MAJOR ARTICLE

Outbreak of Variant Influenza A(H3N2) Virus in the United States

Michael A. Jhung,[1] Scott Epperson,[1] Matthew Biggerstaff,[1] Donna Allen,[8] Amanda Balish,[1] Nathelia Barnes,[1] Amanda Beaudoin,[9] LaShondra Berman,[1] Sally Bidol,[6] Lenee Blanton,[1] David Blythe,[15] Lynnette Brammer,[1] Tiffany D'Mello,[1] Richard Danila,[7] William Davis,[1] Sietske de Fijter,[12] Mary DiOrio,[12] Lizette O. Durand,[2] Shannon Emery,[1] Brian Fowler,[12] Rebecca Garten,[1] Yoran Grant,[5] Adena Greenbaum,[2] Larisa Gubareva,[1] Fiona Havers,[2] Thomas Haupt,[13] Jennifer House,[8] Sherif Ibrahim,[14] Victoria Jiang,[1] Seema Jain,[1] Daniel Jernigan,[1] James Kazmierczak,[13] Alexander Klimov,[1] Stephen Lindstrom,[1] Allison Longenberger,[10] Paul Lucas,[4] Ruth Lynfield,[7] Meredith McMorrow,[1] Maria Moll,[10] Craig Morin,[7] Stephen Ostroff,[10] Shannon L. Page,[12] Sarah Y. Park,[11] Susan Peters,[6] Celia Quinn,[3] Carrie Reed,[1] Shawn Richards,[8] Joni Scheftel,[7] Owen Simwale,[10] Bo Shu,[1] Kenneth Soyemi,[4] Jill Stauffer,[8] Craig Steffens,[1] Su Su,[1] Lauren Torso,[10] Timothy M. Uyeki,[1] Sara Vetter,[7] Julie Villanueva,[1] Karen K. Wong,[2] Michael Shaw,[1] Joseph S. Bresee,[1] Nancy Cox,[1] and Lyn Finelli[1]

[1]Influenza Division, National Center for Immunization and Respiratory Disease, and [2]Epidemic Intelligence Service assigned to the Influenza Division, Centers for Disease Control and Prevention, Atlanta, Georgia; [3]Epidemic Intelligence Service assigned to the Ohio Department of Health, Columbus; [4]Illinois Department of Public Health, Springfield; [5]Epidemic Intelligence Service assigned to the Illinois Department of Public Health, Springfield; [6]Michigan Department of Community Health, Lansing; [7]Minnesota Department of Health, St. Paul; [8]Indiana State Department of Health, Indianapolis; [9]Epidemic Intelligence Service assigned to the Pennsylvania Department of Health, Harrisburg; [10]Pennsylvania Department of Health, Harrisburg; [11]Hawaii Department of Health, Honolulu; [12]Ohio Department of Health, Columbus; [13]Wisconsin Department of Health Services, Madison; [14]West Virginia Bureau for Public Health, Charleston; and [15]Maryland Department of Health and Mental Hygiene, Baltimore

(See the Editorial Commentary by Gray and Cao on pages 1713–4.)

Background. Variant influenza virus infections are rare but may have pandemic potential if person-to-person transmission is efficient. We describe the epidemiology of a multistate outbreak of an influenza A(H3N2) variant virus (H3N2v) first identified in 2011.

Methods. We identified laboratory-confirmed cases of H3N2v and used a standard case report form to characterize illness and exposures. We considered illness to result from person-to-person H3N2v transmission if swine contact was not identified within 4 days prior to illness onset.

Results. From 9 July to 7 September 2012, we identified 306 cases of H3N2v in 10 states. The median age of all patients was 7 years. Commonly reported signs and symptoms included fever (98%), cough (85%), and fatigue (83%). Sixteen patients (5.2%) were hospitalized, and 1 fatal case was identified. The majority of those infected reported agricultural fair attendance (93%) and/or contact with swine (95%) prior to illness. We identified 15 cases of possible person-to-person transmission of H3N2v. Viruses recovered from patients were 93%–100% identical and similar to viruses recovered from previous cases of H3N2v. All H3N2v viruses examined were susceptible to oseltamivir and zanamivir and resistant to adamantane antiviral medications.

Conclusions. In a large outbreak of variant influenza, the majority of infected persons reported exposures, suggesting that swine contact at an agricultural fair was a risk for H3N2v infection. We identified limited person-to-person H3N2v virus transmission, but found no evidence of efficient or sustained person-to-person transmission. Fair managers and attendees should be aware of the risk of swine-to-human transmission of influenza viruses in these settings.

Keywords. influenza; outbreak; pandemic; variant influenza.

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Correspondence: Michael Jhung, MD, MPH, Influenza Division, Centers for Disease Control and Prevention, 1600 Clifton Road NE, MS A-32, Atlanta, GA 30333 (mjhung@cdc.gov).

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Variant influenza viruses are swine-origin influenza A viruses that are rare causes of influenza virus infection in humans. From January 2005 through June 2011, only 35 US cases of variant influenza virus infection were reported to the Centers for Disease Control and Prevention (CDC) [1, 2]. Because variant influenza

viruses are antigenically distinct from circulating human influenza A(H1) and A(H3) subtypes, cross-protective immunity against variant viruses conferred by recent infection with seasonal influenza viruses or influenza vaccination is likely to be limited. Although most previous cases of influenza due to variant viruses have occurred after contact with swine, sporadic person-to-person transmission demonstrates the epidemic and pandemic potential of these viruses [2].

From July 2011 to March 2012, 13 cases of infection with an influenza A(H3N2) variant virus (H3N2v) possessing the matrix (M) gene from the 2009 pandemic H1N1 virus (pdm09 H1N1) were identified [2–4]. The emergence of this new H3N2v virus with the pdm09 H1N1 M gene in 2011 was concerning because animal models suggested that the M gene contributed to increased transmissibility of the pdm09 H1N1 virus in swine and humans [5–7]. Furthermore, serological studies suggested broad susceptibility to this H3N2v virus among segments of the population, notably young children [8–12]. In July 2012, the CDC received reports of new H3N2v cases in multiple states, prompting an investigation to determine the magnitude of the outbreak, assess possible person-to-person transmission of H3N2v virus, and identify risk factors for illness. In this report, we summarize the epidemiology of a multistate outbreak of H3N2v, the largest outbreak of human infections with a swine-origin influenza virus since the 2009 H1N1 pandemic.

