Clinical Characteristics and 30-Day Outcomes for Influenza A 2009 (H1N1), 2008-2009 (H1N1), and 2007-2008 (H3N2) Infections

Edward A. Belongia, MD
Stephanie A. Irving, MHS
Stephen C. Waring, DVM, PhD
Laura A. Coleman, PhD
Jennifer K. Meece, PhD
Mary Vandermause, BSMT
Stephen Lindstrom, PhD
Debra Kempf, BSN
David K. Shay, MD, MPH

Context The clinical characteristics of pandemic 2009 influenza A(H1N1) infections have not been compared directly with illnesses caused by other influenza A strains.

Objective To compare clinical features and outcomes for 2009 H1N1, seasonal H1N1, and H3N2 influenza in a population-based cohort.

Design, Setting, and Participants Active surveillance with 30-day follow-up for influenza cases among children and adults living in a 14–zip code area in Wisconsin. Patients with subjective fever, chills, or cough of fewer than 8 days' duration were screened for eligibility during an outpatient or inpatient encounter. Consenting patients were interviewed and tested for influenza A during the 2007-2008 and 2008-2009 influenza seasons and from May to November 2009; 6874 patients (70%-86% of eligible patients) agreed to participate. Medical records were reviewed to assess outcomes.

Main Outcome Measures Hospital admission, radiographically confirmed pneumonia, and clinical characteristics of influenza A by strain.

Results We identified 545 2009 H1N1, 221 seasonal H1N1, and 632 H3N2 infections. The median ages of infected participants were 10, 11, and 25 years, respectively ($P<.001$). Hospital admission occurred within 30 days for 6 of 395 children with 2009 H1N1 (1.5%; 95% confidence interval [CI], 0.6%-3.1%), 5 of 135 with seasonal H1N1 (3.7%; 95% CI, 1.4%-8.0%), and 8 of 255 with H3N2 (3.1%; 95% CI, 1.5%-5.9%). Among adults, hospital admission occurred in 6 of 150 with 2009 H1N1 (4.0%; 95% CI, 1.6%-8.1%), 2 of 86 with seasonal H1N1 (2.3%; 95% CI, 0.3%-8.1%), and 17 of 377 with H3N2 (4.5%; 95% CI, 2.7%-7.0%). Pneumonia occurred in 10 children with 2009 H1N1 (2.5%; 95% CI, 1.3%-4.5%), 2 with seasonal H1N1 (1.5%; 95% CI, 0.2%-5.2%), and 5 with H3N2 (2.0%; 95% CI, 0.7%-4.3%). Among adults, pneumonia occurred in 6 with 2009 H1N1 (4.0%; 95% CI, 1.6%-8.1%), 2 with seasonal H1N1 (2.3%; 95% CI, 0.3%-8.1%), and 4 with H3N2 (1.1%; 95% CI, 0.3%-2.7%).

Conclusions In this population, individuals with 2009 H1N1 infection were younger than those with H3N2. The risk of most serious complications was not elevated in adults or children with 2009 H1N1 compared with recent seasonal strains.

JAMA. 2010;304(10):1091-1098 www.jama.com

THE PANDEMIC 2009 INFLUENZA A(H1N1) virus caused widespread transmission in the United States and other countries. The Centers for Disease Control and Prevention (CDC) estimates that 43 million to 89 million infections occurred in the United States from April 2009 through April 10, 2010, with midrange estimates of 274 000 H1N1-related hospitalizations and 12 470 deaths (http://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm). Children, young adults, pregnant women, and individuals with underlying chronic medical conditions appear to have a higher risk of hospital admission and critical illness when infected with the pandemic virus.[1-6] Serologic studies suggest that most children and young adults do not have preexisting cross-reactive antibodies against 2009 H1N1 and that they are highly susceptible to infection.[7]

It is difficult to compare the spectrum of illness and outcomes for 2009 H1N1 and seasonal influenza A infections because most reports of 2009 H1N1 influenza have been based on surveillance reports, particularly those for hospital admissions and fatalities.[5,8-11] These reports have provided valuable descriptive information, but differing criteria for influenza testing by season and the lack of uniform standards for data collection and reporting limit comparisons with other influenza viruses. The objective of this study was to compare the characteristics of pandemic and seasonal influenza A infections occurring in a defined population, identified using

CME available online at www.jamaarchivescme.com and questions on p 1131.

Author Affiliations: Marshfield Clinic Research Foundation, Marshfield, Wisconsin (Drs Belongia, Waring, Coleman, and Meece and Mss Irving, Vandermause, and Kempf); and Influenza Division, Centers for Disease Control and Prevention, Atlanta, Georgia (Drs Lindstrom and Shay).
Corresponding Author: Edward A. Belongia, MD, Epidemiology Research Center (ML2), Marshfield Clinic Research Foundation, 1000 N Oak Ave, Marshfield, WI 54449 (belongia.edward@marshfieldclinic.org).

consistent enrollment and laboratory methods.

METHODS

Source Population

The source population included approximately 50 000 persons living in 14 zip codes surrounding Marshfield, Wisconsin. In this area, nearly all residents receive their inpatient and outpatient care from Marshfield Clinic facilities, which use an electronic medical record that captures 90% of outpatient visits, 99% of deaths, and 95% of hospital discharges for the population.[12,13] This population and the enrollment procedures described herein have been used to estimate the effectiveness of influenza vaccines for several seasons.[14,15] Major types of insurance coverage for the population include private commercial (54%), Medicaid (10%), Medicare (10%), and mixed public/private insurance (15%).

