ORIGINAL ARTICLE

Pediatric Hospitalizations Associated with 2009 Pandemic Influenza A (H1N1) in Argentina

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ABSTRACT

BACKGROUND

While the Northern Hemisphere experiences the effects of the 2009 pandemic influenza A (H1N1) virus, data from the recent influenza season in the Southern Hemisphere can provide important information on the burden of disease in children.

METHODS

We conducted a retrospective case series involving children with acute infection of the lower respiratory tract or fever in whom 2009 H1N1 influenza was diagnosed on reverse-transcriptase polymerase-chain-reaction assay and who were admitted to one of six pediatric hospitals serving a catchment area of 1.2 million children. We compared rates of admission and death with those among age-matched children who had been infected with seasonal influenza strains in previous years.

RESULTS

Between May and July 2009, a total of 251 children were hospitalized with 2009 H1N1 influenza. Rates of hospitalization were double those for seasonal influenza in 2008. Of the children who were hospitalized, 47 (19%) were admitted to an intensive care unit, 42 (17%) required mechanical ventilation, and 13 (5%) died. The overall rate of death was 1.1 per 100,000 children, as compared with 0.1 per 100,000 children for seasonal influenza in 2007. (No pediatric deaths associated with seasonal influenza were reported in 2008.) Most deaths were caused by refractory hypoxemia in infants under 1 year of age (death rate, 7.6 per 100,000).

CONCLUSIONS

Pandemic 2009 H1N1 influenza was associated with pediatric death rates that were 10 times the rates for seasonal influenza in previous years.

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Three times in the past century, pandemic influenza viruses have circulated globally and caused increased morbidity and mortality among persons who were not generally at risk for severe seasonal influenza.[1] In March 2009, a new strain of pandemic influenza A (H1N1) virus emerged in Mexico, where it caused extensive disease in young adults,[2,3] and was associated with increased morbidity in the United States.[4,5]

The 2009 H1N1 virus spread rapidly across the Southern Hemisphere.[6,7] Morbidity and mortality were particularly high in Argentina, with numbers of confirmed cases and deaths second only to those in the United States. Although seasonal influenza viruses have been associated with a high rate of hospitalization but low mortality among children, the effect and severity of 2009 H1N1 influenza in children are unknown. We studied the effect of 2009 H1N1 virus infection during the winter of 2009 in six pediatric hospitals in Buenos Aires.

Methods

Study Period and Population

The Buenos Aires metropolitan area has an estimated pediatric population (<18 years of age) of 3.8 million.[8] Of these children, more than 2 million do not have private medical insurance and may be admitted for free care at public hospitals.[8] We conducted a retrospective study involving patients who were hospitalized at six public pediatric facilities in Buenos Aires from May 1 to July 31, 2009. The total catchment population of these hospitals is estimated at 1.2 million children (accounting for 57% of all children eligible for care at public hospitals).[8] These hospitals are the reference public institutions in their regions.

The study began during the first week in which the 2009 H1N1 virus was detected in two hospitalized children and extended through the last week in which the virus was detected in two inpatients. Eligible patients were infants under 1 year of age and children under the age of 18 years who were admitted to pediatric wards and intensive care units (ICUs) with a diagnosis of acute respiratory infection or fever (temperature, >38.3°C). All eligible children were tested for influenza viruses. Cases of 2009 H1N1 influenza were confirmed by testing nasal aspirates or combined nasal and throat swabs with the use of a real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay at regional laboratories (for 66 samples) or national laboratories (for 185 samples) according to the protocol recommended by the U.S. Centers for Disease Control and Prevention (CDC).[9]

Testing for seasonal influenza in 2007 and 2008 was routinely performed in public hospitals in Buenos Aires for all children who were admitted with respiratory symptoms with the use of a direct immunofluorescence assay, which has a sensitivity of 78 to 81%, as compared with RT-PCR.[10,11] In addition, respiratory tract specimens were tested for respiratory syncytial virus (RSV), adenovirus, and parainfluenza virus types I, II, and III by means of a direct immunofluorescence assay and culture. Microbial growth in blood cultures was assessed with the use of the BACTEC 9240 system (Becton Dickinson).

