ARTICLE

Hospitalization of Children With Influenza A(H1N1) Virus in Israel During the 2009 Outbreak in Israel

A Multicenter Survey

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Objectives: To describe the clinical characteristics of children hospitalized with 2009 influenza A(H1N1) infection in Israel and the risk factors associated with this infection.

Design: Prospective collection of data on children hospitalized with 2009 influenza A(H1N1) infection.

Setting: Seven medical centers around Israel.

Patients: From July 12, 2009, to December 24, 2009, all patients 18 years or younger hospitalized with acute respiratory or acute unspecified febrile illness were screened for 2009 influenza A(H1N1) virus by reverse transcription–polymerase chain reaction.

Intervention: Prospective data collection for patients with confirmed infection.

Main Outcome Measures: Clinical characteristics of patients and hospitalization rates.

Results: The mean age of 478 patients studied was 6.1 years. Forty-two patients (8.8%) were admitted to the pediatric intensive care unit; 3 patients (0.6%) died. The most frequent clinical presentations were pneumonia, influenza-like illness, wheezing exacerbation, and convulsions. Predisposing underlying illnesses were detected in 48.7% of patients. Patients with metabolic and neurologic disorders were at highest risk for severe complications (relative risk, 6.5 and 2.9, respectively). In addition, patients with cyanotic heart lesions and infants 3 months or younger who were born at 33 weeks' gestation or earlier tended to require higher rates of mechanical ventilation. The hospitalization rate for 2009 influenza A(H1N1) was 0.7 per 1000 children. The mortality rate was 3.6 per 1 000 000 children.

Conclusions: The severity variables for 2009 influenza A(H1N1) were similar to the figures reported for seasonal influenza. Patients with underlying metabolic and neurologic metabolic disorders and presumably patients with cyanotic heart lesions and infants born prematurely are at highest risk for severe complications following 2009 influenza A(H1N1) infection.

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THE NEW STRAIN OF PANdemic influenza A(H1N1) virus that appeared in Mexico in March 2009 caused extensive disease, especially in young adults.[1-3] Information on the clinical spectrum of illness and risk factors for development of severe disease in children infected with 2009 influenza A(H1N1) is still emerging for different phases of the virus activity and from several geographic areas of the world, where different ways of coping with the disease were used.[4-7] Despite previous investigations of 2009 influenza A(H1N1) infection in children, the clinical spectrum, severity, and risk factors had not been fully elucidated.

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In this multicenter study, we prospectively collected information about children hospitalized with 2009 influenza A(H1N1) over a 5-month period before, during, and after the peak activity period of this virus in Israel. Data were collected from individual patients rather than via a computerized database. This information was used to determine the hospitalization rate in pediatric populations and to characterize the clinical spectrum of 2009 influenza A(H1N1) virus infection among hospitalized children in different age groups and among specific groups of patients at risk.

METHODS

STUDY DESIGN

We prospectively collected clinical and epidemiologic data on patients 18 years or younger

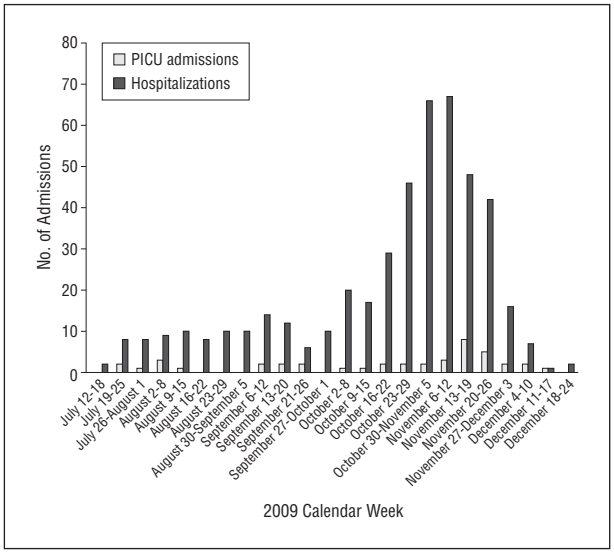

Figure 1. Number of admissions to 7 medical centers and to the pediatric intensive care units (PICUs) for 2009 influenza A(H1N1) among the Israeli pediatric population by 2009 calendar week.

hospitalized with laboratory-confirmed 2009 influenza A(H1N1) infection in 7 medical centers representing different areas of Israel from July 12, 2009, to December 24, 2009. Only centers that routinely tested patients with suspected influenza (any patient admitted with acute respiratory or acute unspecified febrile illness) were included in the study. The test was a reverse transcription–polymerase chain reaction assay performed at the Israeli Ministry of Health reference virology laboratories.

HOSPITALIZATION RATES

To minimize underestimation of influenza-related admissions in determining hospitalization rates, we used data from 3 medical centers that had the highest percentages of 2009 influenza A(H1N1) testing and cases per total number of hospitalizations. Because these hospitals represent 15.2% of all annual pediatric hospitalizations in the country, we multiplied the number of patients hospitalized with 2009 influenza A(H1N1) at these 3 centers by 6.6. The number of calculated influenza hospitalizations in the country was then divided by the number of Israeli children in the different age groups. Information on the population size of the different age groups of children in Israel, as well as the number of hospitalizations at the various hospitals in the country, was obtained from the Israeli Statistical Bureau.

The mortality rate was determined based on official numbers provided by the Israeli Ministry of Health. To calculate the mortality rate, we used the pediatric population in Israel as the denominator.

Distribution comparisons between dichotomous variables and continuous variables were performed using the χ^2 and *t* tests, respectively. The study was approved by the ethics committee of Edith Wolfson Medical Center, Holon, Israel.