For each season, we restricted enrollments to community-dwelling individuals with at least 12 months of continuous residency (or since birth if <12 months old) to ensure availability of relevant data in the electronic medical record. The cohort of individuals who met residency criteria was identified at the beginning of each enrollment period, and only those individuals were eligible to be screened and enrolled during a clinical encounter. We classified individuals as having a chronic medical condition if they had 2 or more visits to the Marshfield Clinic during the prior calendar year with an *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis code for an underlying chronic disease conferring elevated risk of influenza complications.[14] Receipt of seasonal influenza vaccine and 2009 H1N1 vaccine was determined by a real-time, Internet-based immunization registry (http://www.recin.org) that captures 95% of all influenza vaccinations in the study population.[16]

Enrollment Criteria

Among persons in our source population meeting residency criteria, those presenting for an outpatient or inpatient health care visit with at least 1 of the symptoms of subjective fever, chills, or cough were screened and enrolled by trained research coordinators. Physicians providing care had no role in identifying or testing patients for inclusion in this study. Patients with illness duration of 8 days or longer were excluded because of the potential for false-negative influenza test results after prolonged illness.[17,18]

Eligible patients were recruited at the main Marshfield Clinic campus, the Colby satellite outpatient facility, and an acute care hospital contiguous with Marshfield Clinic (St Joseph's Hospital). This hospital provides nearly all inpatient care for the source population. Some patients were contacted at home on the following day if they were not approached during the clinical encounter. Those who consented were screened for eligibility and tested for influenza infection. Each participant (or parent) completed a short interview to assess symptoms, self-reported severity, and onset date.

Laboratory Methods

A Dacron-tipped nasopharyngeal swab (adults and children ≥13 years old) or nasal swab (children 6 months to 12 years old) was obtained from all participants. Nasal swabs were obtained from children aged 12 years or younger because they were more acceptable to parents and children and because studies have suggested that nasal and nasopharyngeal samples have comparable sensitivity for influenza detection in children.[19,20] During 4 seasons, we found that the proportion of children with a positive influenza real-time reverse transcriptase polymerase chain reaction (rRT-PCR) result was the same for participants aged 7 to 12 years (nasal swab) and those aged 13 to 19 years (nasopharyngeal swab), suggesting that using the nasal swab did not adversely affect influenza detection in children.

Most swabs were obtained by research coordinators, but an aliquot was obtained from physician-collected swabs when available to avoid collection of multiple swabs. Swabs were placed in M4 viral transport media and refrigerated or stored on ice until they were delivered to the laboratory on the same day. Samples were routinely tested within 1 day after collection; samples obtained on weekends were processed on Mondays. Total nucleic extractions were performed using the Roche MagNA Pure Total Nucleic Acid Kit (Roche Diagnostics, Indianapolis, Indiana) on 200 µL of clinical sample. Real-time RT-PCR was performed on nucleic acid extracts using the Roche LightCycler 480 Real-Time PCR System. All rRT-PCR protocols and probe and primer sequences were provided by the CDC (protocols available from the CDC on request).[21] Real-time RT-PCR subtyping was performed on all samples with a positive influenza A result (crossing threshold of <40 cycles) during each season.

Study Periods

Patients were recruited for a 10-week period beginning January 21, 2008, for the 2007-2008 season and for a 12-week period beginning January 19, 2009, for the 2008-2009 season. Recruitment and testing was restarted on May 4, 2009, for pandemic influenza surveillance and continued until November 6, 2009 (27 weeks). Enrollment was then suspended to complete a previously scheduled software update of the research application that is used for screening, enrollment, and sample tracking. During the pandemic enrollment period, the number of recruitment days per week varied from 2 to 5 based on influenza activity as documented by rRT-PCR testing, with fewer days of recruitment per week when influenza activity was absent. During the seasonal enrollment periods, patients were recruited and tested 6 days per week. Patients could be reenrolled with a new respiratory illness after an exclusion period to allow time for recovery from the first illness episode.

We compared the number of influenza A cases in study participants with the weekly incidence of all medically

attended influenza-like illness in the source population. *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis codes were used to estimate the incidence of influenza-like illness. For adults, these codes included 487 (influenza), 078.8 (other specified viral and chlamydial diseases), 780.6 (fever), 079.9 (unspecified viral and chlamydial infections), or 465.9 (acute upper respiratory tract infection). In multivariable analyses of adult enrollments in 4 prior seasons, each of these codes was significantly associated with influenza detection by rRT-PCR performed independent of physician evaluation and diagnostic coding. The following codes were used to define a pediatric encounter for influenza-like illness: 487, 079.9, 078.8, 780.6, 490 (bronchitis), 462 (acute pharyngitis), or 786.2 (cough).

Illness Characteristics and Outcomes

Medical records were reviewed for each participant with rRT-PCR–confirmed influenza A to ascertain treatment, hospital admission, and complications during the 30-day period after illness onset. For this analysis, an episode of influenza-related pneumonia required a physician diagnosis, antimicrobial treatment for pneumonia, and an opacity or infiltrate on chest radiograph that was not known to be chronic.[22] Diagnoses without radiographic confirmation were excluded to limit misclassification due to lack of standardized clinical criteria for pneumonia diagnosis. A physician (E.A.B.) reviewed all cases of pneumonia and all hospital admissions. A serious outcome was defined as a pneumonia diagnosis or hospital admission within 30 days after onset.

A subjective severity score was calculated for adults and children aged at least 24 months based on self-reported (or parent-reported) severity of 12 symptoms: cough, subjective fever, chills, fatigue, nasal congestion, wheezing, vomiting, headache, muscle aches, sore throat, ear pain, and nausea. Each symptom was scored on a 4-point scale (0 = absent; 1 = mild; 2 = moderate; and 3 = severe). The severity score was calculated by summing the points for the 12 individual symptoms. Possible scores ranged from 1 (a single mild symptom) to 36 (all symptoms severe). The score has not been validated against objective measures of influenza severity, but a similar severity score (based on 7 symptoms) was significantly reduced by oseltamivir treatment in a randomized clinical trial.[18]

We estimated the minimum cumulative incidence of medically attended influenza A in the source population for each strain and time period, as well as the cumulative incidence of hospital admission. Separate incidence estimates were generated for children and adults. Incident cases included all participants with rRT-PCR–confirmed influenza A during each enrollment period (for medically attended influenza incidence) and all hospital admissions within 30 days after onset of influenza A illness (hospital admission incidence). The denominators included all individuals in the 14–zip code area who met the age and residency criteria. These data underestimate the cumulative incidence because some patients declined to participate or were not approached by research staff during the clinical encounter, particularly during fall 2009, when the volume of patients with respiratory illness exceeded the capacity of research staff to perform outpatient enrollments.