METHODS

Because human infection with novel influenza A viruses, including variant influenza viruses, are notifiable conditions, such cases are investigated and reported to the CDC. We identified H3N2v cases as part of national influenza surveillance in accordance with reporting guidelines of the Nationally Notifiable Diseases Surveillance System [13]. Because the initial cases occurred in patients who were reported to have developed illness after swine contact at agricultural events, we encouraged increased respiratory specimen collection and real-time reverse transcription polymerase chain reaction (rRT-PCR) testing of patients with influenza-like illness (ILI) during and after agricultural fairs and in areas where H3N2v cases had been identified. We defined a case as laboratory confirmation of H3N2v by rRT-PCR test results consistent with H3N2v virus infection [14, 15].

We used a standard investigation form to collect information describing clinical course, medical treatment, and exposure risks in the 7 days prior to illness onset. We investigated possible cases of person-to-person transmission of H3N2v virus under the assumption that the incubation period for the majority of swine-to-human transmission of H3N2v would be ≤4 days [16–20]. We considered a case to be the result of person-to-person transmission if (1) no direct (touching) or indirect (coming within approximately 6 feet or attending an agricultural event where swine were exhibited) swine contact was identified, or (2) swine contact occurred >4 days before illness onset and a close contact with ILI onset prior to the patient's illness onset was identified. We ascertained daily swine exposure during the 7 days prior to illness onset and calculated the mean incubation period and 95% confidence interval for cases, excluding those where swine exposure information was unavailable or there was no swine exposure reported. To account for uncertainty in cases with multiple instances of swine exposure prior to illness onset, we fit exposure dates to a γ distribution using maximum likelihood estimation methods [21].

Respiratory specimens from patients underwent diagnostic testing for influenza at public health laboratories using the CDC Human Influenza rRT-PCR Diagnostic Panel. At the CDC, H3N2v virus in all respiratory specimens was confirmed by rRT-PCR testing; amplified RNA of a subset of specimens also underwent full genome sequencing or partial genome sequencing (sequencing of the entire genes encoding the surface proteins (hemagglutinin [HA], neuraminidase [NA], and M genes). We assessed susceptibility to antiviral medications by (1) phenotypic neuraminidase inhibition assays on viral isolates, and (2) sequencing of the NA and M genes to identify known genetic markers associated with decreased sensitivity to NA inhibitors and adamantanes.

We estimated the number of agricultural fairs that occurred during the outbreak using a list of 1097 US events registered with the International Association of Fairs and Expositions (IAFE); this list represents approximately 40% of fairs occurring annually in the United States (personal communication, IAFE Marla Calico, December 2012). We maintained all data in a secure database at the CDC and conducted analysis using Microsoft Excel and SAS version 9.2 (SAS Institute, Cary, North Carolina) software. This activity was deemed to be a public health response to an outbreak and not considered to be human subjects research in accordance with federal human subjects protection regulations and exempt from review by an institutional review board.

RESULTS

We identified 306 cases of H3N2v with illness onset from 9 July through 7 September 2012 (Figure 1). With the exception of Hawaii, in each state reporting cases, the number of swine per county was calculated to be in the upper quartile of swine density in the United States (Figure 2). More than 80% of H3N2v cases were identified in Ohio and Indiana, and the outbreak affected 28% and 26% of counties in these states, respectively (Table 1). For 297 (97%) cases for which information was available, the median duration between the date of illness onset

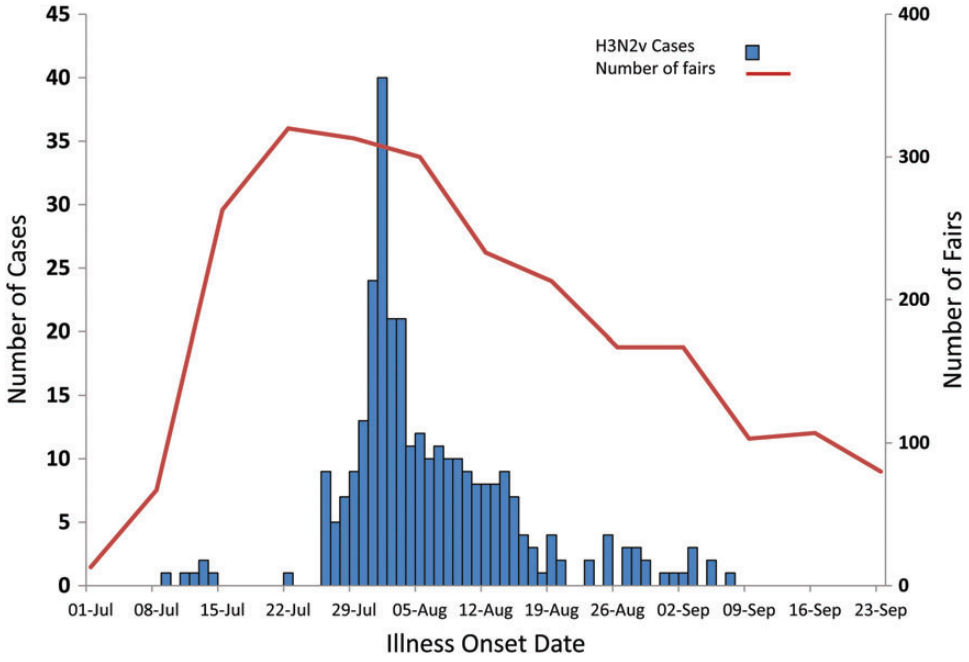

Figure 1. Epidemic curve of confirmed cases of influenza A(H3N2) variant virus infection in the United States, July–September 2012 (N = 306) and estimate of the number of fairs occurring in the United States. Data on fairs were obtained from a directory of registered fairs from the International Association of Fairs and Expositions, which includes information on the location and date of voluntarily registered fairs (approximately 40% of the estimated 3000 fairs held annually in the United States). Estimates of the number of total fairs occurring each week were obtained by extrapolating the time distribution of registered fairs to the estimated number of total fairs.