RESULTS

Data on 478 patients (267 male and 211 female) with laboratory-confirmed 2009 influenza A(H1N1) were collected. During the study period, which paralleled the activity of 2009 influenza A(H1N1) virus in Israel, more than 98% of influenza virus isolates in Israel were of this strain.

The distribution of hospitalizations according to 2009 calendar week is shown in **Figure 1**. The mean age of patients studied was 6.1 years (age range, 0.03-18 years), and the mean hospitalization duration was 3.9 days (range, 1-50 days) (**Table 1**). The mean interval from onset of symptoms to hospitalization was 2.9 days (median, 2 days; range, 0-21days).

Forty-two patients (8.8%) were admitted to the pediatric intensive care unit (PICU), and 15 (3.1%) required mechanical ventilation. The PICU admission rate was higher after the week beginning November 13 compared with earlier weeks (15.5% vs 6.8% of all patients hospitalized with 2009 influenza A[H1N1], $P=.02$) (Figure 1).

Three patients in our series died. According to the Israeli Ministry of Health registry, 9 patients 18 years and younger infected with 2009 influenza A(H1N1) had died in Israel since the beginning of the outbreak; all of them had severe underlying medical conditions.

HOSPITALIZATION AND MORTALITY RATES

The hospitalization rate for patients in the Israeli population 18 years or younger was 0.7 per 1000 (Table 1). The rates for the different age groups are given in **Figure 2**. The mortality rate in Israel was 3.6 per 1 million children.

CLINICAL MANIFESTATIONS BY AGE GROUP

The most common clinical syndrome was pneumonia, affecting 172 patients (36.0%), and 134 patients (28.0%) who had no evidence of pneumonia on their chest radiographs were discharged with the diagnosis of influenza-like illness or upper respiratory tract infection (ILI/URI) symptoms. These results are summarized in Table 1.

Patients initially seen with pneumonia tended to be younger and had higher rates of predisposing respiratory system illnesses and of tachypnea and hypoxemia compared with patients admitted with ILI/URI symptoms. In addition, patients with pneumonia had higher white blood cell counts, absolute neutrophil counts, and C-reactive protein levels, as well as longer mean (SD) intervals from onset of symptoms to hospitalization (3.7 [2.9] vs 2.6 [2.9] days, $P<.001$) and to initiation of oseltamivir phosphate treatment (4.7 [8.0] vs 2.5 [2.6] days, $P=.002$) (**Table 2**).

Forty-two patients (8.8%), most with asthma, were hospitalized for exacerbation of their underlying respiratory illness, and 41 patients (8.6%) had seizures, mostly febrile. Thirty-one patients were admitted with a nonspecific febrile illness, and 29 patients had predominant gastrointestinal tract symptoms. Central nervous system involvement affected 5 patients, including meningococcal meningitis (1 patient), aseptic meningitis (1 patient), encephalitis (1 patient), and encephalopathy (2 patients). Two patients were diagnosed as having Kawasaki disease in temporal association with 2009 influenza A(H1N1) infection.

LABORATORY MARKERS

Mild elevation in liver enzymes (aspartate aminotransferase or alanine aminotransferase level >60 U/L) was

Table 1. Clinical Characteristics and Hospital Discharge Diagnoses of Patients by Age Group