We compared the clinical and demographic characteristics of patients with 2009 H1N1 infection with those with seasonal H1N1 and H3N2 infection. Cases of influenza B were identified during the 2007-2008 season and the 2008-2009 season, but there were no influenza B infections during the pandemic enrollment period. Influenza B cases were not included in this analysis because our objective was to compare 2009 H1N1 with other influenza A strains. Most subgroup comparisons were preplanned, although there were some post hoc comparisons such as that of severity score across virus types stratified into 2 different pediatric age groups (5-17 years vs <5 years). Medians and interquartile ranges (IQRs) were calculated for continuous variables. Univariate comparisons were made using the χ^2 test for categorical variables and the nonparametric Wilcoxon rank sum test for continuous variables. The significance level was set at $P<.05$ based on a 2-sided test. Analyses were performed using SAS software, version 9.1 (SAS Institute Inc, Cary, North Carolina); confidence intervals (CIs) for proportions were calculated using WINPEPI.[23]

The study procedures were reviewed and approved by the Marshfield Clinic Institutional Review Board. All participants or parents provided oral consent for influenza testing and received written information on study procedures. Documentation of written consent was waived by the institutional review board because the research presented no more than minimal risk and did not involve procedures for which written consent is normally required outside of the research context.

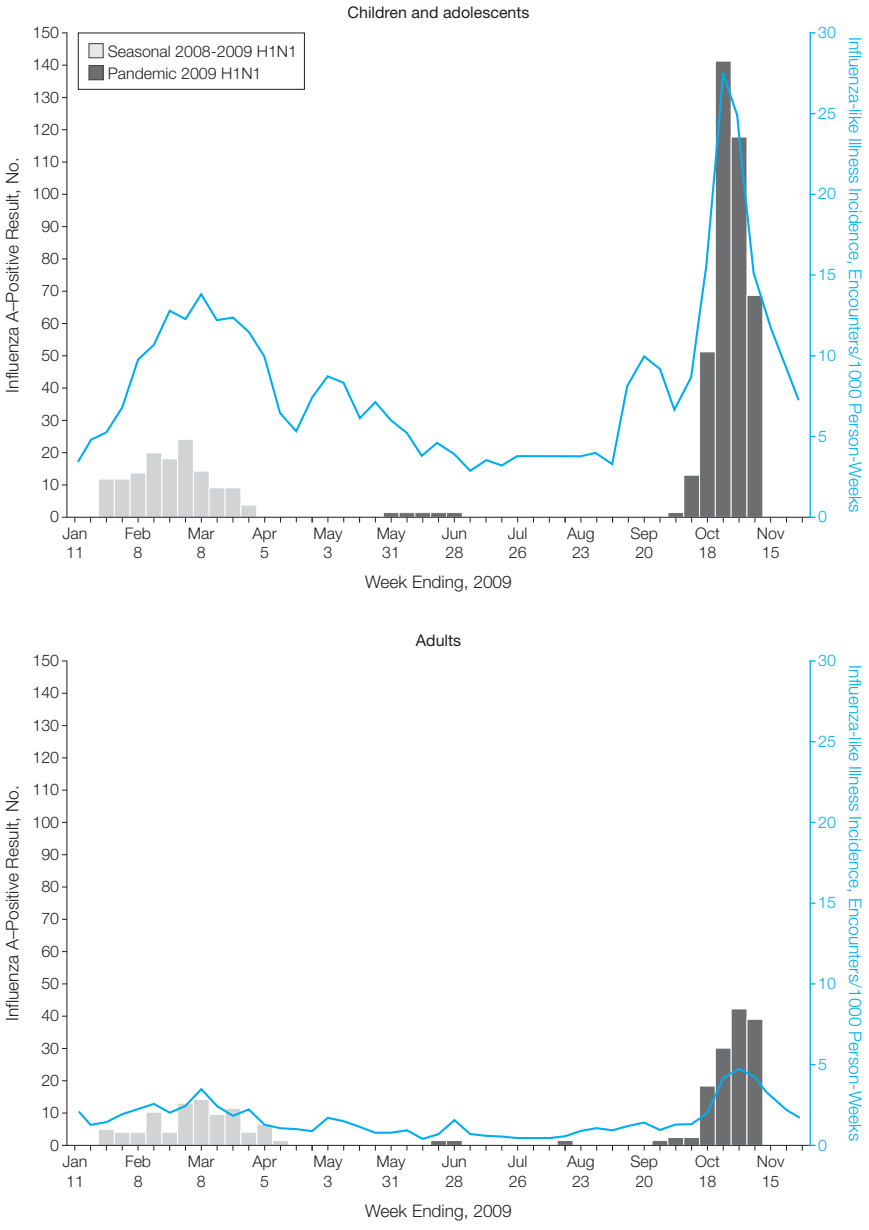
RESULTS

Eighty-six percent of eligible patients enrolled during the 2009 pandemic enrollment period (May 4–November 6), 74% during the 2008-2009 influenza season, and 70% during the 2007-2008 season. We identified 2009 H1N1 influenza in 545 (24%) of 2280 enrolled patients (2136 unique individuals) with subjective fever, chills, or cough from May 4 through November 6, 2009. Illness due to 2009 H1N1 was clustered in October and early November. The temporal distribution of influenza A cases in study participants was consistent with the weekly incidence of medically attended influenza-like illness in the source population (FIGURE). By early December, influenza activity had declined to normal preseason levels. No seasonal H1N1 or H3N2 infections were identified during the pandemic enrollment period.

In the 2008-2009 season, we identified 221 seasonal influenza A H1N1 in-

fections among 262.2 participants enrolled before the pandemic period. During the 2007-2008 influenza season, we identified 632 cases of influenza A H3N2 among 1972 participants. Real-time RT-PCR subtyping of all positive samples demonstrated that seasonal H1N1 was the only influenza A subtype in study participants during the 2008-2009 season and H3N2 was the only subtype in study participants during the 2007-2008 season.