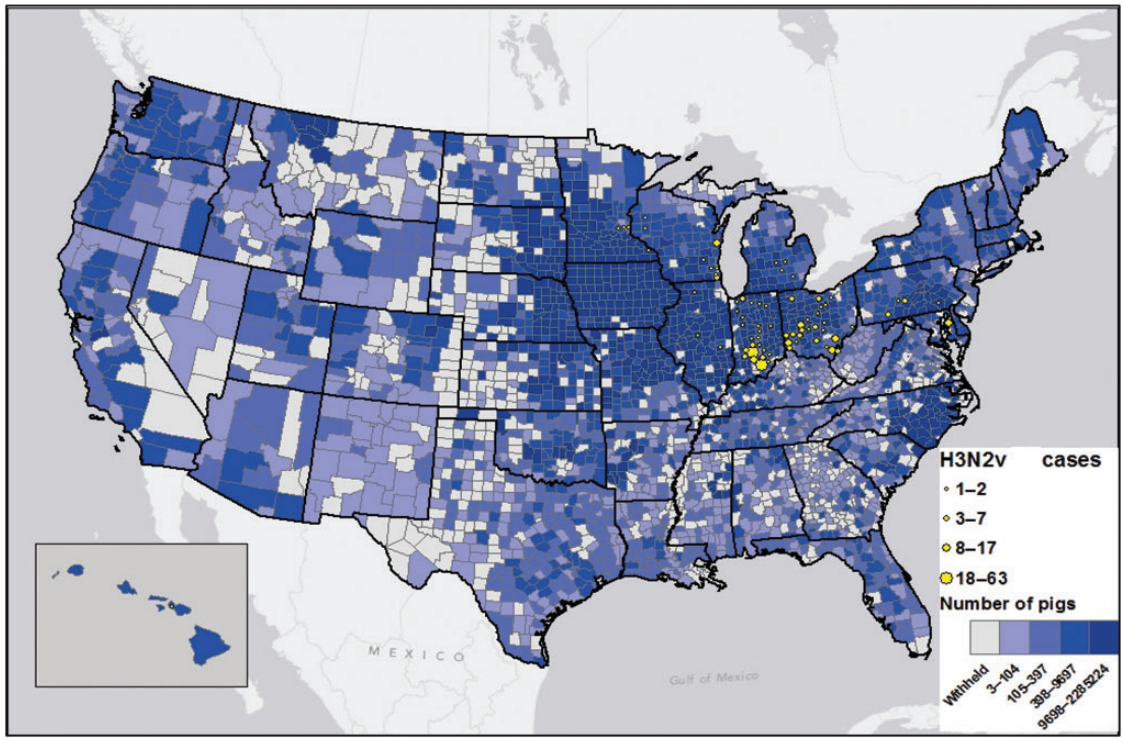

Figure 2. Geographic distribution of influenza A(H3N2) variant virus cases, by county, United States, July–September 2012, and number of pigs by county (2007). Number of pigs by county obtained from the 2007 Census of Agriculture, United States Department of Agriculture, National Agricultural Statistics Service.

Table 1. Cases of Influenza A(H3N2) Variant Virus Infection by State of Residence—United States, July–September 2012 (N = 306)

State	No. of Cases[a] (% of All Cases)	No. of Counties With Cases (% of Counties in State)	No. of Fairs in State Linked to Cases (Range of Cases per Fair)[a]
Hawaii	1 (< 1)	1/5 (20)	0[b]
Illinois	4 (1.3)	3/102 (2.9)	3 (1–2)
Indiana	138 (45)	24/92 (26)	10 (1–73)
Maryland	12 (4)	1/24 (4.2)	1 (12)
Michigan	6[c] (2)	4/83 (4.8)	2 (1–3)
Minnesota[d]	4 (1.3)	4/87 (4.6)	1 (2)
Ohio	107 (35)	25/88 (28)	14 (1–21)
Pennsylvania	11 (3.6)	4/67 (6)	3 (1–6)
West Virginia	3 (1)	1/55 (1.8)	0[e]
Wisconsin	20 (6.5)	8/72 (11)	4 (3–8)

[a] The number of cases reported in each state may exceed the number linked to fairs, as not all patients reported fair attendance prior to illness onset.

[b] The case in Hawaii was associated with swine contact on a farm.

[c] One patient in Michigan reported attendance at an agricultural fair in Ohio.

[d] Two cases in Minnesota were associated with a live animal market.

[e] Three unrelated patients in West Virginia reported attendance at an agricultural fair in Ohio.

and the date that case information was entered into the secure CDC database was 5 days (range, 1–24 days).

The median age of all patients was 7 years (range, 3 months to 74 years), and 92% were aged <18 years; 47% were male. The most commonly reported signs and symptoms were fever (98%), cough (85%), and fatigue (83%); 88% of patients reported ILI (fever plus cough or sore throat). Overall, 23% of cases had at least 1 underlying medical condition known to confer increased risk for complications from influenza [22], the most common of which were asthma (16%), other chronic lung diseases (1.8%), and neurological or neurodevelopmental disorders (1.8%). Of the 293 cases for which information was known, 282 (96%) patients sought healthcare for their illness. Sixteen (5.2%) patients were hospitalized with H3N2v, and 1 fatality occurred in an adult who had prolonged direct contact with swine and multiple underlying medical conditions (Table 2).

The majority of H3N2v cases were associated with direct (69%) or indirect (26%) swine contact prior to illness onset, and most swine exposure occurred at an agricultural fair (Table 2). Two unrelated patients in Minnesota reported that their only swine contact prior to illness was during a visit to a live animal market. The mean duration between the last date of swine exposure and illness onset (ie, the estimated incubation period) for 234 cases for which information was available was 2.91 days (95% confidence interval, 2.7–3.1 days). The number

Table 2. Demographic and Exposure Characteristics, Symptoms, and Clinical Course of Cases of Influenza A(H3N2) Variant Virus Infection—United States, July–September 2012 (N = 306)