We abstracted data from medical records, using a standardized report form modeled on the case-assessment form prepared by the CDC.[12] We obtained demographic, clinical, laboratory, epidemiologic, and radiologic data from a chart review. Chest radiographs were reevaluated by an independent pediatric radiologist who was not aware of the original interpretations. Hypoxemia was defined as an oxygen saturation of less than 93% while the patient was breathing ambient air.[13] Nosocomial acquisition of the 2009 H1N1 virus was defined as an onset of illness more than 72 hours after hospital admission. The study was conducted as a retrospective public health analysis of deidentified data, so approval by the institutional review board at each participating institution and informed consent were not required.

Statistical Analysis

We compared the characteristics of the children who had 2009 H1N1 influenza alone with those who had viral coinfection, using Fisher's exact test or the chi-square test for covariates and the Wilcoxon rank-sum test for continuous variables. Denominators that were used to calculate proportions varied according to the number of patients with available data. Rates of hospitalization and death associated with 2009 H1N1 influenza were calculated with the use of denominators totaling the pediatric population in the total catchment area of the hospitals since 2007, as reported by the National Institute of Statistics.[8] All analyses were performed with Stata software, version 10.1. A P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

STUDY POPULATION

We included 251 infants and children with confirmed 2009 H1N1 influenza in the study. The median number of patients who were admitted to each hospital was 39 (range, 14 to 71). The hospitalization rate for children with 2009 H1N1 influenza was 20.9 per 100,000 children (95% confidence interval [CI], 18.4 to 23.7), as compared with 10.3 per 100,000 (95% CI, 8.4 to 12.5) for seasonal influenza during 2008.

Of the children with confirmed 2009 H1N1 influenza, 47 (19%) had a viral coinfection (Table 1); of these, 42 had a positive test for RSV. The other five children with coinfection had a positive test for either parainfluenza virus (in three children) or adenovirus (in two children). Nonpandemic seasonal influenza viruses were confirmed in six hospitalized children who were excluded from the analysis per study protocol (three children with type A [H3N2] influenza virus, two with type B influenza virus, and one with coinfection with both H3N2 and influenza B viruses). None of the children who were infected with seasonal strains required intensive care.

Hospitalizations for 2009 H1N1 influenza first occurred during the first week of May and peaked at the end of June. According to a government directive, school and social activities were suspended for 3 to 4 weeks on June 28. The number of cases declined during this period, but the timing of the directive coincided with the natural decline in the number of influenza cases seen in previous seasonal influenza epidemics.[14] By the first of August, no additional children were admitted to the participating hospitals (Fig. 1A).

The majority of admitted children (75%) were younger than 2 years of age; 60% were infants under the age of 1 year (Fig. 1B). Eighty-one children (32%) had one or more preexisting conditions, including asthma, immunosuppression, chronic lung disease, neurologic disorder, and heart disease (Table 1). Among parents for whom data regarding educational background were available, 28 of 205 mothers (14%) and 24 of 186 fathers (13%) had incomplete primary education; neither parent completed primary school in 10

Table 1. Epidemiologic Features and Preexisting Conditions in Children Hospitalized with 2009 H1N1 Influenza Alone or with Viral Coinfection.

