahan, L. Chen, N. Cohen, A. Coh, L. Conklin, N. Cox, J. Cortes, C. Davis, V. Deyde, D. Dee,* M. Desai,* N. Dharan,* R. Donis, S. Doshi,* S. Emery, S. Epperson, D. Erdman, D.H. Esposito,* B. Fields, A. Fiore, G. Fischer, M. Fisher, M. Fonseca, A. Foust, A. Fowlkes, A. Fry, R.M. Gladden,* H. Gould, D. Gross, A. Guh,* H. Hall, G.S. Han,* B.H. Harcourt, M. Hillman, M. Honein, M. Hughes, I. Hwang, W. Hwang,* D. Iuliano,* M. Iwomoto, M.L. Jackson,* J.L. Jaeger,* K. Janusz,* V. Jarquin,* D. Jernigan, J. Jernigan, J. Johnson, A. Kallen, J. Katz, K. Katz,* A.A. Klimov, K. Kniss, L. Kamimoto, C. Kent, P. Kutty, F. Loustalot,* M. Lynch, T. Maccannella, M. Massoudi, C. McDonald, M. McMorrow, M. Menon, S. Montiel, M. Moore, O.W. Morgan,* C.L. Mattson,* R. Novak, T. Nguyen, M. Nowell, M. Okomo-Adhiambo, S. Olsen, C. O'Reilly, O. Oyervides, *M.K. Patel,* S. Parks,* *P. Peebles, P. Peters,* C. Petrowski, *T. Pilishvili, P. Pordell,* S. Redd, *C. Reed,* M. Reynolds, S.L. Schrag, C. Scott, F. Serdarevic,* W. Sessions, C. Smith, A. Srinivasan, E. Staples, A. Stuart, D. Sugerman,* A. Suryaprasad,* D. Swerdlow, B. Shu, B.J. Silk,* J.E. Tate, K. Toews, J.R. Verani, J. Villenueva, R. Wang, S. Waterman, A. Williams, P. Weidle, E. Weston, K.H. Wu, H. Wu,* J. Zipprich.

REFERENCES

1. Olsen CW. The emergence of novel swine influenza viruses in North America. Virus Res 2002;85:199-210.
2. Vincent AL, Ma W, Lager KM, Janke BH, Richt JA. Swine influenza viruses: a North American perspective. Adv Virus Res 2008;72:127-54.
3. 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.
4. 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.)
5. *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.
6. Dolin R, Wise TG, Mazur MH, Tuazon CU, Ennis FA. Immunogenicity and reactogenicity of influenza A/New Jersey/76 virus vaccines in normal adults. J Infect Dis 1977;136:Suppl:S435-S442.
7. 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.)
8. *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).
9. 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.
10. Boone SA, Gerba CP. The occurrence of influenza A virus on household and day care center fomites. J Infect 2005;51: 103-9.
11. 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, Wohlrabe J. Handwashing and respiratory illness among young adults in military training. Am J Prev Med 2001;21:79-83.

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.

別紙様式第2-1
番号17

医薬品
医薬部外品　　研究報告　調査報告書
化粧品

識別番号・報告回数			報告日	第一報入手日 2009年9月18日	新医薬品等の区分 該当なし	厚生労働省処理欄
一般的名称	乾燥人フィブリノゲン		研究報告の公表状況	THE CANADIAN PRESS/2009/09/16	公表国 カナダ	
販売名（企業名）	フィブリノゲンHT静注用1g「ベネシス」　(ベネシス)					

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。

報告企業の意見	今後の対応
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。	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。

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。

YAHOO! NEWS CANADA

Back to Story - Help

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 suffer 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 levels 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 of 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.

-

Follow Canadian Press Medical Writer Helen Branswell's flu updates on Twitter at CP-Branswell

---

Need help? Want to send feedback?