Characteristic	No. (%)
Male sex	145 (47)
Age, y, median (range)	7 (3 mo–74 y)
<1 y	7 (2.2)
1–4 y	93 (30)
5–11 y	152 (50)
12–17 y	31 (10)
18–49 y	18 (6)
≥50 y	5 (1.6)
Race (n = 288)	
White	279 (97)
Black	3 (1.0)
Asian	3 (1.0)
Multiracial	3 (1.0)
Ethnicity (n = 235)	
Hispanic	8 (3.4)
Non-Hispanic	227 (97)
Signs and symptoms	
Fever/feverishness	294/300 (98)
Cough	241/285 (85)
Fatigue	214/258 (83)
Sore throat	171/253 (68)
Headache	161/240 (67)
Myalgia	139/227 (61)
Vomiting	80/265 (30)
Diarrhea	66/264 (25)
Eye irritation/redness	57/243 (23)
Exposure characteristic[a]	
Any (direct or indirect) swine contact within ≤4 d of illness onset[b]	281/296 (95)
Direct contact with swine within ≤4 d of illness onset[b]	205/296 (69)
Indirect contact with swine within ≤4 d of illness onset[b]	76/296 (26)
Attended fair within ≤4 d of illness onset but swine exposure denied or unknown[c]	19/296 (6.4)
Agricultural fair attendance ≤4 d of illness onset	274/296 (93)
Swine contact in a nonfair setting only within ≤4 d of illness onset	7/296 (2.4)
Swine contact or fair attendance > 4 d prior to illness onset[d]	10/296 (3.4)
No swine contact or fair attendance reported prior to illness onset[d]	5/296 (1.7)
No. of days with swine contact in week prior to illness (n = 238)	
1 d	83 (35)
2–3 d	42 (18)
4–6 d	48 (20)
7 d	65 (27)
Estimated incubation period, d, mean (95% confidence interval)[e]	2.9 (2.7–3.1)
Illness duration, d, median (range)	4 (1–16)

Table 2 continued.

Characteristic	No. (%)
Household size, median (range)[f]	4 (1–12)
Underlying medical condition[g]	61/271 (23)
Received antiviral treatment	170/281 (60)
Received influenza vaccination in past year	135/244 (55)
Sought healthcare for illness	282/293 (96)
Hospitalized	16 (5.2)
Fatal	1 (<1)

[a] Exposure data exclude 10 of 306 cases (3.6%) for which swine exposure and agricultural fair attendance information was not reported.

[b] Direct contact refers to touching or handling a pig (eg, petting, holding, or grooming); indirect contact refers to standing within 6 feet of a pig or attending an event where swine were exhibited, without known direct contact.

[c] Categorized as patients with indirect swine contact.

[d] These cases are presumed to be the result of person-to-person transmission of H3N2v.

[e] Swine-to-human transmission, among 234 individuals reporting swine contact prior to illness onset.

[f] Including patient.

[g] Includes asthma, chronic lung disease, chronic heart or circulatory disease, diabetes mellitus, kidney disease, immunosuppressive conditions, and neurologic/neurodevelopmental disorders.

of fairs implicated in the outbreak ranged from 1 each in Maryland and Minnesota to 14 in Ohio (Table 1), and whereas the majority of fairs were associated with ≤5 cases each, 1 fair in Maryland was associated with 12 cases, 2 fairs in Indiana were associated with 25 and 73 cases, and 3 fairs in Ohio were associated with 21, 17, and 17 cases. The estimated number of agricultural fairs occurring in the United States peaked at 320 during the week of 22 July 2012, approximately 1 week prior to the peak of the epidemic curve depicting illness onset of cases (Figure 1).

The median age of the 16 hospitalized patients was 5 years (range, 11 months to 61 years); 14 of them (88%) were aged <18 years, and 7 (44%) were aged <5 years (Table 3). Eleven hospitalized patients (69%) were at increased risk for complications from influenza due to young age (n = 3) or the presence of ≥1 underlying medical condition (n = 8). One case required intensive care unit admission, and this patient died after a 1-day hospitalization [23]. The median length of stay for all hospitalized patients was 1 day (range, 1–8 days). For the 9 (56%) patients receiving an influenza antiviral medication while hospitalized, treatment start date ranged between 2 days before to 2 days after admission.

We identified 15 cases of possible person-to-person transmission of H3N2v virus, including 5 cases in which swine contact was not reported at any time prior to illness onset; all cases were in children <10 years of age (Table 4). For 3 of 15 (20%) patients, prior swine exposure could not be identified within 2 illness generations of the case; for patients 1 and 2, there were no other ill contacts identified, and for patient 14, swine exposure was not reported prior to illness onset of the only ill contact.

H3N2v virus was detected in clinical specimens or virus isolates from all 306 patients by rRT-PCR at CDC or state public health laboratories. The 126 viruses that were sequenced were 93%–100% identical in all genes, with the most diversity seen in the NA gene. Phylogenetic analysis of 104 of the viruses identified the presence of the M gene from the pdm09 H1N1

Table 3. Hospitalized Patients With Influenza A(H3N2) Variant Virus Infection—United States, July–September 2012

Patient No.	Age, y	Sex	Length of Stay	Outcome	Underlying Medical Conditions
1	<1	M	1 d	Recovered	Previously healthy
2	1	F	1 d	Recovered	Previously healthy
3	1	F	1 d	Recovered	Asthma
4	2	M	6 d	Recovered	Lymphocytic leukemia
5	3	M	1 d	Recovered	Previously healthy
6	4	F	1 d	Recovered	Asthma
7	4	F	5 d	Recovered	Developmental delay, pulmonary hypertension, asthma
8	5	M	2 d	Recovered	Developmental delay, neurological disorder
9	5	F	2 d	Recovered	Previously healthy
10	6	F	1 d	Recovered	Previously healthy
11	6	F	3 d	Recovered	Previously healthy
12	6	M	1 d	Recovered	Previously healthy
13	7	F	1 d	Recovered	Lymphocytic leukemia
14	12	F	1 d	Recovered	Previously healthy
15	44	F	8 d	Recovered	Multiple myeloma
16	61	F	1 d	Died	Diabetes mellitus, congestive heart failure, hypertension

Table 4. Cases of Influenza A(H3N2) Variant Virus Infection With Possible Person-to-Person Transmission—United States, July–September 2012