Figure. Number of Study Participants With Positive rRT-PCR Results for Influenza A and Incidence of Medically Attended Influenza-like Illness in the Source Population by Week During 2009



Positive real-time reverse transcriptase polymerase chain reaction (rRT-PCR) results for influenza A are shown as vertical bars with the y-axis on the left. Incidence of medically attended influenza-like illness is shown as a line with the y-axis on the right and is based on *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis codes. All influenza A–positive results prior to May were identified as the seasonal 2008-2009 H1N1 strain; all subsequent positive results were identified as the pandemic 2009 H1N1 strain. No enrollments occurred from April 12 through May 3 (because of the conclusion of seasonal enrollment) or from November 7 through 29.

Visits for pandemic 2009 H1N1 influenza occurred in a narrow time window relative to seasonal influenza A infections: 98% of 2009 H1N1 cases were enrolled in the 5-week period of highest incidence (ie, 2 weeks before and after the week with the greatest number of rRT-PCR–confirmed cases). In contrast, 61% of seasonal H1N1 cases and 63% of H3N2 cases were enrolled during the 5-week period of highest incidence.

The minimum cumulative incidences of medically attended influenza A were 34.9 cases per 1000 children for 2009 H1N1, 12.0 for seasonal H1N1, and 21.7 for H3N2. The risk ratio for medically attended influenza A in children vs adults was 8.7 (95% CI, 7.2-10.6) for 2009 H1N1, 5.2 (95% CI, 3.9-6.8) for seasonal H1N1, and 2.2 (95% CI, 1.9-2.6) for H3N2. The median ages were 10 years (IQR, 6-20 years), 11 years (IQR, 6-36 years), and 25 years (IQR, 9-45 years) for participants with 2009 H1N1, seasonal H1N1, and H3N2 infection, respectively ($P<.001$).

The distribution of symptoms was similar for patients with 2009 H1N1 infection compared with those infected with seasonal H1N1 or H3N2 strains (**TABLE 1**). Children and adolescents infected with the 2009 H1N1 strain were less likely to have sore throat compared with those infected with seasonal H1N1 ($P=.03$) or H3N2 ($P<.001$) strains. Nausea and vomiting occurred with similar frequency by strain and time period. We did not record diarrheal symptoms. Among participants older than 24 months, the median symptom severity score was 14 (IQR, 10-19) for 2009 H1N1, 16 (IQR, 13-20) for seasonal H1N1, and 17 (IQR, 13-20) for 2007-2008 H3N2 infections. The severity score was significantly lower (ie, milder perceived illness) in children with 2009 H1N1 infection relative to those with H3N2 infection ($P=.009$). We found a significant association between virus type and severity score for children 5 to 17 years

old but not for children younger than 5 years. Among children 5 to 17 years old, the median symptom severity score was 14 (IQR, 10-18) for 2009 H1N1 infections and 15 (IQR, 13-18) for H3N2 infections ($P<.001$). Among adults, the symptom severity score was also significantly lower for 2009 H1N1 infections (median, 16; IQR, 12-20) compared with H3N2 infections (median, 18; IQR, 14-21; $P=.04$).

For each influenza A strain, antiviral agents were prescribed more often for adults than children. Both children and adults infected with 2009 H1N1 viruses were significantly more likely to receive antiviral therapy relative to those infected with 2008-2009 H1N1 viruses, a strain known to be resistant to oseltamivir.[24] Antiviral use was not significantly different for 2009 H1N1 infections compared with H3N2 infections in children or adults.

Twelve patients with 2009 H1N1 infections were hospitalized within 30 days after symptom onset. Influenza A was a known or suspected contributing factor for all 12 admissions. The most common pediatric discharge diagnosis was dehydration, present in 4 of 6 hospitalized children and adolescents. Among adults, discharge diagnoses included pneumonia (n=2), exacerbation of chronic obstructive pulmonary disease with hyponatremia (n=1), and influenza (n=3). No children or adults with 2009 H1N1 were admitted to the intensive care unit and no deaths occurred.

The cumulative incidence of hospital admission within 30 days of onset (per 1000 residents) was 0.25 (95% CI, 0.1-0.4) for 2009 H1N1, 0.15 (95% CI, 0.1-0.3) for seasonal H1N1, and 0.5 (95% CI, 0.3-0.7) for H3N2. In children, 2009 H1N1 infection was not associated with either hospital admission or pneumonia compared with H1N1 or H3N2 (**Table 2**). Among adults, pneumonia occurred in 4.0% (95% CI, 1.6%-8.1%) of those with 2009 H1N1 infection and 1.1% (95% CI, 0.3%-2.7%) of those with H3N2 infection ($P=.03$). There were no signifi-

Table 1. Clinical and Demographic Characteristics of Participants With rRT-PCR–Confirmed Influenza A in a Central Wisconsin Population[a]