Variable	<3 mo (n=30)	3-23 mo (n=126)	24-59 mo (n=97)	5-18 y (n=225)	Total (N=478)
Age, mean (SD), y	0.12 (0.05)	1.07 (0.43)	3.10 (0.84)	10.94 (3.80)	6.06 (5.36)
Rate per 1000					
Hospitalizations	3.20	1.15	0.74	0.63	0.72
PICU admissions	0.25	0.07	0.04	0.03	0.04
Mechanical ventilation	0.125	0.013	0.015	0.009	0.014
Predisposing illness, No. (%)					
Any	6 (20.0)[a]	49 (38.9)[a]	56 (57.7)	122 (54.2)	**233** (48.7)
Respiratory	3 (10.0)	29 (23.0)	29 (29.9)	64 (28.4)	**125** (26.2)
Neurologic	0	11 (8.7)	10 (10.3)	20 (8.9)	**41** (8.6)
Cardiovascular	2 (6.7)	7 (5.6)	5 (5.2)	16 (7.1)	**30** (6.3)
Oncologic	0	1 (0.8)	6 (6.2)	13 (5.8)	**20** (4.2)
Metabolic	0	2 (1.6)	3 (3.1)	6 (2.7)	**11** (2.3)
Renal	0	1 (0.8)	3 (3.1)	7 (3.1)	**11** (2.3)
Endocrine	0	1 (0.8)	1 (1.0)	6 (2.7)	**8** (1.7)
Hematologic	0	2 (1.6)	1 (1.0)	4 (1.8)	**7** (1.5)
≥2	0	6 (4.8)	8 (8.2)	17 (7.6)	**31** (6.5)
Initial symptom, No. (%)					
Fever	26 (86.7)	116 (92.1)	89 (91.8)	222 (98.7)	**453** (94.8)
Cough	20 (66.7)	107 (84.9)	78 (80.4)	181 (80.4)	**386** (80.8)
Tachypnea	13 (43.3)	52 (41.3)	37 (38.1)	76 (33.8)	**178** (37.2)
Diarrhea	3 (10.0)	27 (21.4)[b]	5 (5.2)	28 (12.4)	**63** (13.2)
Abdominal pain	NA	NA	10 (10.3)	43 (19.1)[a]	**53** (11.1)
Sore throat	NA	1 (0.8)	2 (2.1)	49 (21.8)[a]	**52** (10.9)
Headache	NA	1 (0.8)	2 (2.1)	48 (21.3)[a]	**51** (10.7)
Clinical syndrome, No. (%)					
Pneumonia	3 (10.0)	54 (42.9)	46 (47.4)[c]	69 (30.7)	**172** (36.0)
ILI/URI symptoms	5 (16.7)	23 (18.3)	27 (27.8)	79 (35.1)[b]	**134** (28.0)
Wheezing exacerbation	1 (3.3)	12 (9.5)	9 (9.3)	20 (8.9)	**42** (8.8)
Seizure	1 (3.3)	15 (11.9)	7 (7.2)	18 (8.0)	**41** (8.6)
Fever	13 (43.3)[a]	5 (4.0)	4 (4.1)	9 (4.0)	**31** (6.5)
Gastrointestinal	1 (3.3)	8 (6.3)	2 (2.1)	18 (8.0)	**29** (6.1)
Syncope	0	0	1 (1.0)	11 (4.9)[d]	**12** (2.5)
Bronchiolitis	3 (10.0)[e]	8 (6.3)	0	0	**11** (2.3)
Stridor	3 (10.0)[e]	0	3 (3.1)	5 (2.2)	**11** (2.3)
Interval from onset of symptoms to hospitalization, mean (SD), d	0.90 (0.79)[a]	3.38 (2.72)	3.52 (3.51)	2.68 (2.77)	2.93 (2.91)
Hospitalization duration, mean (SD), d	4.24 (3.63)	3.62 (2.80)	4.36 (4.60)	3.75 (5.06)	3.86 (4.40)
PICU admissions, No. (%)	4 (13.3)	5 (4.0)[f]	10 (10.3)	23 (10.2)	**42** (8.8)
Mechanical ventilation, No. (%)	2 (6.7)	1 (0.8)[g]	5 (5.2)	7 (3.1)	**15** (3.1)
Laboratory test values, mean (SD)					
White blood cell count, /μL	8580 (4040)	13 650 (11 100)	11 590 (7200)	9010 (6300)	10 760 (8200)
Absolute neutrophil count, /μL	3490 (2650)	8020 (7930)	7870 (5840)	6940 (4990)	7210 (6100)
Lymphocyte count, /μL	3620 (2390)	3960 (3300)	2650 (2020)	1400 (2100)	2460 (2700)
Hemoglobin, g/dL	11.60 (2.05)	11.54 (1.30)	11.53 (1.70)	12.36 (1.60)	11.92 (1.60)
Platelet count, /μL	388 (148)	320 (132)	294 (123)	238 (139)	261 (141)
C-reactive protein, U/L	22.1 (44.2)	39.5 (66.8)	55.7 (67.3)	50.2 (90.4)	46.0 (76.0)
Alkaline phosphatase, μ/L	208.0 (180.0)	174.9 (117.3)	135.8 (60.1)	145.8 (69.3)	153.3 (87.9)
Aspartate aminotransferase, U/L	132.8 (223.3)	64.7 (57.9)	47.8 (37.3)	49.2 (106.6)	55.0 (78.9)
Alanine aminotransferase, U/L	64.5 (57.6)	33.3 (32.7)	40.2 (60.3)	62.9 (184.3)	50.2 (132.6)
Antiviral treatment, No. (%)	22 (73.3)	109 (86.5)	86 (88.7)	196 (87.4)	413 (87.1)
Interval from clinical presentation to antiviral treatment, mean (SD), d	1.88 (1.60)[a]	4.16 (4.97)	4.91 (10.60)	2.95 (2.74)	3.59 (5.76)
Treatment, No. (%)					
Antibiotics	10 (33.3)	69 (54.8)	48 (49.5)	88 (39.1)	**215** (45.0)
Bronchodilators	5 (16.7)	41 (32.5)	21 (21.6)	43 (19.1)	**110** (23.0)
Systemic corticosteroids	3 (10.0)	22 (17.5)	11 (11.3)	28 (12.4)	**64** (13.4)
Inhaled corticosteroids	1 (3.3)	13 (10.3)	9 (9.3)	16 (7.1)	**39** (8.2)
Immunoglobulins	0	0	0	5 (2.2)	**5** (1.0)

Abbreviations: ILI/URI, influenza-like illness or upper respiratory tract infection; NA, not available; PICU, pediatric intensive care unit.

SI conversion factors: To convert alanine aminotransferase, alkaline phosphatase, and aspartate aminotransferase levels to microkatals per liter, multiply by 0.0167; C-reactive protein level to nanomoles per liter, multiply by 9.524; hemoglobin level to grams per liter, multiply by 10.0; lymphocyte count to $\times 10^9$/L, multiply by 0.001; platelet count to $\times 10^9$/L, multiply by 1.0; and white blood cell count to $\times 10^9$/L, multiply by 0.001.

[a] $P < .001$ vs other age groups.
[b] $P = .001$ vs other age groups.
[c] $P = .009$ vs other age groups.
[d] $P = .002$ vs other age groups.
[e] $P = .02$ vs other age groups.
[f] $P = .03$ vs other age groups.
[g] $P = .05$ vs other age groups.

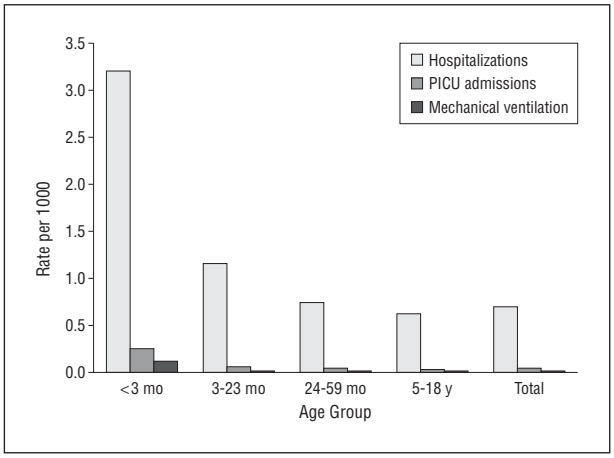

Figure 2. Rates of hospitalization, admission to the pediatric intensive care unit (PICU), and mechanical ventilation for 2009 influenza A(H1N1) among the Israeli pediatric population by age group.

found in 30 of 363 patients (8.3%) in whom these tests were performed (Table 1) (to convert aspartate aminotransferase and alanine aminotransferase levels to microkatals per liter, multiply by 0.0167). The mean (SD) aspartate aminotransferase and alanine aminotransferase levels in these patients were 140 (128) and 110 (93) U/L, respectively, with no variability among various age groups.