Patient No.	Last Swine Exposure	Illness Onset	Interval[a]	Age	Notes
1	None	2 Aug 2012	. . .	4	Sibling of patient 2; went to petting zoo but denied swine contact.
2	None	2 Aug 2012	. . .	6	Sibling of patient 1; went to petting zoo but denied swine contact.
3	None	4 Aug 2012	. . .	1	Sibling had swine contact and was ill 29–30 July but was not tested for influenza.
4	None	8 Aug 2012	. . .	1	Sibling had swine contact at multiple fairs, was ill on 5 Aug, but tested negative for influenza.
5	None	25 Aug 2012	. . .	6	Grandmother had indirect swine contact but was not ill and was not tested for influenza.
6	25 July 2012	2 Aug 2012	8	6	Cousin of a confirmed case; both had single exposure to same swine at a fair.
7	27 July 2012	3 Aug 2012	7	8	Sibling of a confirmed case; both had swine exposure at a fair, and sibling had illness onset on 2 Aug.
8	28 July 2012	3 Aug 2012	6	<1	Three siblings had swine exposure on 28 July and illness onsets 30 July, 1 Aug, and 2 Aug; none were tested for influenza.
9	29 July 2012	4 Aug 2012	5	5	Multiple relatives were confirmed cases with swine exposure and illness onset on 30 July.
10	1 Aug 2012	8 Aug 2012	8	<1	Two cousins and a friend were ill with onsets 5 Aug, 6 Aug, 8 Aug. All had swine exposure and none were tested for influenza.
11	1 Aug 2012	11 Aug 2012	10	9	Sibling was a confirmed case with swine exposure on 1 Aug and illness onset on 3 Aug.
12	7 Aug 2012	16 Aug 2012	9	4	Mother and a sibling had swine exposure on 7 Aug; both became ill on 10 Aug but were not tested for influenza.
13	9 Aug 2012	15 Aug 2012	6	9	Sibling was a confirmed case with illness onset 11 Aug after multiple days of swine exposure.
14	16 Aug 2012	27 Aug 2012	11	2	A cousin who denied swine exposure and was not tested for influenza had illness 2 d prior to illness onset of patient.
15	31 Aug 2012	7 Sept 2012	7	5	Five household members who had swine exposure at the same fair as the patient reported illness prior to illness onset of patient; none were tested for influenza.

[a] No. of days between most recent swine exposure reported and illness onset.

virus and 7 gene segments (PB2, PB1, PA, HA, NP, NA, and NS) that were similar to those previously found in triple-reassortant H3N2 swine influenza viruses (SIVs) circulating in swine in North America. Genetic sequencing results and data from phenotypic NA inhibition assays conducted on 117 isolates indicated that all H3N2v viruses examined were susceptible to the NA inhibitors oseltamivir and zanamivir and resistant to adamantane antiviral medications. All sequence data were submitted to the Global Initiative on Sharing All Influenza Data (GISAID).

During the course of the H3N2v outbreak, 4 cases of variant influenza virus infection with other influenza A virus subtypes were identified. These included 3 H1N2v cases in Minnesota and 1 H1N1v case in Missouri; all 4 of these non-H3N2v variant viruses contained the M gene from the pdm09 H1N1 virus, and each case was associated with swine exposure.

DISCUSSION

From 9 July to 7 September 2012, we identified 306 cases of H3N2v virus infection in 10 US states; all specimens that were sequenced contained the M gene from the pdm09 H1N1 virus and were nearly identical to each other. The majority of cases reported swine exposure at an agricultural fair, a setting that has been implicated in previous outbreaks of variant influenza [2, 19, 24–27]. Although we identified instances of limited person-to-person H3N2v virus transmission, we found no evidence of efficient or sustained transmission of H3N2v virus among humans in this outbreak. This is consistent with reports from 2011, which described 3 instances (comprising 6 cases) among 12 cases of H3N2v virus infection in which person-to-person transmission was suspected [2, 3]. In the 2012 outbreak, H3N2v virus infection resulted in self-limited illness for the majority of persons. However, the increased prevalence of underlying medical conditions among the single fatality and 16 hospitalized patients in this outbreak underscores the importance of treatment and prevention strategies for patients with known risk factors for influenza complications [22]

The H3N2v cases in this outbreak represent 88% of the 348 variant influenza cases identified by the CDC in the United States from 2005 through 2012, and at least 3 factors may have contributed to the magnitude of this outbreak. First, H3N2v

viruses with the M gene from the pdm09 H1N1 virus may be more readily transmitted from swine to humans than other variant influenza viruses. Whereas 7 of the 8 gene segments in the H3N2v viruses involved in this outbreak are similar to those of triple-reassortant SIVs circulating in North America since the late 1990s, the M gene, which was acquired from the pdm09 H1N1 virus [14], is thought to facilitate efficient transmission of pdm09 H1N1 in animal models [5, 6]. Additional studies have concluded that H3N2v and similar triple-reassortant, swine-origin influenza viruses transmit efficiently in ferrets; however, in these studies the role of the pdm09 H1N1 M gene in this process was either unclear or not investigated [28–30]. Second, the majority of cases in this report were associated with agricultural fairs, which are congregate settings for people and animals. Although this H3N2 SIV appears prevalent in swine populations in the United States [31–33], agricultural fairs may represent increased risk for infection; the introduction of 1 infected animal into a fair may have allowed multiple opportunities for subsequent swine-to-human transmission, as this H3N2 virus appears to transmit efficiently among swine [31]. Third, the high prevalence of cases among children is consistent with the susceptibility profile of this H3N2v virus seen in literature describing a relative increase in cross-protective immunity in persons approximately 10 years or older [8–10]. These serologic studies show an age-dependent immune response to this H3N2v virus, which suggests that adults may have more preexisting immunity than younger children. Therefore, this large outbreak may have been the result of a confluence of a highly susceptible population exposed to a readily transmissible influenza virus at agricultural fairs with swine exhibits.