Characteristics	Children/Adolescents (6 mo–17 y)			Adults		
	2009 H1N1 (n = 395)	Seasonal H1N1 (n = 135)	H3N2 (n = 255)	2009 H1N1 (n = 150)	Seasonal H1N1 (n = 86)	H3N2 (n = 377)
Age, y						
<5	93 (24)	39 (29)	95 (37)			
5-17	302 (76)	96 (71)	160 (63)			
18-49				113 (75)	74 (86)	255 (68)
50-64				32 (21)	11 (13)	77 (20)
≥65				5 (3)	1 (1)	45 (12)
Male	204 (52)	75 (56)	120 (47)	52 (35)	24 (28)	168 (45)[b]
Symptoms						
Chills	280 (71)	97 (72)	183 (72)	125 (83)	77 (90)	337 (89)
Cough	386 (98)	131 (97)	246 (96)	149 (99)	83 (97)	372 (99)
Fatigue	354 (90)	128 (95)	239 (94)	137 (91)	83 (97)	348 (92)
Subjective fever	376 (95)	128 (95)	244 (96)	131 (87)	75 (87)	336 (89)
Nasal congestion	336 (85)	124 (92)[b]	222 (87)	126 (84)	75 (87)	317 (84)
Vomiting	92 (23)	31 (23)	69 (27)	27 (18)	13 (15)	51 (14)
Wheezing	140 (35)	37 (27)	81 (32)	84 (56)	34 (40)[b]	198 (53)
Sore throat[c]	238 (64)	92 (75)[b]	179 (80)[d]	102 (68)	70 (81)[b]	276 (73)
Ear pain[c]	82 (22)	32 (26)	61 (27)	54 (36)	38 (44)	133 (35)
Headache[c]	261 (71)	88 (72)	146 (65)	129 (86)	75 (87)	314 (83)
Myalgia[c]	183 (49)	59 (48)	111 (50)	128 (85)	69 (80)	324 (86)
Nausea[c]	150 (41)	47 (38)	95 (42)	55 (37)	39 (45)	143 (38)
Symptom severity score, median (IQR)[e]	14 (10-18)	15 (11-19)	15 (12-18)[f]	16 (12-20)	17 (14-21)	18 (14-21)[b]
Interval from symptom onset to swab, median (IQR), d	2 (1-4)	2 (1-4)	2 (1-4)	2 (2-4)	3 (2-4)	2.5 (2-4)
Any chronic medical condition	45 (11)	11 (8)	16 (6)[b]	33 (22)	10 (12)[b]	71 (19)
Received antiviral therapy	79 (20)	15 (11)[b]	42 (16)	63 (42)	14 (16)[d]	147 (39)
Interval from symptom onset to antiviral therapy, median (IQR), d	1 (1-2)	1 (1-1)	1 (1-2)	2 (1-3)	2 (1-3)	2 (1-3)[b]

Abbreviations: IQR, interquartile range; rRT-PCR, real-time reverse transcriptase polymerase chain reaction.
[a] Data are expressed as No. (%) of participants unless otherwise indicated.
[b] $P<.05$ vs 2009 H1N1.
[c] Sore throat, ear pain, headache, myalgia, and nausea were not assessed in children younger than 24 months, and these participants were excluded from the denominator.
[d] $P<.001$ vs 2009 H1N1.
[e] Each of 12 symptoms was rated by the participant or parent as absent (0), mild (1), moderate (2), or severe (3). The severity score was calculated as the sum of the scores for individual symptoms. Possible scores ranged from 1 (1 mild symptom) to 36 (all symptoms severe). Children younger than 24 months were excluded because of difficulty assessing symptom severity.
[f] $P<.01$ vs 2009 H1N1.

Table 2. Complications Within 30 Days of Illness Onset for Children and Adults With Different Strains of Influenza A

	No. (%) [95% Confidence Interval]					
	Children/Adolescents (6 mo–17 y)			Adults		
Complications	2009 H1N1 (n = 395)	Seasonal H1N1 (n = 135)	H3N2 (n = 255)	2009 H1N1 (n = 150)	Seasonal H1N1 (n = 86)	H3N2 (n = 377)
Acute otitis media diagnosis	43 (10.9) [8.1-14.3]	17 (12.6) [7.8-19.0]	56 (22.0) [17.2-27.4][a]	10 (6.7) [3.4-11.6]	2 (2.3) [0.3-8.1]	5 (1.3) [0.5-2.9][a]
Acute sinusitis diagnosis	20 (5.1) [3.2-7.6]	8 (5.9) [2.8-10.9]	9 (3.5) [1.7-6.4]	16 (10.7) [6.4-16.4]	8 (9.3) [4.4-16.9]	32 (8.5) [6.0-11.6]
Pneumonia[b]	10 (2.5) [1.3-4.5]	2 (1.5) [0.2-5.2]	5 (2.0) [0.7-4.3]	6 (4.0) [1.6-8.1]	2 (2.3) [0.3-8.1]	4 (1.1) [0.3-2.7][c]
Hospital admission for any reason	6 (1.5) [0.6-3.1]	5 (3.7) [1.4-8.0]	8 (3.1) [1.5-5.9]	6 (4.0) [1.6-8.1]	2 (2.3) [0.3-8.1]	17 (4.5) [2.7-7.0]
Hospital admission with respiratory signs/symptoms	6 (1.5) [0.6-3.1]	5 (3.7) [1.4-8.0]	6 (2.4) [1.0-4.8]	6 (4.0) [1.6-8.1]	2 (2.3) [0.3-8.1]	16 (4.2) [2.5-6.7]
Intensive care unit admission	0 (0.0) [0.0-0.9]	1 (0.7) [0.0-4.1]	2 (0.8) [0.1-2.8]	0 (0.0) [0.0-2.4]	0 (0.0) [0.0-4.2]	0 (0.0) [0.0-1.0]
Serious outcome (pneumonia or hospital admission)	14 (3.5) [2.0-5.7]	7 (5.2) [2.3-10.0]	11 (4.3) [2.3-7.4]	10 (6.7) [3.4-11.6]	4 (4.7) [1.3-11.5]	18 (4.8) [2.9-7.3]

[a] $P < .001$ vs 2009 H1N1.
[b] Episodes of pneumonia required a physician diagnosis, antimicrobial treatment, and new opacity or infiltrate on chest radiograph.
[c] $P < .05$ vs 2009 H1N1.

cant differences by strain in the proportion of children or adults with any serious outcome (pneumonia or hospital admission) during the 30 days after onset. Among adults with any serious outcome, the median age was 31.9 years (IQR, 24.8-37.6 years) for 2009 H1N1, 30.5 years (IQR, 29.5-43.7 years) for seasonal H1N1, and 63.0 years (IQR, 28.1-71.2 years) for H3N2 ($P = .02$ for 2009 H1N1 vs H3N2). The median ages of children with any serious outcomes were 5.8 years (IQR, 4.1-8.1 years), 4.9 years (IQR, 2.5-6.4 years), and 8.3 years (IQR, 3.1-12.5 years), respectively.