UNDERLYING MEDICAL CONDITIONS

Two hundred forty-five patients (51.3%) had no known predisposing medical conditions (**Table 3**). Patients younger than 2 years were less likely to have underlying medical conditions than older patients (35.3% vs 55.3%, $P<.001$) (Table 1).

One hundred twenty-five patients (26.2%) had underlying respiratory system diseases; 108 of them had asthma or recurrent wheezing. Forty-one patients (8.6%) had preexisting neurologic illnesses.

Thirty patients had underlying cardiovascular illnesses. Among these, 8 patients with cyanotic heart lesions were more likely than the rest of the patients to require mechanical ventilation (relative risk [RR], 9; 95% confidence interval [CI], 2.4-25.3; $P<.001$).

Twenty patients (4.2%) had neoplastic diseases. They were most likely to be seen initially with fever alone, and 5 of them had fever and neutropenia at the time of influenza infection diagnosis. Eleven patients each (2.3%) had metabolic or renal predisposing illnesses.

INFANTS YOUNGER THAN 3 MONTHS

The most frequent initial clinical syndrome (43.3%) affecting 30 infants younger than 3 months was fever without source (Table 1). Apnea was the initial symptom in 2 patients. Four of 30 infants (13.3%) were born prematurely at 33 weeks' gestation or earlier. Four infants (all but 1 were born prematurely) required PICU admission; 2 of them (both were premature, and 1 also had cyanotic heart lesions) required mechanical ventilation. None of them died.

Table 2. Comparison of Patients Initially Seen With Pneumonia vs Influenza-Like Illness or Upper Respiratory Tract Infection (ILI/URI) Symptoms

Variable	Pneumonia (n=172)	ILI/URI Symptoms (n=134)	*P* Value
Age, mean (SD), y	5.26 (4.87)	7.75 (5.78)	<.001
Predisposing illness, No. (%)			
Any	84 (48.8)	72 (53.7)	.30
Respiratory	58 (33.7)	31 (23.1)	.04
Interval from onset of symptoms to hospitalization, mean (SD), d	3.73 (2.86)	2.56 (2.90)	<.001
Initial symptom, No. (%)			
Fever	163 (94.8)	127 (94.8)	.60
Cough	148 (86.0)	114 (85.1)	.90
Vomiting	50 (29.1)	50 (37.3)	.10
Abdominal pain	16 (9.3)	22 (16.4)	.06
Diarrhea	21 (12.2)	17 (12.7)	.90
Tachypnea	92 (53.5)	29 (21.6)	<.001
Hypoxemia	71 (41.3)	15 (11.2)	<.001
Hospitalization duration, mean (SD), d	4.58 (5.90)	3.17 (2.90)	.007
PICU admissions, No. (%)	23 (13.4)	6 (4.5)	.008
Mechanical ventilation, No. (%)	11 (6.4)	1 (0.7)	.01
Laboratory test values, mean (SD)			
White blood cell count, /μL	12 680 (7710)	9230 (7610)	<.001
Absolute neutrophil count, /μL	8980 (6570)	6020 (5030)	<.001
Lymphocyte count, /μL	2480 (2150)	2360 (2900)	.73
Hemoglobin, g/dL	11.80 (1.61)	12.06 (1.86)	.20
Platelet count, /μL	306 (163)	236 (91)	<.001
C-reactive protein, mg/L	56.1 (71.6)	29.8 (41.3)	.009
Aspartate aminotransferase, U/L	43.8 (30.5)	51.1 (77.2)	.54
Alanine aminotransferase, U/L	29.4 (32.1)	39.9 (74.0)	.47
Bacteremia, No. (%)	4 (2.3)[a]	0	.08
Interval from clinical presentation to antiviral treatment, mean (SD), d	4.73 (7.99)	2.53 (2.61)	.002
Treatment, No. (%)			
Antivirals	162 (94.2)	110 (82.1)	.001
Antibiotics	135 (78.5)	31 (23.1)	<.001
Bronchodilators	56 (32.6)	18 (13.4)	<.001
Inhaled corticosteroids	15 (8.7)	8 (6.0)	.40
Systemic corticosteroids	28 (16.3)	8 (6.0)	.005

Abbreviation: PICU, pediatric intensive care unit.

SI conversion factors: To convert alkaline phosphatase and aspartate aminotransferase levels to microkatals per liter, multiply by 0.0167; C-reactive protein level to nanomoles per liter, multiply by 9.524; hemoglobin level to grams per liter, multiply by 10.0; lymphocyte count to $\times 10^9$/L, multiply by 0.001; platelet count to $\times 10^9$/L, multiply by 1.0; and white blood cell count to $\times 10^9$/L, multiply by 0.001.

[a] Two patients with *Streptococcus pneumoniae* and 2 patients with *Pseudomonas aeruginosa.*

CHEST RADIOGRAPHS

Chest radiographic data were available in 374 patients. Radiographs were interpreted by radiologists; 166 (44.4%) were normal. The most frequent radiographic diagnosis was pneumonia (41.2%), which was lobar in 27.3% and showed diffuse infiltrates in 13.9%. Thirteen patients had pleural effusion.