別紙様式第2-1
番号16

医薬品
医薬部外品　　研究報告　調査報告書
化粧品

識別番号・報告回数			報告日	第一報入手日 2009年7月24日	新医薬品等の区分	厚生労働省処理欄
一般的名称	①ポリエチレングリコール処理人免疫グロブリン ②人免疫グロブリン	研究報告の公表状況	CDC/MMWR 58(28);773-778/2009/07/24	公表国 アメリカ		
販売名 (企業名)	①献血ヴェノグロブリン-IH ヨシトミ（ベネシス） ②グロブリン-Wf（ベネシス）					

研究報告の概要

てんかん発作、脳炎、脳症、ライ症候群と他の神経学的障害を含む神経学的合併症は、季節性インフルエンザAまたはBウイルスの気道感染に関連していることは以前に報告されているが、新型インフルエンザA（H1N1）ウイルスでは報告されていなかった。
2009年5月28日、保健社会福祉省（DCHHS）は新型インフルエンザA（H1N1）ウイルス感染症と関連した神経学的合併症を発症し5月18日～5月28日にかけてテキサス州ダラスの病院に入院した小児4人についてCDCに報告した。
この報告は、それら4人の症例の臨床的特徴をまとめたものである。
患者は7歳、10歳、11歳、17歳でインフルエンザ様疾患（ILI）とてんかん発作の徴候、精神状態の変化が認められた。4人の患者のうち3人は、脳波図（EEG）の異常を示した。
4人の患者全てにおいて、鼻咽頭検体から新型インフルエンザA（H1N1）ウイルスRNAが検出されたが、脳脊髄液（CSF）では検出されなかった。
抗ウイルス薬療法は、オセルタミビル（4人の患者）とリマンタジン（3人の患者）であった。
4人全ての患者は、完全に回復し、退院後、神経学的後遺症は見られなかった。
これらの所見は、新型インフルエンザA（H1N1）ウイルスによる気道感染の後でも季節性インフルエンザと同様に神経学的合併症が発現することがあることを示している。

使用上の注意記載状況・その他参考事項等

代表として献血ヴェノグロブリン-IH ヨシトミの記載を示す。
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ポリエチレングリコール4000処理、DEAEセファデックス処理等により人免疫グロブリンを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において60℃、10時間の液状加熱処理及びろ過膜処理（ナノフィルトレーション）及びpH3.9～4.4の条件下での液状インキュベーション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	今後の対応
新型インフルエンザA（H1N1）ウイルスについても、季節性インフルエンザと同様に神経学的合併症が発現し得るとの報告である。 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。	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。

(21)

MMWR
Weekly
July 24, 2009 / 58(28);773-778

Neurologic Complications Associated with Novel Influenza A (H1N1) Virus Infection in Children --- Dallas, Texas, May 2009

Neurologic complications, including seizures, encephalitis, encephalopathy, Reye syndrome, and other neurologic disorders, have been described previously in association with respiratory tract infection with seasonal influenza A or B viruses (*1*--*2*), but not with novel influenza A (H1N1) virus. On May 28, 2009, the Dallas County Department of Health and Human Services (DCHHS) notified CDC of four children with neurologic complications associated with novel influenza A (H1N1) virus infection admitted to hospitals in Dallas County, Texas, during May 18--28. This report summarizes the clinical characteristics of those four cases. Patients were aged 7--17 years and were admitted with signs of influenza-like illness (ILI) and seizures or altered mental status. Three of the four patients had abnormal electroencephalograms (EEGs). In all four patients, novel influenza A (H1N1) viral RNA was detected in nasopharyngeal specimens but not in cerebrospinal fluid (CSF). Antiviral therapy included oseltamivir (four patients) and rimantadine (three patients). All four patients recovered fully and had no neurologic sequelae at discharge. These findings indicate that, as with seasonal influenza, neurologic complications can occur after respiratory tract infection with novel influenza A (H1N1) virus. For children who have ILI accompanied by unexplained seizures or mental status changes, clinicians should consider acute seasonal influenza or novel influenza A (H1N1) virus infection in the differential diagnosis, send respiratory specimens for appropriate diagnostic testing, and promptly initiate empirical antiviral treatment, especially in hospitalized patients.