We compared the characteristics of patients with 2009 H1N1 infections and those with noninfluenza respiratory illness (negative rRT-PCR result) during the pandemic enrollment period (TABLE 3). The median age was 10.4 years (IQR, 5.8-20.2 years) for those with 2009 H1N1 infection and 18.1 years (IQR, 5.7-42.2 years) for those with noninfluenza respiratory illness ($P < .001$). Among children younger than 18 years, those infected with 2009 H1N1 were significantly older than those with a noninfluenza respiratory illness. Children with 2009 H1N1 infections were also more likely to have had a prior diagnosis of asthma compared with those testing negative for influenza. For both children and adults, symptom severity scores were significantly higher among those infected with the 2009 H1N1 strain relative to those with noninfluenza respiratory illness.

Thirty-one children (23%) with seasonal H1N1 infection and 61 (24%) with H3N2 infection were fully immunized with seasonal influenza vaccine at the time of enrollment (vaccine received at least 14 days before enrollment). Among adults, 25 (29%) with seasonal H1N1 and 117 (31%) with H3N2 infection had received seasonal influenza vaccine at least 14 days before enrollment. Distribution of monovalent H1N1 vaccine began as the 2009 H1N1 outbreak was reaching its peak in our population; no participants infected with the 2009 H1N1 strain and only 4 with a negative rRT-PCR result had received monovalent vaccine 14 or more days before enrollment.

COMMENT

We were able to directly compare the epidemiologic and clinical characteristics of 2009 H1N1 and seasonal influenza A infections in the same population using identical enrollment, laboratory diagnostic, and follow-up methods. We found that participants with the 2009 H1N1 strain were similar in age to those with seasonal H1N1 infection, but participants with H3N2 infection were significantly older. This age differential between H1N1 and H3N2 is consistent with sentinel surveillance reports from Australia, although the patients with 2009 H1N1 infection in Australia were older (median, 18-22 years) than those identified in this study (median, 10 years).[25] The minimum cumulative incidence of medically attended influenza in the population was higher in children than adults for every influenza A strain, and the relative increase in children was highest for the 2009 H1N1 strain.

Our results suggest that the clinical manifestations and risk of hospital admission are similar for 2009 H1N1 and other seasonal influenza A strains among those presenting for medical care and documented to have influenza infection. Our finding that adults with 2009 H1N1 infection had an increased risk of radiographically confirmed pneumonia compared with those with H3N2 infection requires confirmation in a different population. Other published studies have reported a higher-than-expected incidence of hospitalization and death associated with 2009 H1N1 infection, particularly in children.[3,10,26] This finding may be due to the greatly elevated incidence of 2009 H1N1 influenza in a highly susceptible population of children and young adults rather than increased virulence of 2009 H1N1 relative to seasonal influenza A viruses. The increased use of highly sensitive rRT-PCR testing for influenza in hospitalized patients during the pandemic period was another factor that may have contributed to improved case detection in severely ill pa-

tients during 2009 relative to prior seasons.

In this study, comparisons of severity by influenza A strain could have been influenced by antiviral therapy, vaccination, and differences in health care–seeking behavior. Antiviral treatment was used more often for patients infected with 2009 H1N1 compared with seasonal H1N1, and this would be expected to reduce serious outcomes. However, antiviral therapy is unlikely to explain any differences between 2009 H1N1 and H3N2 outcomes, since the proportion of infected participants receiving antiviral therapy was similar. Influenza vaccination may have also reduced the occurrence of serious outcomes in vaccinated patients with seasonal H1N1 or H3N2 strains but not those with 2009 H1N1 infections, since monovalent H1N1 vaccine was first available in our population when H1N1 infections were peaking in mid October. Finally, publicity surrounding the H1N1 pandemic may have caused more mildly ill individuals to seek health care compared with a normal influenza season. If this occurred, a smaller proportion of pandemic cases would be expected to be hospitalized or diagnosed as having pneumonia compared with seasonal cases. However, even if present, this effect is likely to be modest because we did not observe significant differences in symptom severity score or mean interval from symptom onset to swab in children or adults with 2009 H1N1 relative to 2008-2009 seasonal H1N1 infection.

Our study had several strengths, including prospective inpatient and outpatient enrollment from a defined population presenting for medical care, use of standardized screening criteria for rRT-PCR testing, collection of detailed data regarding clinical manifestations of illness, and medical record review to ascertain influenza-related pneumonia and hospitalizations. This study also has several limitations, including the aforemen-

Table 3. Prevalence of Demographic and Clinical Characteristics at Enrollment in Participants With 2009 H1N1 Infection and Noninfluenza Respiratory Illness During the Pandemic Period (May 4–November 6, 2009)