Variable	H1N1 Influenza Alone (N=204)	H1N1 Influenza plus Viral Coinfection (N=47)	All Patients (N=251)
Age — mo*			
Median	10	7	10
Range	<1–226	<1–151	<1–226
Male sex — no. (%)	110 (54)	21 (45)	131 (52)
Preexisting condition — no./total no. (%)†			
Any	68/196 (35)	13/45 (29)	81/241 (34)
Asthma	12/199 (6)	2/46 (4)	14/245 (6)
Chronic lung disease	21/198 (11)	4/44 (9)	25/242 (10)
Heart disease	11/199 (6)	4/45 (9)	15/244 (6)
Metabolic disorder	3/200 (2)	1/46 (2)	4/246 (2)
Renal disease	5/200 (2)	2/45 (4)	7/245 (3)
Cancer	8/202 (4)	0	8/247 (3)
Immunosuppression	15/199 (8)	1/44 (2)	16/243 (7)
Neurologic disease	18/199 (9)	3/46 (7)	21/245 (9)
Malnutrition	12/198 (6)	4/45 (9)	16/243 (7)
Smoking at home — no. (%)	86/169 (51)	20/42 (48)	106/211 (50)

* P=0.009 for the between-group comparison.
† Children may have had more than one preexisting illness.

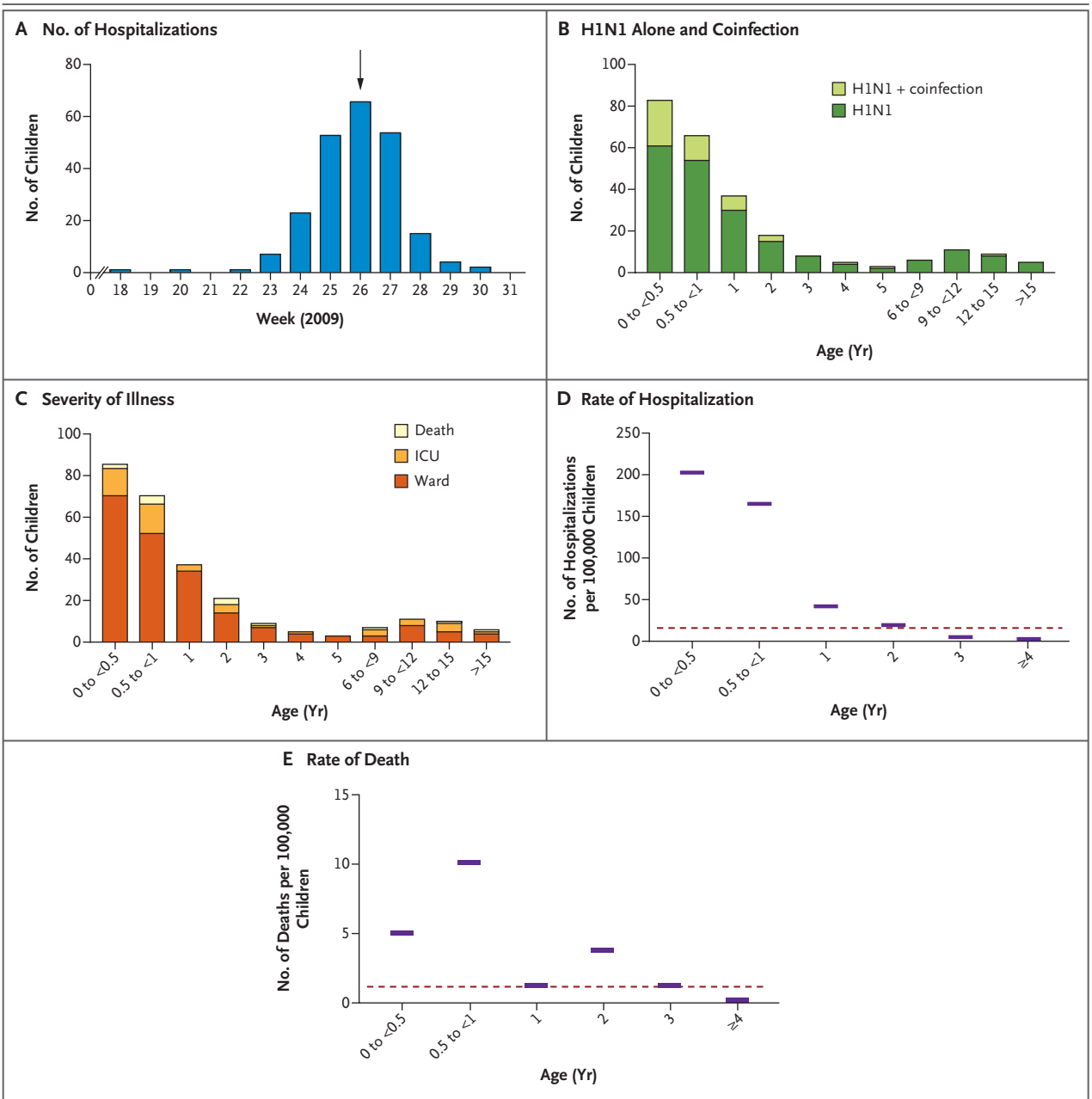

Figure 1. Distribution of Hospitalizations and Rates of Disease Severity among Children with 2009 H1N1 Influenza in Buenos Aires.

Panel A shows the number of hospitalizations of children with 2009 H1N1 influenza between May 1 and July 31, 2009. The arrow indicates the government-mandated suspension of educational and social activities for 3 to 4 weeks on June 28, which was followed by a decline in the number of cases. Panel B shows the number of hospitalized children who were found to be infected with only 2009 H1N1 influenza and those with coinfection. Hospitalized children who were infected with only the 2009 H1N1 virus were older than those who were coinfected with another virus (median age, 10 months vs. 7 months; P=0.009). Panel C shows the severity of illness in children with 2009 H1N1 influenza, according to age, with the number of children who were admitted to a pediatric ward or an intensive care unit (ICU) and those who died. Panel D shows the number of children who were hospitalized per 100,000 children, according to age, for an overall rate of 20.9 per 100,000 children (as represented by the dashed line). Panel E shows the number of deaths from 2009 H1N1 influenza, according to age, for an overall rate of 1.1 per 100,000 children (dashed line).

homes. Fifty-eight of 191 families (30%) lived in homes with more than three persons per room. Ten of 205 children (5%) had received seasonal influenza vaccine before the 2009 season. Smoking at home was frequent. Among 159 children with available information, 66 (42%) had had close contact with someone with influenza-like symptoms in the 7 days before admission.