Case Identification

Since April 22, DCHHS has requested all hospitals in Dallas County to report details concerning patients admitted with novel influenza A (H1N1) virus infection. As of July 20, DCHHS had identified 405 persons with laboratory-confirmed novel influenza A (H1N1) virus infection in the greater Dallas area, including 44 hospitalized patients. No deaths had been reported. Of confirmed novel influenza A (H1N1) virus infections, 83% were in patients aged <18 years. Among these pediatric cases, 145 children, including 26 who were hospitalized, were identified through the Children's Medical Center of Dallas (CMCD) laboratory-based surveillance program. Medical records from admission and discharge for all hospitalized H1N1 patients are routinely screened by DCHHS epidemiology staff. Characteristics of hospitalized patients are compiled on an ongoing basis, with further investigation of cases noted to have unusual features and severe illness.

A patient with acute neurologic complications associated with novel influenza A (H1N1) virus infection was defined as having laboratory-confirmed novel influenza A (H1N1) virus infection of the respiratory tract associated with seizures, encephalopathy, or encephalitis within 5 days of ILI symptom onset, without evidence of an alternative etiology. Encephalopathy was defined as

altered mental status lasting ≥24 hours. Encephalitis was defined as encephalopathy plus two or more of the following: fever ≥100.4°F (≥38.0°C), focal neurologic signs, CSF pleocytosis, EEG indicative of encephalitis, or abnormal neuroimaging indicative of infection or inflammation (*1--2*).

During April 22--July 20, seven possible cases of neurologic complications associated with novel A (H1N1) virus infection were identified. Three cases were excluded because the neurologic complications were determined to have alternative etiologies (e.g., hypocalcemia and apnea related to prematurity) or did not meet the case definition (e.g., altered mental status for <24 hours). Of the remaining four cases described in this report, one patient (patient A) was initially reported by a community hospital in Dallas on May 18. The three other cases were reported by CMCD to DCHHS during May 23--27. No additional cases had been reported in Dallas County through July 20.

Nasopharyngeal swab specimens collected from all three patients admitted to CMCD were tested for influenza A and B antigens by either Directigen EZ Flu A+B rapid enzyme immunoassay (EIA) (BD [Becton, Dickinson, and Company], Sparks, Maryland), QuickVue Influenza A+B test (EIA) (Quidel, San Diego, California), or D3 Ultra direct fluorescent assay (Diagnostic Hybrids, Athens, Ohio). All positive specimens were sent to DCHHS, and novel influenza A (H1N1) virus was identified by real-time reverse transcription--polymerase chain reaction (rRT-PCR) using CDC-approved primers and probe sets. All CSF samples were tested at CDC using rRT-PCR for influenza, enteroviruses, parechovirus, adenovirus, and human parainfluenza virus serotype 3. CSF for patients B and D were tested for additional viruses by a commercial laboratory (Viracor).*

Case Reports

Patient A. On May 17, a previously healthy black male aged 17 years visited a community hospital emergency department after 1 day of fever reaching 102.6°F (39.2°C), cough, headache, dizziness, and weakness. Influenza A was diagnosed by EIA, and the patient was discharged home with a prescription for oseltamivir. The patient was admitted the next day to another community hospital because of increased generalized weakness, disorientation to place, and markedly slow and intermittent responsiveness to questions. On physical examination, the patient was noted to be confused and unable to provide history of his own illness. He also was unable to lift his arms above his shoulders or stand. He had taken 1 dose of oseltamivir the morning of admission. A computed tomography (CT) head scan revealed pan-sinusitis, and CSF was normal (Table). The patient received ceftriaxone for 2 days, which was discontinued when CSF bacterial cultures indicated no growth. He received oseltamivir throughout his hospital admission. His mental status returned to normal on day three. He was discharged on day four with no apparent sequelae and completed a 5-day total course of oseltamivir.