Patients having a diffuse pattern on chest radiographs had a more severe course of influenza, with higher

Table 3. Primary Underlying Medical Conditions of Hospitalized Patients With 2009 Influenza A(H1N1)[a]

Variable	No Underlying Illness (n=245)	Recurrent Wheezing (n=108)	*P* Value	Cardiovascular Condition (n=30)	*P* Value	Neurologic Disorder (n=41)	*P* Value	Metabolic Disorder (n=11)	*P* Value	Oncologic Disease (n=20)	*P* Value
Age, mean (SD), y	5.39 (5.38)	7.36 (4.96)	.004	7.45 (6.11)	.08	6.63 (5.34)	.17	6.86 (5.45)	.40	8.18 (5.37)	.03
Initial symptom, No. (%)											
Fever	238 (97.1)	99 (91.7)	.02	26 (86.7)	.006	39 (95.1)	.50	9 (81.8)	.007	20 (100.0)	.40
Cough	196 (80.0)	94 (87.0)	.11	21 (70.0)	.20	34 (82.9)	.07	11 (100.0)	.10	14 (70.0)	.30
Tachypnea	75 (30.6)	64 (59.3)	<.001	15 (50.0)	.03	12 (29.3)	.80	4 (36.4)	.70	5 (25.0)	.60
Hypoxemia	37 (15.1)	46 (42.6)	<.001	13 (43.3)	<.001	13 (31.7)	.01	3 (27.3)	.30	5 (25.0)	.02
Clinical syndrome, No. (%)											
Pneumonia	82 (33.5)	39 (36.1)	.60	10 (33.3)	.97	15 (36.6)	.70	3 (27.3)	.70	6 (30.0)	.70
ILI/URI symptoms	68 (27.8)	31 (28.7)	.92	11 (36.7)	.30	13 (31.7)	.30	6 (54.5)	.05	8 (40.0)	.30
Seizure	28 (11.4)	4 (3.7)	.02	1 (3.3)	.20	9 (22.0)	.07	0	.20	0	.10
Fever[b]	25 (10.2)	0	.07	4 (13.3)	.60	2 (4.9)	.30	0	.30	9 (45.0)	<.001
Gastrointestinal	20 (8.2)	2 (1.9)	.02	2 (6.7)	.08	2 (4.9)	.52	2 (18.2)	.20	0	.20
Wheezing exacerbation	5 (2.0)	32 (29.6)	<.001	3 (10.0)	<.001	5 (12.2)	.001	0	.60	0	.50
Interval from onset of symptoms to hospitalization, mean (SD), d	3.2 (2.9)	3.0 (2.8)	.73	1.8 (1.8)	.001	2.2 (1.8)	.01	2.4 (2.2)	.30	2.6 (5.5)	.70
Hospitalization duration, mean (SD), d	3.4 (4.2)	3.2 (2.3)	.72	4.7 (4.0)	.11	4.9 (7.0)	.19	9.8 (12.1)	.11	6.4 (6.1)	.05
Mechanical ventilation, No. (%)	3 (1.2)	2 (1.9)	.60	3 (10.0)	.002	4 (9.8)	.001	3 (27.3)	<.001	0	.62
Laboratory test values, mean (SD)											
White blood cell count, /μL	1130 (820)	1080 (1130)	.88	990 (520)	.25	950 (420)	.03	850 (310)	.02	550 (680)	.001
Absolute neutrophil count, /μL	7.2 (6.2)	8.0 (7.8)	.14	6.3 (4.2)	.56	6.9 (3.9)	.53	5.2 (2.8)	.05	3.7 (5.5)	.02
Lymphocyte count, /μL	2800 (2800)	2000 (3500)	.11	1900 (1900)	.05	1770 (1480)	.02	2500 (1500)	.56	1300 (1500)	.003
Hemoglobin, g/dL	11.90 (1.46)	12.30 (1.16)	.38	12.90 (2.30)	.60	12.00 (1.67)	.34	11.90 (1.60)	.37	10.50 (1.30)	<.001
Platelet count, /μL	293 (146)	258 (101)	.08	257 (158)	.29	253 (140)	.12	271 (150)	.34	184 (138)	.003
C-reactive protein, mg/L	47.6 (79.5)	53.8 (93.6)	.70	21.4 (34.7)	.02	55.6 (84.7)	.72	30.2 (29.6)	.12	44.9 (91.2)	.95
Interval from clinical presentation to antiviral treatment, mean (SD), d	3.54 (3.01)	3.31 (2.83)	.90	2.40 (1.8)	<.01	2.75 (1.67)	.02	2.50 (1.84)	.11	1.30 (1.30)	<.001
Treatment, No. (%)											
Antivirals	200 (81.6)	96 (88.9)	.09	28 (93.3)	.10	39 (95.1)	.03	11 (100.0)	.10	19 (95.0)	.10
Antibiotics	100 (40.8)	50 (46.3)	.30	11 (36.7)	.70	17 (41.5)	.90	8 (72.7)	.04	16 (80.0)	.001
Bronchodilators	36 (14.7)	56 (51.9)	<.001	3 (10.0)	.50	8 (19.5)	.40	1 (9.1)	.60	2 (10.0)	.60
Systemic corticosteroids	18 (7.3)	38 (35.2)	<.001	2 (6.7)	.90	1 (2.4)	.20	0	.30	0	.20
Inhaled corticosteroids	13 (5.3)	17 (15.7)	.001	2 (6.7)	.80	5 (12.2)	.09	1 (9.1)	.60	0	.30

Abbreviation: ILI/URI, influenza-like illness or upper respiratory tract infection.