CLINICAL MANIFESTATIONS AND HOSPITAL COURSE

Two thirds of the patients with available information (156 of 236) presented more than 48 hours after the onset of symptoms. The median time to consultation (either on an outpatient basis or on hospital admission) was 4 days (range, 1 to 30). No differences were observed in the time to consultation between surviving patients and those who died.

Hospitalized children who were infected with only the 2009 H1N1 virus were older than those who were coinfected with another virus (median age, 10 months vs. 7 months; P=0.009) (Table 1 and Fig. 1B). Nosocomial transmission of 2009 H1N1 influenza was observed in three patients, including a 14-year-old boy who had previously been admitted with multiple traumatic injuries and died of 2009 H1N1 influenza.

Signs and symptoms on admission included fever (in 88% of the children), cough (in 70%), rhinorrhea (in 32%), and hypoxemia (in 82%) (Table 2). Wheezing was noted in 16% of the patients, and gastrointestinal symptoms were frequent in patients who were infected only with the 2009 H1N1 virus (P=0.06 for the comparison between single infection and coinfection) (Table 2). In children who were older than 5 years of age, pain-related symptoms were infrequent (6% with odynophagia or myalgia). Three children (12, 16, and 28 months of age) presented with febrile seizures, with only one having a history of neurologic disease.

Among children with available data, oseltamivir was administered within 48 hours after the onset of symptoms in 4 of 34 children (12%) in the ICU and in 18 of 137 children (13%) in the pediatric ward. Among 194 patients with available data on the duration of therapy, 19 were treated for less than 5 days, 150 for 5 days, and 25 for 10 or more days; 118 were under 1 year of age, and only 7 of these patients received treatment within 48 hours after the onset of symptoms. Timely antiviral administration increased from 9% in early June (from June 1 to June 15) to 54% the following month (from July 1 to July 15) after specific guidelines were issued by public health authorities on June 16. However, the use of antiviral therapy did not significantly affect the risk of admission to an ICU (odds ratio for risk of admission, 0.88; 95% CI, 0.20 to 2.95; P=0.83).