Patient B. On May 23, a previously healthy Hispanic male aged 10 years was taken to a Dallas community hospital via emergency medical services after a 3-minute generalized tonic-clonic seizure and subsequent postictal mental state. The seizure occurred after 4 days of fever reaching 104.0°F (40.0°C), cough, decreased appetite, and fatigue. His family reported that the patient had contact with another child with ILI symptoms before the patient's illness onset. Upon initial evaluation in the emergency department, the patient was afebrile. A chest radiograph revealed a left lower lobe infiltrate, and a CT head scan was normal except for an incidentally noted single punctuate calcification in left frontal cortex. Influenza A was detected in a nasopharyngeal swab specimen by EIA. Three hours later, the patient had a second 3-minute generalized seizure. Intravenous (IV) lorazepam and ceftriaxone were administered, and the patient was transferred to a CMCD intensive-care unit.

On admission to CMCD, the patient was febrile, confused, and drowsy. He had difficulty

answering questions and made frequent inappropriate attempts to get out of bed. CSF analysis was normal. He was administered IV fosphenytoin to prevent additional seizures, vancomycin and ceftriaxone for empirical treatment of bacterial pneumonia, supplemental oxygen via bilevel positive airway pressure for oxygen saturations <92%, and anticonvulsants. Over the ensuing 2 days, he had intermittent fevers reaching 102.0°F (38.9°C). On hospital day four, he had a prolonged partial complex seizure with focal onset (eye deviation to the right) and secondary generalization, lasting 30--40 minutes, which eventually was controlled by 4 doses of IV lorazepam and a bolus of IV fosphenytoin. Oseltamivir and rimantadine were initiated. Brain magnetic resonance imaging (MRI) with magnetic resonance angiography was normal, and an EEG was consistent with encephalopathy (Table). His mental status returned slowly to baseline by hospital day seven, when he was discharged without apparent sequelae to continue levetiracetam, amoxicillin, and clindamycin, and complete a 5-day course of oseltamivir.

Patient C. On May 26, a white male aged 7 years with a history of a simple febrile seizure 1 year previously was taken to a Dallas community hospital via emergency medical services after a seizure and 2 days of cough, nasal congestion, and fatigue. On the day of admission, he had been found at home on the floor, with tonic movements of his upper and lower extremities lasting at least 2 minutes. On admission to the community hospital, he was noted to have postictal drowsiness and a temperature of 100.8°F (38.2°C). A diagnosis of influenza A was made by EIA. Blood tests, CSF, and a CT head scan were normal (Table).

The patient was transferred the same day to CMCD, where he exhibited normal mental status and no fever or seizures. A brain MRI showed nonspecific white matter abnormalities not characteristic of infection or inflammation. Localized cerebral dysfunction was evident on EEG (Table). Oseltamivir and rimantadine were started on hospital day one, and the patient was discharged on hospital day three without any neurologic sequelae, to complete a 5-day course of both antivirals and to continue levetiracetam until reassessment by neurologists in 3 months.

Patient D. On May 27, a black male aged 11 years with a history of asthma was taken to CMCD because of 1 day of fever and vomiting. A household contact, his grandmother, had an upper respiratory infection 3 days before his illness. One day before admission, he had a fever of 102.0° F (38.9°C), fatigue, headache, abdominal pain, and vomiting, and was given bismuth subsalicylate twice and one 81 mg aspirin. At CMCD, he was febrile. Neurologic examination revealed ataxia. Soon after admission, the patient had a seizure consisting of episodic eye rolling and tongue thrusting. An EIA test for influenza A was positive, and oseltamivir, rimantadine, cefotaxime, and acyclovir were initiated.

During the first 2 hospital days, the patient was disoriented, had visual hallucinations, had difficulty responding to questions and following commands, had slow speech, and required supplemental oxygen via facemask for mild hypoxia and hypopnea attributed to decreased respiratory drive associated with encephalopathy. Chest radiograph was normal. An EEG was consistent with encephalopathy, and a CT head scan was normal (Table). The patient's mental status returned to normal by hospital day four. He completed a 5-day course of oseltamivir.