SI conversion factors: To convert C-reactive protein level to nanomoles per liter, multiply by 9.524; hemoglobin level to grams per liter, multiply by 10.0; lymphocyte count to $\times 10^9$/L, multiply by 0.001; platelet count to $\times 10^9$/L, multiply by 1.0; and white blood cell count to $\times 10^9$/L, multiply by 0.001.

[a] *P* values are vs patients with no underlying medical conditions.

[b] As the primary initial symptom.

rates of PICU admission compared with patients having an alveolar pattern (RR, 3.1; 95% CI, 1.4-6.5, *P*=.003). These results are summarized in **Table 4**.

PATIENTS ADMITTED TO THE PICU

Patients admitted to the PICU had higher rates of underlying medical conditions compared with patients admitted to the ward (64.3% vs 47.2%, *P*=.04). These results are summarized in Table 4.

The 2 main underlying conditions associated with PICU admission were metabolic (RR, 6.5; 95% CI, 1.9-21.7; *P*=.01) and neurologic (2.9; 1.3-6.6; *P*=.02) disorders. No significant differences were noted in laboratory markers between patients admitted to the PICU compared with patients admitted to the wards, nor were there differences between these groups in the intervals from onset of symptoms to initiation of oseltamivir treatment.

SECONDARY BACTERIAL INFECTIONS

Ten patients had confirmed bacterial infections. These included 3 *Pseudomonas aeruginosa* bacteremias, 2 bacteremias and 2 empyemas caused by *Streptococcus pneumoniae*, 1 empyema and 1 case of tracheitis caused by *Staphylococcus aureus*, and 1 case of *Neisseria meningitidis* meningitis and bacteremia.

OSELTAMIVIR TREATMENT

There were no differences between patients treated with oseltamivir within 48 hours from the onset of influenza symptoms and those treated later. Both groups had similar hospitalization durations, PICU admissions, and rates of underlying medical conditions.

MORTALITY

Nine children from different age groups (including 3 patients in our series) died with evidence of 2009 influenza A(H1N1) virus infection during the outbreak in Israel. All had serious underlying illnesses. Fatal cases in our series included 2 patients with inherited metabolic disorder and 1 patient with leukemia.

Table 4. Comparison of Patients Admitted to the Pediatric Intensive Care Unit (PICU) vs Pediatric Wards

Variable	PICU (n=42)	Pediatric Ward (n=436)	*P* Value
Age, mean (SD), y	6.90 (5.71)	5.98 (5.32)	.31
Predisposing illness, No. (%)			
Any	27 (64.3)	206 (47.2)	.04
Respiratory	9 (21.4)	116 (26.6)	.50
Neurologic	8 (19.0)	33 (7.6)	.02
Cardiovascular	6 (14.3)	25 (5.7)	.03
Oncologic	3 (7.1)	17 (3.9)	.35
Metabolic	4 (9.5)	7 (1.6)	.01
Renal	0	11 (2.5)	.30
Endocrine	1 (2.4)	7 (1.6)	.70
Hematologic	1 (2.4)	6 (1.4)	.60
Other immunodeficiency states, congenital or acquired	0	12 (2.8)	.61
≥2	5 (11.9)	26 (6.0)	.30
Clinical syndrome, No. (%)			
Pneumonia	23 (54.8)	149 (34.2)	.008
ILI/URI symptoms	6 (14.3)	128 (29.4)	.04
Wheezing exacerbation	3 (7.1)	39 (8.9)	.70
Seizure	5 (11.9)	36 (8.3)	.40
Fever[a]	0	31 (7.1)	.30
Gastrointestinal	2 (4.8)	27 (6.2)	.30
Syncope	0	12 (2.8)	.30
Bronchiolitis	2 (4.8)	9 (2.1)	.30
Stridor	1 (2.4)	10 (2.3)	.97
Meningitis or encephalitis	2 (4.8)	3 (0.7)	.01
Interval from onset of symptoms to hospitalization, mean (SD), d	2.02 (2.50)	3.01 (2.90)	.02
Hospitalization duration, mean (SD), d	11.1 (10.4)	3.2 (2.5)	<.001
Initial symptom, No. (%)			
Tachypnea	26 (61.9)	152 (34.9)	.001
Hypoxemia	24 (57.1)	95 (21.8)	<.001
Laboratory test values, mean (SD)			
White blood cell count, /μL	12 880 (11 100)	10 550 (7800)	.20
Absolute neutrophil count, /μL	8650 (7500)	7060 (5900)	.94
Lymphocyte count, /μL	2970 (4600)	2400 (2400)	.49
Hemoglobin, g/dL	11.90 (2.20)	11.92 (1.50)	.30
Platelet count, /μL	310 (225)	280 (129)	.15
C-reactive protein, mg/L	57.7 (95.0)	45.1 (73.5)	.55
Aspartate aminotransferase, U/L	93.6 (187.4)	47.4 (57.1)	.22
Alanine aminotransferase, U/L	118.5 (290.0)	35.4 (51.1)	.20
Bacteremia, No. (%)	3 (7.1)	3 (0.7)	<.001
Chest radiograph findings, No. (%)			
Lobar pneumonia	9 (21.4)	93 (21.3)	.96
Pleural effusion	4 (9.5)	9 (2.1)	.005
Perihilar thickening	0	34 (7.8)	.06
Hyperinflation	1 (2.4)	15 (3.4)	.70
Diffuse infiltrate	14 (33.3)	38 (8.7)	<.001
Interval from clinical presentation to antiviral treatment, mean (SD), d	3.13 (2.88)	3.64 (6.00)	.35
Treatment, No. (%)			
Antivirals	40 (95.2)	373 (85.6)	.07
Antibiotics	28 (66.7)	187 (42.9)	.003
Bronchodilators	8 (19.0)	102 (23.4)	.50
Systemic corticosteroids	5 (11.9)	59 (13.5)	.80
Inhaled corticosteroids	1 (2.4)	38 (8.7)	.003
Immunoglobulins	3 (7.1)	2 (0.5)	<.001

Abbreviation: ILI/URI, influenza-like illness or upper respiratory tract infection.