	Children/Adolescents (6 mo–17 y)				Adults			
Characteristics	2009 H1N1 (n= 395)[a]	Noninfluenza Respiratory Illness (n= 866)[a]	Prevalence Ratio (95% CI)	*P* Value	2009 H1N1 (n= 150)[a]	Noninfluenza Respiratory Illness (n= 869)[a]	Prevalence Ratio (95% CI)	*P* Value
Age, y								
Mean (SD)	8.4 (4.2)	6.8 (5.0)		<.001	37.8 (14.4)	44.2 (17.2)		<.001
Median (IQR)	7.6 (5.2-11.3)	5.7 (2.2-10.6)		<.001	36.0 (25.2-48.9)	42.2 (29.9-55.9)		<.001
Male	204 (52)	432 (50)	1.04 (0.92-1.16)		52 (35)	299 (34)	1.01 (0.79-1.28)	.95
Any high-risk medical condition	45 (11)	72 (8)	1.37 (0.96-1.95)	.08	33 (22)	198 (23)	0.97 (0.70-1.34)	.83
History of asthma	69 (17)	106 (12)	1.43 (1.08-1.88)	.01	15 (10)	92 (11)	0.95 (0.56-1.58)	.83
Symptoms								
Chills	280 (71)	405 (47)	1.52 (1.38-1.67)	<.001	125 (83)	612 (70)	1.18 (1.09-1.29)	.001
Cough	386 (98)	726 (84)	1.17 (1.13-1.21)	<.001	149 (99)	757 (87)	1.14 (1.11-1.17)	<.001
Fatigue	354 (90)	650 (75)	1.19 (1.13-1.26)	<.001	137 (91)	770 (89)	1.03 (0.98-1.09)	.32
Subjective fever	376 (95)	673 (78)	1.23 (1.17-1.28)	<.001	131 (87)	617 (71)	1.23 (1.14-1.32)	<.001
Nasal congestion	336 (85)	657 (76)	1.12 (1.06-1.19)	<.001	126 (84)	645 (74)	1.13 (1.04-1.23)	.01
Vomiting	92 (23)	183 (21)	1.10 (0.88-1.37)	.39	27 (18)	129 (15)	1.21 (0.83-1.77)	.32
Wheezing	140 (35)	243 (28)	1.26 (1.07-1.50)	.008	84 (56)	374 (43)	1.30 (1.11-1.53)	.003
Ear pain[b]	82 (22)	202 (31)	0.71 (0.57-0.89)	.002	54 (36)	345 (40)	0.91 (0.72-1.14)	.39
Headache[b]	261 (71)	350 (54)	1.32 (1.20-1.46)	<.001	129 (86)	640 (74)	1.17 (1.08-1.26)	.001
Myalgia[b]	183 (49)	233 (36)	1.39 (1.20-1.61)	<.001	128 (85)	628 (72)	1.18 (1.09-1.28)	.001
Nausea[b]	150 (41)	232 (36)	1.14 (0.97-1.34)	.12	55 (37)	342 (39)	0.93 (0.74-1.17)	.53
Sore throat[b]	238 (64)	465 (72)	0.90 (0.83-0.99)	.02	102 (68)	653 (75)	0.91 (0.81-1.02)	.07
Symptom severity score, median (IQR)[c]	14 (10-18)	11 (7-15)		<.001	16 (12-20)	14 (10-18)		.001
Interval from symptom onset to swab, median (IQR), d	2 (1-4)	2 (1-4)		.17	2 (2-4)	3 (2-5)		.002
Received 2008-2009 seasonal influenza vaccine[d]	190 (48)	405 (47)	1.03 (0.91-1.17)	.66	66 (44)	372 (43)	1.03 (0.84-1.25)	.79
Smoking status[e]								
Current					35 (24)	210 (24)	0.99 (0.73-1.35)	
Former					28 (19)	242 (28)	0.69 (0.49-0.98)	.15
Never smoked					82 (57)	411 (48)	1.19 (1.01-1.39)	

Abbreviations: CI, confidence interval; IQR, interquartile range.
[a] Data are expressed as No. (%) of participants unless otherwise indicated.
[b] Ear pain, headache, myalgia, nausea, and sore throat were not assessed in children younger than 24 months.
[c] Children younger than 24 months were not included in the severity score.
[d] Only 4 participants received monovalent H1N1 vaccine at least 14 days before enrollment, and all had a negative real-time reverse transcriptase polymerase chain reaction test result.
[e] Smoking status was not assessed in children and adolescents younger than 18 years; 1 adult participant declined to answer this question.

tioned differences in antiviral use and vaccination. The cumulative incidence proportions underestimate the actual incidence of medically attended influenza in the population, particularly during October 2009, when patient volume exceeded the capacity of research staff to enroll outpatients. Although the source population was approximately 50 000, analyses of serious outcomes (pneumonia or hospital admission) had limited power because of the low number of events. We cannot conclude that there was no difference; however, if the clinical symptoms and severity were truly different, the actual magnitude of difference would be small and likely not of clinical relevance. We were also unable to compare outcomes and severity for high-risk individuals, including pregnant women. We did not enroll children younger than 6 months because data from the 2007-2008 and 2008-2009 seasons were originally obtained for a study to assess vaccine effectiveness and children younger than 6 months are not eligible for influenza vaccination. One study showed that children in this age group had a high rate of hospital admission for 2009 H1N1 infection.[10] Finally, our source population was predominantly white and non-Hispanic, and we could not examine racial and ethnic subgroups across influenza subtypes. Other studies have suggested that certain racial or ethnic groups experienced higher rates of hospital admission or other complications because of 2009 H1N1 infection.[26,27]

In summary, we found that children were disproportionately affected by 2009 H1N1 infection, but the perceived severity of symptoms and risk of serious outcomes (pneumonia or hospital admission) were not increased in children with 2009 H1N1 infection relative to seasonal influenza A viruses. This study demonstrates the benefit of ongoing active influenza surveillance in a defined cohort with standardized testing criteria and uniform collection of clinical and epidemiologic data. The use of consistent enrollment and testing procedures offers the opportunity to directly compare illness patterns and outcomes over multiple seasons, and these results complement information obtained through traditional public health surveillance systems.

Author Contributions: Dr Belongia had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Belongia, Waring, Coleman, Meece, Lindstrom, Shay.
Acquisition of data: Vandermause, Lindstrom, Kempf.
Analysis and interpretation of data: Belongia, Irving, Waring, Coleman, Shay.
Drafting of the manuscript: Belongia, Meece, Shay.
Critical revision of the manuscript for important intellectual content: Belongia, Irving, Waring, Coleman, Meece, Vandermause, Lindstrom, Kempf, Shay.
Statistical analysis: Irving, Waring.
Obtained funding: Belongia.
Administrative, technical, or material support: Vandermause, Lindstrom, Shay.
Study supervision: Meece, Kempf.
Financial Disclosures: None reported.
Funding/Support: Funding for this research was provided by a cooperative agreement with the CDC (grant 1 U01 CI000192-01).
Role of the Sponsor: The manuscript was reviewed and approved for submission by the CDC.
Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the CDC.
Additional Contributions: We thank Burney Kieke, MS, Marshfield Clinic Research Foundation, for statistical review (no compensation) and the research coordinators, interviewers, programmer/analysts, core laboratory staff, and administrative support staff at the Marshfield Clinic Research Foundation for their contributions to this project.