Reported by: *AS Evans, MD, S Agadi, MD, JD Siegel, MD, Univ of Texas Southwestern Medical Center; WM Chung, MD, JT Carlo, MD, Dallas County Health and Human Svcs, Dallas, Texas. TM Uyeki, MD, J Sejvar, MD, S Lindstrom, PhD, D Erdman, DrPH, S Oberste, PhD, National Center for Immunization and Respiratory Diseases; SJ Olsen, PhD, Div of Emerging Infections and Surveillance Svcs, National Center for Preparedness, Detection, and Control of Infectious Diseases; F Dawood, MD, OW Morgan, PhD, EIS officers, CDC.*

Editorial Note: Infection with seasonal influenza virus can be associated with neurologic complications (*1--2*), but the frequency with which these occur with novel influenza A (H1N1) virus infection is unknown. This is the first report describing patients with neurologic

complications associated with novel influenza A (H1N1) virus infection. The severity of the neurologic disease in the four patients described in this report was less than the typical disease described in two studies of neurologic complications associated with seasonal influenza (*1--2*), which included reports of severe static encephalopathy and death. Only two of the four patients described in this report had seizures, and none died or had neurologic sequelae at discharge. Considering that clusters of influenza-associated encephalopathy in children have been reported during previous community outbreaks of seasonal influenza (*1--2*) and that children appear to be infected with novel influenza A (H1N1) virus more frequently than adults (*3*), additional neurologic complications in children are likely to be reported as the pandemic continues. Clinicians should consider influenza associated encephalopathy in the differential diagnosis of children with ILI and seizures or mental status changes, and remain aware of the potential for severe neurologic sequelae associated with seasonal or novel influenza A (H1N1) virus infection.

Neurologic complications in children associated with seasonal influenza have included acute cognitive and behavioral problems, focal neurologic deficits, and death from neurologic complications (*4*). Influenza-associated neurologic complications are estimated to account for up to 5% of cases of acute childhood encephalitis or encephalopathy (*4*) and were reported in 6% of influenza-associated deaths among children during one influenza season (2003--04) in the United States (*5*). The epidemiology of influenza-associated encephalopathy has been described extensively in Japan, where incidence has appeared to be higher than in other countries (*1*). In Japan, approximately 80% of influenza-associated encephalopathy cases occur in children aged <5 years (*1,6*), and neurologic signs typically develop within 1--2 days of influenza symptom onset (*1,6*). Manifestations have included seizures, altered consciousness, incoherence, irritability, and psychotic behaviors (*1,6*). Outcomes reported in one case-series from Japan ranged from complete resolution (in nearly 50% of cases), to mild (20%) or severe neurologic sequelae (10%), to death (20%) (*6*).

Neuroimaging results in influenza-associated encephalopathy might be normal, but in severe cases, abnormalities can include diffuse cerebral edema and bilateral thalamic lesions. EEG might show diffuse abnormalities (*1,2,4*). Only rarely is influenza virus detected in CSF, suggesting that neurologic manifestations might be an indirect effect of influenza respiratory tract infection (*2,7*).

For patients with respiratory illness and neurologic signs, diagnostic testing for possible etiologic pathogens associated with neurologic disease, including influenza viruses, is recommended (*8*). Health-care providers also should consider a diagnosis of Reye syndrome in patients with viral illness and altered mental status. Although one of the patients described in this report, patient D, received a salicylate-containing product and aspirin, no evidence of Reye syndrome was observed. Salicylates and salicylate-containing products should not be administered to children with influenza or other viral infections because of the increased risk for developing Reye syndrome (*9*).