SI conversion factors: To convert alanine aminotransferase and aspartate aminotransferase levels to microkatals per liter, multiply by 0.0167; C-reactive protein level to nanomoles per liter, multiply by 9.524; hemoglobin level to grams per liter, multiply by 10.0; lymphocyte count to $\times 10^9$/L, multiply by 0.001; platelet count to $\times 10^9$/L, multiply by 1.0; and white blood cell count to $\times 10^9$/L, multiply by 0.001.

[a] As the primary initial symptom.

COMMENT

Previous studies[8,9] that assessed the burden of seasonal influenza in hospitalized children used epidemiologic models based on cumulative data rather than data collected from individual patients. In the present study, patients admitted for acute respiratory or acute unspecified febrile illness were routinely monitored for 2009 influenza A(H1N1) virus. Therefore, we had the opportunity to estimate directly the burden and clinical characteristics of this influenza.

Our series included 478 patients with laboratory-confirmed 2009 influenza A(H1N1) infection, representing the largest series published to date involving children hospitalized with this infection. According to our results, the hospitalization rate for 2009 influenza A(H1N1) infection in Israeli patients 18 years or younger was 0.7 per 1000. Forty-two of our patients (8.8%) were admitted to the PICU. The mortality associated with this infection in Israel was 3.6 per 1 million children, and it was evenly distributed among the different age groups. All fatal cases involved patients with severe underlying illnesses.

The highest rates of hospitalization (3.2 per 1000), PICU admission, and mechanical ventilation were detected in infants younger than 3 months. The rate of prematurity (≤33 weeks' gestation) was higher in this group of children (13.3%) compared with that among the newborn population in Israel (1.8%).

From our results, it seems that the morbidity and mortality associated with the 2009 influenza A(H1N1) in the pediatric population in Israel was milder than that perceived from earlier studies.[1-7] Because data about the burden of seasonal influenza in Israeli children are unavailable, we were unable to compare the burden of 2009 influenza A(H1N1) with that caused by seasonal strains. However, our study showed that the hospitalization rates and the severity and mortality of the 2009 influenza A(H1N1) virus in Israeli children were similar to figures reported on seasonal influenza in the United States.[8-11]

The mortality and frequency of required mechanical ventilation in our series were much lower than those in a series from Argentina[6] that reported increased severity and mortality of 2009 influenza A(H1N1) infection compared with seasonal influenza in children. Our results differ for several reasons. The patients in Argentina had different opportunities to access health care facilities, and the median time from onset of symptoms to any medical consultation (outpatient or inpatient) was 4 days, while in our series the median interval from symptom onset to hospitalization was 2 days. Therefore, our results may more closely represent the consequences of 2009 influenza A(H1N1) infection in a population with better access to medical care. Our results are closer to the rates reported in an Australian study[12] for hospitalization, PICU admission, and mortality associated with 2009 pandemic influenza. However, the Australian study was based on cumulative data and did not focus on a pediatric population. Our results on severity of illness are also similar to a those of a recently published Canadian study,[7] although this series was small (including 58 children from a single medical center). It is possible that the coordi-

nated efforts of the Israeli National Health System abated the severity of the epidemic and resulted in consequences similar to those of seasonal influenza.

Our results also differ from findings of a study by the Centers for Disease Control and Prevention[4] that reported on 272 patients (including 45% children) who were hospitalized during the early phase of the outbreak; 25% of the hospitalized patients were admitted to the intensive care unit; 7% died. This study included only selected hospitalizations and may not have been representative of the total group of hospitalized children.

In contrast to some earlier studies,[3,4,6] we collected data during almost the entire influenza season in Israel. This might be important because reporting data from only part of the outbreak may skew the findings. The severity of cases might differ in various stages of the outbreak, possibly due to synergistic coinfection with other microorganisms circulating simultaneously. This phenomenon was shown in our study by the fact that the rates of patient admission to the PICU were higher toward the end of the influenza outbreak compared with the earlier phase.

The main clinical presentation in our series was pneumonia, followed by ILI/URI symptoms, asthma exacerbation, febrile seizures, and predominant gastrointestinal tract involvement. No specific pattern on chest radiographs was typical for influenza-associated pneumonia; however, patients with a diffuse pattern on chest radiographs had a more severe course, with higher rates of PICU admission compared with patients having an alveolar pattern on chest radiographs.

One of the main clinical features differentiating patients admitted with pneumonia vs ILI/URI symptoms was the interval from onset of symptoms to hospitalization. In patients admitted with pneumonia, this interval was significantly longer, and they received oseltamivir later in the course of illness. We cannot rule out that oseltamivir treatment among patients with ILI/URI symptoms who were hospitalized early in the course of influenza infection might have prevented the development of pneumonia. However, late initiation of oseltamivir treatment (>48 hours after onset of symptoms) was unassociated with other variables of illness severity, such as PICU admission or hospitalization duration, among our cohort of patients. Our study was not designed to assess the role of oseltamivir treatment in influenza A(H1N1) infection, and the lack of effect of early oseltamivir treatment on the PICU admission rate could be due to the fact that most of the patients were admitted directly to the PICU before they had a chance to receive oseltamivir.

About 49% of our patients had 1 or more underlying medical conditions predisposing them to complicated influenza. Children younger than 2 years had a significantly lower rate of underlying illnesses compared with older patients and are at risk for hospitalization even without preexisting underlying illnesses.