Most patients reported mild illness with symptoms similar to those of seasonal influenza. Although vomiting and diarrhea were commonly reported, the majority of H3N2v patients were aged <18 years, a population in which gastrointestinal symptoms are more frequent with seasonal influenza [34–36]. Of note, nearly one-fourth of cases reported eye redness/irritation as a symptom of illness. Although conjunctivitis is a rare symptom of seasonal influenza and previous variant influenza virus infections [1, 37], it has been reported in cases of human infection with avian influenza A(H7) viruses [38, 39] and with greater frequency in hospitalized children with pdm09 H1N1 compared to seasonal influenza [40]. Whether or not conjunctivitis is also an indicator of H3N2v infection is unclear. The case hospitalization (5.2%) and case fatality (0.3%) proportions for this outbreak are higher than reported during the 2009 H1N1 pandemic [41, 42]. However, it is likely that we identified a disproportionate number of clinically severe cases during this outbreak, and due to the small number of H3N2v cases relative to seasonal influenza cases, the clinical severity of this H3N2v virus is currently unknown. The majority of hospitalized patients, including the single fatality, were at increased risk for complications from influenza due to young age or the presence of an underlying medical condition [22].

A distinguishing characteristic of this outbreak was direct contact with swine on multiple days prior to illness onset. Although swine exposure has been associated with variant influenza virus infection [37, 43], the nature and duration of exposure have not been previously available for such a large number of cases. In this outbreak, the majority of patients reported direct contact with swine, in contrast to recent reports of H3N2v[2] and H1N1v[1] in which only 42% of cases reported direct contact with swine prior to illness. Furthermore, nearly two-thirds of patients in this outbreak reported swine exposure on >1 day, and more than one-quarter reported daily exposure during the week preceding illness onset. Although transmission of influenza virus from swine to humans is influenced by many factors [44, 45], our findings suggest that direct exposure to swine on multiple occasions may make a considerable contribution to infection with this H3N2v influenza virus.

This report is subject to at least 2 limitations. First, the 306 cases we identified may not accurately represent all H3N2v cases that occurred during the outbreak. Laboratory-confirmed H3N2v cases likely underestimate the true number of cases because not all persons with ILI will seek healthcare and not all persons who seek healthcare will be tested for influenza using a method that will allow detection of a variant influenza virus (generally an RT-PCR test) [46–49]. Therefore, the true number of H3N2v cases that occurred may be higher than described in this report [50]. Furthermore, there may be a difference in how diagnostic testing for influenza is implemented during the typical influenza season in the United States, compared to during the summer months. The number of patients with ILI who present for care during the typical influenza season, when influenza viruses are widely circulating, will likely be much greater than the number presenting for care during summer months, when this outbreak occurred. It is therefore more likely that any individual patient presenting with ILI during a summer month will be tested for influenza using RT-PCR, as clinicians typically test fewer outpatients for influenza during the influenza season, when they know influenza viruses are circulating and more likely to be the underlying etiology of ILI. Thus, it is possible that we would be more likely to identify a patient with H3N2v infection in the summer than during the typical influenza season, amidst the "noise" of seasonal influenza cases. However, as H3N2v is a nationally notifiable condition, and because all state public health laboratories have the capability to detect H3N2v viruses, it is unlikely that we failed to identify a large number of H3N2v cases after September, given that the 2012–2013 influenza season did not begin until mid-November, 2 months after the outbreak was thought to have ended [51]. Second, recall bias could have affected our ability to evaluate the relationship between swine exposure and

infection for H3N2v cases. However; in 297 cases, the median duration between the date of symptom onset and the date of case report to the CDC was 5 days. This suggests that in the majority of cases, it took approximately 5 days for the following to occur: illness onset, case identification by the local health department, interview by the local health department, and case report to the CDC. Because we asked about exposure history in the 7 days prior to illness onset, most patients were likely interviewed within ≤12 days of their relevant exposures. Furthermore, because exposure questions pertained to relatively uncommon events (ie, under the assumption that attending a fair or coming into direct contact with swine would not be considered common, everyday events), we do not believe that our analysis was subject to significant recall bias.

To prevent variant influenza virus infection during the outbreak, the CDC recommended that persons at increased risk for complications from influenza, including those aged <5 years or ≥65 years, and with certain underlying medical conditions avoid swine and swine barns at agricultural fairs in 2012 [52]. This recommendation was based in part on evidence suggesting that transmission of influenza viruses to humans can occur from healthy-appearing swine at agricultural events [53, 54]. (Additional recommendations for the public can be found at http://www.cdc.gov/flu/swineflu/h3n2v-outbreak.htm.

Clinical management of H3N2v is similar to management of seasonal influenza virus infections; for patients who are hospitalized, have severe or progressive illness, or are in a high-risk group, empiric antiviral treatment with oral oseltamivir or inhaled zanamivir should be started as soon as possible, without waiting for the results of influenza testing. (More information on diagnosing, reporting, and treating H3N2v infection can be found at http://www.cdc.gov/flu/swineflu/h3n2v-clinician.htm.)

Although seasonal influenza vaccination may offer only minimal protection against H3N2v viruses [55], the CDC recommends it for all persons ≥6 months of age. Prevention of seasonal influenza in children and adults may limit transmission of influenza virus from humans to swine, thereby reducing opportunities for reassortment in swine and subsequent generation of new variant influenza viruses. A candidate vaccine virus (A/Minnesota/11/2010) has been identified, from which clinical investigational lots of an inactivated subunit H3N2v monovalent vaccine has been manufactured; clinical trials by the National Institutes of Health Vaccine and Therapeutics Evaluation Unit are in progress.

Despite enhanced surveillance for ILI in states where H3N2v cases were identified, we identified only 15 instances where person-to-person transmission was suspected. Thus, there is little epidemiological evidence from this outbreak that supports efficient or sustained person-to-person transmission of this H3N2v virus. However, because H3N2 SIVs containing the pdm09 H1N1 M gene seem prevalent in swine populations in the United States [31–33], additional cases associated with future agricultural fairs are possible.

In conclusion, we report a multistate outbreak of variant influenza virus infection among patients with exposure histories, suggesting that swine contact at an agricultural fair was a key risk factor for infection. Although we found no evidence of sustained transmission, infrequent instances of limited person-to-person H3N2v transmission indicate that person-to-person spread of this virus is possible. Although the majority of patients had mild illness, documented risk factors for complications from seasonal influenza, including young age and the presence of underlying medical conditions, were prevalent among H3N2v patients who were hospitalized and/or died. Two H3N2v cases were identified in 2012 after 7 September [56], and 14 cases were reported to the CDC in June and July of 2013; additional cases may occur during the remainder of the 2013 agricultural fair season. Thus, it remains important for fair managers, swine exhibitors, and fair attendees to be aware of the risk of swine-to-human transmission of influenza viruses in these settings, especially among high-risk individuals. The outbreak of H3N2v described in this report also underscores the need for continued cooperation among animal and public health agencies in surveillance, preparedness, and response activities involving novel influenza A viruses.