Antiviral treatment should be initiated as soon as possible for any hospitalized patient with neurologic symptoms and suspected seasonal influenza or novel influenza A (H1N1) virus infection (2).† Although respiratory specimens should be obtained for appropriate diagnostic testing before administering antiviral agents, clinicians should not wait for the results before beginning treatment. Antiviral medications have been shown to decrease the risk for complications from influenza (*10*); however, the effectiveness of antiviral treatment to prevent influenza-associated encephalopathy sequelae is unknown. Clinicians also should send respiratory specimens for appropriate diagnostic testing. Although no vaccination against novel influenza A (H1N1) virus is available currently, CDC recommends that all children aged >6 months receive annual seasonal influenza vaccination to prevent illness and complications from infection with seasonal influenza virus strains.§

Acknowledgments

The findings in this report are based, in part, on contributions by E Brock, A Varghese, Children's Medical Center Dallas; L Miller, Charleton Methodist Hospital; C Rowe, Las Colinas Medical Center; J Stringer, E Bannister, PhD, J Rodriguez, S Hughes, K Baumgart, MPH, A Friedman, Dallas County Health and Human Svcs; and N Pascoe, Texas Dept of State Health Svcs.

References

1. Morishima T, Togashi T, Yokota S, et al. Encephalitis and encephalopathy associated with an influenza epidemic in Japan. Clin Infect Dis 2002;35:512--7.
2. Maricich SM, Neul JL, Lotze TE, et al. Neurologic complications associated with influenza A in children during the 2003--2004 influenza season in Houston, Texas. Pediatrics 2004;114:e626--33.
3. Dawood FS, Jain S, Finelli L, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med 2009;360:2605--15.
4. Amin R, Ford-Jones E, Richardson SE, et al. Acute childhood encephalitis and encephalopathy associated with influenza: a prospective 11-year review. Pediatr Infect Dis J 2008;27:390--5.
5. Bhat N, Wright JG, Broder KR, et al. Influenza-associated deaths among children in the United States, 2003--2004. N Engl J Med 2005;353:2559--67.
6. Wada T, Morishima T, Okumura A, et al. Differences in clinical manifestations of influenza-associated encephalopathy by age. Microbiol Immunol 2009;53:83--8.
7. Ito Y, Ichiyama T, Kimura H, et al. Detection of influenza virus RNA by reverse transcription-PCR and proinflammatory cytokines in influenza-virus-associated encephalopathy. J Med Virol 1999;58:420--5.
8. Tunkel A, Glaser C, Bloch K, et al. Management of encephalitis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2008;47:303--27.
9. Belay ED, Bresee JS, Holman RC, Khan AS, Shahriari A, Schonberger LB. Reye's syndrome in the United States from 1981 through 1997. N Engl J Med 1999;340:1377--82.
10. Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. Arch Intern Med 2003;163:1667--72.

* Viruses detected by the Luminex multiplex respiratory viral panel [xTAG] are influenza A and B; parainfluenza 1, 2, and 3; respiratory syncytial virus A and B; adenovirus; human metapneumovirus; and rhinovirus.

† CDC guidance on antiviral therapy available at http://www.cdc.gov/h1n1flu/recommendations.htm.

§ CDC recommendations for seasonal influenza vaccination available at http://www.cdc.gov/mmwr/pdf/rr/rr5707.pdf.

TABLE. Selected characteristics and laboratory, radiologic, and neurodiagnostic results for four patients with neurologic complications associated with novel influenza A (H1N1) virus infection* — Dallas, Texas, May 2009

Characteristic	Patient A	Patient B	Patient C	Patient D
Age (yrs)	17	10	7	11
Sex	Male	Male	Male	Male
Race/Ethnicity	Black, non-Hispanic	Hispanic	White, non-Hispanic	Black, non-Hispanic
Dates of hospitalization	May 18--21	May 23--29	May 26--28	May 27--30