Similar to other investigations of seasonal influenza,[13] asthma was a major risk factor for hospitalization in our series. About 23% of our patients had preexisting recurrent wheezing disorder compared with 7% to 11% in the general pediatric population in Israel.[14,15]

The 2 main underlying conditions predisposing for PICU admission were metabolic and neurologic disorders. Our findings are in agreement with results of recent studies[16,17] and of earlier studies[18,19] suggesting that children with neurodevelopmental illness are at greatest risk for 2009 influenza A(H1N1) mortality and for seasonal influenza complications. The susceptibility of patients with inherited metabolic disorders to influenza complications and mortality in our study was more prominent than that reported in the literature.[20] Our study is also the first to describe higher rates of severe disease among patients with cyanotic heart lesions and possibly among infants born prematurely.

Ten of our patients (2.1%) had evidence of invasive secondary bacterial infections. The rate of bacterial superinfection in our series was low. We cannot rule out that some of the pneumonia cases, especially those with lobar infiltrates, represented secondary bacterial infections, as it is almost impossible to detect a bacterial origin of pneumonia in pediatric patients without invasive procedures.

Our study had several limitations. The primary one is possible underestimation of hospitalization rates due to lack of inclusion of patients hospitalized with influenza but not tested for the disease, particularly those without respiratory symptoms. However, because the study team collected the data prospectively, it is reasonable to conclude that most patients were adequately monitored for 2009 influenza A(H1N1) virus. In addition, we calculated the hospitalization rate based on figures reported from 3 hospitals with the highest rates of testing per total number of hospitalized patients.

The indications for hospitalization may have been more liberal in Israel, and this admission policy may have "diluted" the percentage of severe cases and resulted in an artificially lower admission rate to the PICU. However, the rates of mechanical ventilation and mortality, which are the 2 most reliable markers of severity of illness, were much lower in our series than in the Argentinean study.[3] Our rates were probably accurate because virtually every severe acute infectious disease case in Israel occurring during the 2009 outbreak was monitored for influenza infection. In addition, availability of vaccine for 2009 influenza A(H1N1) did not affect the results of this study because the vaccine was introduced late in the outbreak and few children in Israel were vaccinated during the study period.

In conclusion, our study showed that the severity and mortality of 2009 influenza A(H1N1) in Israel were milder than those described in earlier publications and were similar to the figures reported in the literature on seasonal influenza. Children with underlying metabolic and neurologic disorders represent the group at highest risk for severe complications following 2009 influenza A(H1N1) infection. Our results also suggest that children with cyanotic heart lesions and infants born prematurely are 2 additional populations at significant risk for a complicated hospital course following infection with 2009 influenza A(H1N1) virus.

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REFERENCES

1. 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.
2. Fraser C, Donnelly CA, Cauchemez S, et al; WHO Rapid Pandemic Assessment Collaboration. Pandemic potential of a strain of influenza A (H1N1): early findings. *Science*. 2009;324(5934):1557-1561.
3. Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S, et al; INER Working Group on Influenza. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. *N Engl J Med*. 2009;361(7):680-689.
4. Centers for Disease Control and Prevention (CDC). 2009 pandemic influenza A (H1N1) virus infections—Chicago, Illinois, April-July 2009. *MMWR Morb Mortal Wkly Rep*. 2009;58(33):913-918.
5. 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.
6. 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.
7. O'Riordan S, Barton M, Yau Y, Read SE, Allen U, Tran D. Risk factors and outcomes among children admitted to hospital with pandemic H1N1 influenza. *CMAJ*. 2010;182(1):39-44.
8. Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. *N Engl J Med*. 2000;342(4):232-239.
9. Neuzil KM, Mellen BG, Wright PF, Mitchel EF Jr, Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. *N Engl J Med*. 2000;342(4):225-231.
10. Rojo JC, Ruiz-Contreras J, Fernández MB, Marín MA, Folgueira L. Influenza-related hospitalizations in children younger than three years of age. *Pediatr Infect Dis J*. 2006;25(7):596-601.
11. Poehling KA, Edwards KM, Weinberg GA, et al; New Vaccine Surveillance Network. The underrecognized burden of influenza in young children. *N Engl J Med*. 2006;355(1):31-40.
12. 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.
13. Neuzil KM, Wright PF, Mitchel EF Jr, Griffin MR. The burden of influenza illness in children with asthma and other chronic medical conditions. *J Pediatr*. 2000;137(6):856-864.
14. Shohat T, Green MS, Davidson Y, Livne I, Tamir R, Garty BZ. Differences in the prevalence of asthma and current wheeze between Jews and Arabs: results from a national survey of schoolchildren in Israel. *Ann Allergy Asthma Immunol*. 2002;89(4):386-392.
15. Varsano S. Bronchial asthma in Israel. *Isr Med Assoc J*. 2002;4(8):661-663.
16. Centers for Disease Control and Prevention (CDC). 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.
17. 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.
18. Keren R, Zaoutis TE, Bridges CB, et al. Neurological and neuromuscular disease as a risk factor for respiratory failure in children hospitalized with influenza infection. *JAMA*. 2005;294(17):2188-2194.
19. Louie JK, Schechter R, Honarmand S, et al. Severe pediatric influenza in California, 2003-2005: implications for immunization recommendations. *Pediatrics*. 2006;117(4):e610-e618. doi:10.1542/peds.2005-1373.
20. Keren R, Zaoutis TE, Saddlemire S, Luan XQ, Coffin SE. Direct medical cost of influenza-related hospitalizations in children [published correction appears in *Pediatrics*. 2007;119(1):227]. *Pediatrics*. 2006;118(5):e1321-e1327. doi:10.1542/peds.2006-0598.