Notes

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References

1. 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.
2. Epperson S, Jhung MA, Richards S, Quinlisk P, Ball L. Human infections with influenza A (H3N2) variant virus in the United States, 2011–2012. Clin Infect Dis **2013**; 57(suppl 1):S4–11.
3. Centers for Disease Control and Prevention. Limited human-to-human transmission of novel influenza A (H3N2) virus—Iowa, November 2011. MMWR Morb Mortal Wkly Rep **2011**; 60:1615–7.

4. Centers for Disease Control and Prevention. Update: influenza A(H3N2)v transmission and guidelines—five states, 2011. MMWR Morb Mortal Wkly Rep **2012**; 60:1741–4.
5. Chou YY, Albrecht RA, Pica N, et al. The M segment of the 2009 new pandemic H1N1 influenza virus is critical for its high transmission efficiency in the guinea pig model. J Virol **2011**; 85:11235–41.
6. Lakdawala SS, Lamirande EW, Suguitan AL Jr, et al. Eurasian-origin gene segments contribute to the transmissibility, aerosol release, and morphology of the 2009 pandemic H1N1 influenza virus. PLoS Pathog **2011**; 7:e1002443.
7. Ma W, Liu Q, Bawa B, et al. The neuraminidase and matrix genes of the 2009 pandemic influenza H1N1 virus cooperate functionally to facilitate efficient replication and transmissibility in pigs. J Gen Virol **2012**; 93(Pt 6):1261–8.
8. Centers for Disease Control and Prevention. Antibodies cross-reactive to influenza A (H3N2) variant virus and impact of 2010–11 seasonal influenza vaccine on cross-reactive antibodies—United States. MMWR Morb Mortal Wkly Rep **2012**; 61:237–41.
9. Lina B, Bouscambert M, Enouf V, Rousset D, Valette M, van der Werf S. S-OtrH3N2 viruses: use of sequence data for description of the molecular characteristics of the viruses and their relatedness to previously circulating H3N2 human viruses. Euro Surveill **2011**; 16:20039.
10. Skowronski DM, De Serres G, Janjua NZ, et al. Cross-reactive antibody to swine influenza A(H3N2) subtype virus in children and adults before and after immunisation with 2010/11 trivalent inactivated influenza vaccine in Canada, August to November 2010. Euro Surveill **2012**; 17:1–8.
11. Skowronski DM, Janjua NZ, De Serres G, et al. Cross-reactive and vaccine-induced antibody to an emerging swine-origin variant of influenza A virus subtype H3N2 (H3N2v). J Infect Dis **2012**; 206:1852–61.
12. Waalen K, Kilander A, Dudman SG, Ramos-Ocao R, Hungnes O. Age-dependent prevalence of antibodies cross-reactive to the influenza A (H3N2) variant virus in sera collected in Norway in 2011. Euro Surveill **2012**; 17:1–5.
13. Council of State and Territorial Epidemiologists. Reportable diseases. Available at: http://www.cste.org/dnn/ProgramsandActivities/SurveillanceInformatics/tabid/346/Agg1419_SelectTab/2/Default.aspx. Accessed 12 October 2012.
14. Lindstrom S, Garten R, Balish A, et al. Human infections with novel reassortant influenza A(H3N2)v viruses, United States, 2011. Emerg Infect Dis **2012**; 18:834–7.
15. Centers for Disease Control and Prevention. Data interpretation update to CDC Flu rRt-PCR Dx Panel. **2012**. Available at: http://www.cdc.gov/flu/pdf/swineflu/data-interpretation-update.pdf. Accessed 12 October 2012.
16. 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.
17. Donnelly CA, Finelli L, Cauchemez S, et al. Serial intervals and the temporal distribution of secondary infections within households of 2009 pandemic influenza A (H1N1): implications for influenza control recommendations. Clin Infect Dis **2011**; 52(suppl 1):S123–30.
18. Lessler J, Reich NG, Brookmeyer R, Perl TM, Nelson KE, Cummings DA. Incubation periods of acute respiratory viral infections: a systematic review. Lancet Infect Dis **2009**; 9:291–300.
19. Wong KK, Greenbaum A, Moll ME, Lando J, Moore EL, Ganatra R. Outbreak of influenza A (H3N2) variant virus infection among attendees of an agricultural fair, Pennsylvania, USA, 2011. Emerg Infect Dis **2012**; 18:1937–44.
20. Hens N, Calatayud L, Kurkela S, Tamme T, Wallinga J. Robust reconstruction and analysis of outbreak data: influenza A(H1N1)v transmission in a school-based population. Am J Epidemiol **2012**; 176:196–203.
21. Donnelly CA, Ghani AC, Leung GM, et al. Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong. Lancet **2003**; 361:1761–6.
22. Fiore AE, Uyeki TM, Broder K, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Recomm Rep **2010**; 59(RR-8):1–62.
23. Centers for Disease Control and Prevention. Influenza A (H3N2) variant virus-related hospitalizations—Ohio, 2012. MMWR Morb Mortal Wkly Rep **2012**; 61:764–7.
24. Vincent AL, Swenson SL, Lager KM, Gauger PC, Loiacono C, Zhang Y. Characterization of an influenza A virus isolated from pigs during an outbreak of respiratory disease in swine and people during a county fair in the United States. Vet Microbiol **2009**; 137:51–9.
25. Killian ML, Swenson SL, Vincent AL, et al. Simultaneous infection of pigs and people with triple-reassortant swine influenza virus H1N1 at a U.S. county fair. Zoonoses and Public Health **2013**; 60:196–201.
26. Wells DL, Hopfensperger DJ, Arden NH, et al. Swine influenza virus infections. Transmission from ill pigs to humans at a Wisconsin agricultural fair and subsequent probable person-to-person transmission. JAMA **1991**; 265:478–81.
27. Cox CM, Neises D, Garten RJ, et al. Swine influenza virus A (H3N2) infection in human, Kansas, USA, 2009. Emerg Infect Dis **2011**; 17:1143–4.
28. Barman S, Krylov PS, Fabrizio TP, et al. Pathogenicity and transmissibility of North American triple reassortant swine influenza A viruses in ferrets. PLoS Pathog **2012**; 8:e1002791.
29. Yen HL, Liang CH, Wu CY, et al. Hemagglutinin-neuraminidase balance confers respiratory-droplet transmissibility of the pandemic H1N1 influenza virus in ferrets. Proc Natl Acad Sci U S A **2011**; 108:14264–9.
30. Pearce MB, Jayaraman A, Pappas C, et al. Pathogenesis and transmission of swine origin A(H3N2)v influenza viruses in ferrets. Proc Natl Acad Sci U S A **2012**; 109:3944–9.
31. Kitikoon P, Vincent AL, Gauger PC, et al. Pathogenicity and transmission in pigs of the novel A(H3N2)v influenza virus isolated from humans and characterization of swine H3N2 viruses isolated in 2010–2011. J Virol **2012**; 86:6804–14.
32. Liu Q, Ma J, Liu H, et al. Emergence of novel reassortant H3N2 swine influenza viruses with the 2009 pandemic H1N1 genes in the United States. Arch Virol **2012**; 157:555–62.
33. Ducatez MF, Hause B, Stigger-Rosser E, et al. Multiple reassortment between pandemic (H1N1) 2009 and endemic influenza viruses in pigs, United States. Emerg Infect Dis **2011**; 17:1624–9.
34. Dilantika C, Sedyaningsih ER, Kasper MR, et al. Influenza virus infection among pediatric patients reporting diarrhea and influenza-like illness. BMC Infect Dis **2010**; 10:3.
35. Wang YH, Huang YC, Chang LY, et al. Clinical characteristics of children with influenza A virus infection requiring hospitalization. J Microbiol Immunol Infect **2003**; 36:111–6.
36. Liou YS, Barbour SD, Bell LM, Plotkin SA. Children hospitalized with influenza B infection. Pediatr Infect Dis J **1987**; 6:541–3.
37. Krueger WS, Gray GC. Swine influenza virus infections in man. Curr Top Microbiol Immunol **2013**; 370:201–25.
38. Belser JA, Bridges CB, Katz JM, Tumpey TM. Past, present, and possible future human infection with influenza virus A subtype H7. Emerg Infect Dis **2009**; 15:859–65.
39. Fouchier RA, Schneeberger PM, Rozendaal FW, et al. Avian influenza A virus (H7N7) associated with human conjunctivitis and a fatal case of acute respiratory distress syndrome. Proc Natl Acad Sci U S A **2004**; 101:1356–61.
40. Heininger U, Baer G, Ryser AJ, Li Y. Comparative analysis of clinical characteristics of pandemic influenza A/H1N1 and seasonal influenza A infections in hospitalized children. Pediatr Infect Dis J **2013**; 32:293–6.
41. Shrestha SS, Swerdlow DL, Borse RH, et al. Estimating the burden of 2009 pandemic influenza A (H1N1) in the United States (April 2009-April 2010). Clin Infect Dis **2011**; 52(suppl 1):S75–82.