Neurologic complication(s) diagnosed	Encephalopathy	Seizures, encephalopathy	Seizures	Encephalopathy
Interval from respiratory illness onset to neurologic symptoms (days)	1	4	2	1
Fever (maximum temperature)	102.6°F (39.2°C)	104.0°F (40.0°C)	100.8°F (38.2° C)	102.0°F (38.9°C)
Admission laboratory data				
Serum electrolytes, chemistry	Normal (except initial creatinine 1.3 mg/dL [normal range for age: 0.3--1.0 mg/dL])	Normal	Normal (except sodium 131 mmol/L [normal range: 134--146 mmol/L])	Normal
Liver function tests (U/L)	ND†	AST§ 28, ALT¶ 51, GGT** 29	AST 36, ALT 12, GGT 29	AST 41, ALT 27, GGT <10, ammonia 28 mmol/L (repeat testing normal)
Blood bacterial culture	ND	*S. epidermidis*, Micrococcus (contaminants), no growth x2	No growth	No growth
Urine bacterial culture	ND	ND	ND	No growth
Other	Creatine kinase 75 U/L (normal range: 22--269 U/L)	Urine toxicology screen positive for benzodiazepines only	---	Urine toxicology screen positive for caffeine, salicylate, and acetaminophen; serum salicylate level <1 mg/dL
Cerebrospinal fluid (CSF) analysis				
WBC†† (per mm3) (differential)	2 (differential ND)	2 (65%L 31%M)	4 (differential ND)	4 (95%L 5%M)
RBC§§ (per mm3)	18	0	2	1
Glucose (mg/dL) (normal range: 50--80 mg/dL)	39	63	58	65
Protein (mg/dL) (normal range: 10--45 mg/dL)	37	50	15	21
Bacterial culture	No growth	No growth	No growth	No growth
Neurodiagnostic testing				
Computed tomography	No intra-parenchymal abnormality; pan-sinusitis	Single punctuate calcification in left frontal cortex	No intracranial abnormality	No intracranial abnormality; sphenoid sinusitis
			Cortical nonspecific	

Magnetic resonance imaging	ND	No parenchymal abnormality	scattered T2 hyperintense foci within the cerebral white matter	No intracranial abnormality
Electroencephalogram	ND	Generalized continuous polymorphic delta slowing, without epileptogenic focus; consistent with mild/moderate encephalopathy	Midline parietal intermittent polymorphic delta slowing, without epileptogenic focus; consistent with localized cerebral dysfunction	Posterior background slowing, no epileptiform activity; consistent with mild encephalopathy
Viral testing and antiviral therapy				
Influenza EIA¶¶	Positive***	Positive	Positive	Positive
Influenza DFA†††	ND	ND	ND	Positive
CSF influenza rRT-PCR§§§	Negative	Negative	Negative	Negative
rRT-PCR	Enteroviruses: negative	Enteroviruses: negative	Enteroviruses: negative	Enteroviruses: negative
	Parechovirus: negative	Parechovirus: negative	Parechovirus: negative	Parechovirus: negative
	Adenovirus: negative	Adenovirus: negative	Adenovirus: negative	Adenovirus: negative
	HPIV-3¶¶¶: negative	HPIV-3: negative	HPIV-3: negative	HPIV-3: negative

TABLE. (Continued) Selected characteristics and laboratory, radiologic, and neurodiagnostic results for four patients with neurologic complications associated with novel influenza A (H1N1) virus infection — Dallas, Texas, May 2009

Characteristic	Patient A	Patient B	Patient C	Patient D
				HSV†††† rRT-PCR: negative
Other testing	ND	CSF respiratory viral panel (RVP)****	ND	Enterovirus rRT-PCR: negative
				CSF RVP: negative
Antiviral therapy	Oseltamivir	Oseltamivir and rimantadine	Oseltamivir and rimantadine	Oseltamivir and rimantadine

* A patient with acute neurologic complications associated with novel influenza A (H1N1) virus infection was defined as having laboratory-confirmed novel influenza A (H1N1) virus infection of the respiratory tract associated with seizures, encephalopathy, or encephalitis within 5 days of influenza-like illness symptom onset, without evidence of an alternative etiology. Encephalopathy was defined as altered mental status lasting ≥24 hours. Encephalitis was defined as encephalopathy plus two or more of the following: fever ≥100.4°F (≥38.0°C), focal