REFERENCES

1. Jain S, Kamimoto L, Bramley AM, et al; 2009 Pandemic Influenza A (H1N1) Virus Hospitalizations Investigation Team. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. *N Engl J Med*. 2009;361(20):1935-1944.
2. Denholm JT, Gordon CL, Johnson PD, et al. Hospitalised adult patients with pandemic (H1N1) 2009 influenza in Melbourne, Australia. *Med J Aust*. 2010; 192(2):84-86.
3. Webb SA, Pettilä V, Seppelt I, et al; ANZIC Influenza Investigators. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. *N Engl J Med*. 2009;361(20):1925-1934.
4. Domínguez-Cherit G, Lapinsky SE, Macias AE, et al. Critically ill patients with 2009 influenza A(H1N1) in Mexico. *JAMA*. 2009;302(17):1880-1887.
5. Kumar A, Zarychanski R, Pinto R, et al; Canadian Critical Care Trials Group H1N1 Collaborative. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. *JAMA*. 2009;302(17):1872-1879.
6. Louie JK, Acosta M, Jamieson DJ, Honein MA; California Pandemic (H1N1) Working Group. Severe 2009 H1N1 influenza in pregnant and postpartum women in California. *N Engl J Med*. 2010;362(1):27-35.
7. Hancock K, Veguilla V, Lu X, et al. Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. *N Engl J Med*. 2009;361(20):1945-1952.
8. Centers for Disease Control and Prevention. Surveillance for pediatric deaths associated with 2009 pandemic influenza A (H1N1) virus infection—United States, April-August 2009. *MMWR Morb Mortal Wkly Rep*. 2009;58(34):941-947.
9. Chowell G, Bertozzi SM, Colchero MA, et al. Severe respiratory disease concurrent with the circulation of H1N1 influenza. *N Engl J Med*. 2009;361 (7):674-679.
10. Libster R, Bugna J, Coviello S, et al. Pediatric hospitalizations associated with 2009 pandemic influenza A (H1N1) in Argentina. *N Engl J Med*. 2010; 362(1):45-55.
11. Louie JK, Acosta M, Winter K, et al; California Pandemic (H1N1) Working Group. Factors associated with death or hospitalization due to pandemic 2009 influenza A(H1N1) infection in California. *JAMA*. 2009; 302(17):1896-1902.
12. DeStefano F, Eaker ED, Broste SK, et al. Epidemiologic research in an integrated regional medical care system: the Marshfield Epidemiologic Study Area. *J Clin Epidemiol*. 1996;49(6):643-652.
13. Greenlee RT. Measuring disease frequency in the Marshfield Epidemiologic Study Area (MESA). *Clin Med Res*. 2003;1(4):273-280.
14. Belongia EA, Kieke BA, Donahue JG, et al; Marshfield Influenza Study Group. Effectiveness of inactivated influenza vaccines varied substantially with antigenic match from the 2004-2005 season to the 2006-2007 season. *J Infect Dis*. 2009;199(2):159-167.
15. Centers for Disease Control and Prevention. Interim within-season estimate of the effectiveness of trivalent inactivated influenza vaccine—Marshfield, Wisconsin, 2007-08 influenza season. *MMWR Morb Mortal Wkly Rep*. 2008;57(15):393-398.
16. Irving SA, Donahue JG, Shay DK, Ellis-Coyle TL, Belongia EA. Evaluation of self-reported and registry-based influenza vaccination status in a Wisconsin cohort. *Vaccine*. 2009;27(47):6546-6549.
17. Sato M, Hosoya M, Kato K, Suzuki H. Viral shedding in children with influenza virus infections treated with neuraminidase inhibitors. *Pediatr Infect Dis J*. 2005;24(10):931-932.
18. Treanor JJ, Hayden FG, Vrooman PS, et al; US Oral Neuraminidase Study Group. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. *JAMA*. 2000; 283(8):1016-1024.
19. Heikkinen T, Salmi AA, Ruuskanen O. Comparative study of nasopharyngeal aspirate and nasal swab specimens for detection of influenza. *BMJ*. 2001; 322(7279):138.
20. Heikkinen T, Marttila J, Salmi AA, Ruuskanen O. Nasal swab versus nasopharyngeal aspirate for isolation of respiratory viruses. *J Clin Microbiol*. 2002; 40(11):4337-4339.
21. World Health Organization. CDC Protocol of Realtime RTPCR for Swine Influenza A(H1N1). April 28, 2009. http://www.who.int/csr/resources/publications/swineflu/CDCrealtimeRTPCRprotocol_20090428.pdf. Accessed June 29, 2010.
22. Jackson ML, Nelson JC, Weiss NS, Neuzil KM, Barlow W, Jackson LA. Influenza vaccination and risk of community-acquired pneumonia in immunocompetent elderly people: a population-based, nested case-control study. *Lancet*. 2008;372(9636):398-405.
23. Abramson JH. WINPEPI (PEPI-for-Windows): computer programs for epidemiologists. *Epidemiol Perspect Innov*. 2004;1(1):6.
24. Dharan NJ, Gubareva LV, Meyer JJ, et al; Oseltamivir-Resistance Working Group. Infections with oseltamivir-resistant influenza A(H1N1) virus in the United States. *JAMA*. 2009;301(10):1034-1041.
25. Kelly HA, Grant KA, Williams S, Fielding J, Smith D. Epidemiological characteristics of pandemic influenza H1N1 2009 and seasonal influenza infection. *Med J Aust*. 2009;191(3):146-149.
26. Baker MG, Wilson N, Huang QS, et al. Pandemic influenza A(H1N1)v in New Zealand: the experience from April to August 2009. *Euro Surveill*. 2009;14(34):19319.
27. Bishop JF, Murnane MP, Owen R. Australia's winter with the 2009 pandemic influenza A (H1N1) virus. *N Engl J Med*. 2009;361(27):2591-2594.