42. Dawood FS, Iuliano AD, Reed C, et al. Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study. Lancet Infect Dis **2012**; 12:687–95.
43. Myers KP, Olsen CW, Gray GC. Cases of swine influenza in humans: a review of the literature. Clin Infect Dis **2007**; 44:1084–8.
44. Torremorell M, Allerson M, Corzo C, Diaz A, Gramer M. Transmission of influenza A virus in pigs. Transbound Emerg Dis **2012**; doi: 10.1111/j.1865-1682.2011.01300.x. [Epub ahead of print].
45. Neumann G, Kawaoka Y. Host range restriction and pathogenicity in the context of influenza pandemic. Emerg Infect Dis **2006**; 12:881–6.
46. Biggerstaff M, Jhung MA, Kamimoto L, et al. Self-reported influenza-like illness and receipt of influenza antiviral drugs during the 2009 pandemic, United States, 2009–2010. Am J Public Health **2012**; 102:e21–6.
47. Reed C, Angulo FJ, Biggerstaff M, et al. Influenza-like illness in the community during the emergence of 2009 pandemic influenza A(H1N1)—survey of 10 states, April 2009. Clin Infect Dis **2011**; 52(suppl 1):S90–3.
48. Jernigan DB, Lindstrom SL, Johnson JR, et al. Detecting 2009 pandemic influenza A (H1N1) virus infection: availability of diagnostic testing led to rapid pandemic response. Clin Infect Dis **2011**; 52 (suppl 1): S36–43.
49. Centers for Disease Control and Prevention. Evaluation of rapid influenza diagnostic tests for influenza A (H3N2)v virus and updated case count—United States, 2012. MMWR Morb Mortal Wkly Rep **2012**; 61: 619–21.
50. Biggerstaff M, Reed C, Epperson S, et al. Estimates of the number of human infections with influenza A(H3N2) variant virus, United States, August 2001–April 2012. Clin Infect Dis **2013**; 57(suppl 1):S12–15.
51. Centers for Disease Control and Prevention. Influenza activity—United States, 2012–13 season and composition of the 2013–14 influenza vaccine. MMWR Morb Mortal Wkly Rep **2013**; 62:473–9.
52. Centers for Disease Control and Prevention. H3N2v prevention: information for the public. **2012**. Available at: http://www.cdc.gov/flu/swineflu/h3n2v-prevention.htm. Accessed 8 November 2012.
53. Gray GC, Bender JB, Bridges CB, et al. Influenza A(H1N1)pdm09 virus among healthy show pigs, United States. Emerg Infect Dis **2012**; 18: 1519–21.
54. Bowman AS, Nolting JM, Nelson SW, Slemons RD. Subclinical influenza virus A infections in pigs exhibited at agricultural fairs, Ohio, USA, 2009–2011. Emerg Infect Dis **2012**; 18:1945–50.
55. Houser KV, Katz JM, Tumpey TM. Seasonal trivalent inactivated influenza vaccine does not protect against newly emerging variants of influenza A (H3N2v) virus in ferrets. J Virol **2013**; 87:1261–3.
56. Centers for Disease Control and Prevention. Flu view. Available at: http://www.cdc.gov/flu/weekly/. Accessed 12 December 2012.