Oxygen supplementation was provided to 82% of hospitalized patients for a median duration of 6 days (range, 1 to 60) (Table 2). The majority of hospitalizations were for severe hypoxemia, with 47 patients (19%) requiring admission to an ICU and 42 patients (17%) requiring mechanical ventilation. High-frequency oscillatory ventilation and extracorporeal membrane oxygenation were not available at these hospitals.

A preexisting diagnosis of asthma was significantly associated with the risk of admission to an ICU (odds ratio, 4.92; 95% CI, 1.38 to 17.33; P=0.002), whereas patients with immunosuppression associated with human immunodeficiency virus infection and those with cancer who were receiving chemotherapy were less likely to be admitted to an ICU (P=0.04).

BACTERIAL COMPLICATIONS

Among patients with 2009 H1N1 influenza, 25 had confirmed or presumptive bacterial pneumonia, with empyema developing in 4 of these children (*Streptococcus pneumoniae* in 1 patient, methicillin-resistant *Staphylococcus aureus* in 1 patient, and negative cultures in 2 patients). Pneumonia developed in five children more than 72 hours after hospitalization. Pneumothorax developed in six children (of whom four were receiving mechanical ventilation); two of the children with pneumothorax had bacterial pneumonia.

Blood cultures were positive in 10 children. The most frequent isolate was coagulase-negative staphylococcus, in four children, followed by *S. pneumoniae*, in two children (*S. pneumoniae* vaccine coverage is low in Argentina[15]) (Table 2). Antibiotics were administered to 143 of 204 children (70%) in pediatric wards, as compared with 43 of 47 children (91%) in ICUs (P=0.002). Eighty-two children received antibiotics on admission. Ceftriaxone and ampicillin were prescribed most frequently. Corticosteroids were administered to 20

of 47 patients (43%) in ICUs; no survival benefit from the use of corticosteroids was observed (P=0.60).

LABORATORY TESTS ON ADMISSION

Mean white-cell and platelet counts were within normal limits on admission (iron-deficiency ane-

Table 2. Clinical Signs and Symptoms, Respiratory Complications, and Results of Laboratory Tests in Children Hospitalized with 2009 H1N1 Influenza Alone or with Viral Coinfection.

Variable	H1N1 Influenza Alone (N=204)	H1N1 Influenza plus Viral Coinfection (N=47)	All Patients (N=251)
Clinical signs and symptoms			
Fever			
Patients — no. (%)	181 (89)	39 (83)	220 (88)
Median duration (range) — days	2 (1–21)	3 (1–16)	3 (1–21)
Cough			
Patients — no. (%)	141 (69)	34 (72)	175 (70)
Median duration (range) — days	5 (1–30)	7 (1–24)	5 (1–30)
Rhinorrhea			
Patients — no. (%)	63 (31)	17 (36)	80 (32)
Median duration (range) — days	5 (1–30)	6 (2–15)	5 (1–30)
Odynophagia — no. (%)	8 (4)	1 (2)	9 (4)
Otalgia — no. (%)	4 (2)	0	4 (2)
Myalgia — no. (%)	6 (3)	0	6 (2)
Headache — no. (%)	6 (3)	0	6 (2)
Vomiting			
Patients — no. (%)	20 (10)	1 (2)	21 (8)
Median duration (range) — days	2 (1–9)	1	2 (1–9)
Diarrhea			
Patients — no. (%)	17 (8)	1 (2)	18 (7)
Median duration (range) — days	2 (1–9)	1	2 (1–9)
Rash — no. (%)	5 (2)	0	5 (2)
Asthenia — no. (%)	13 (6)	1 (2)	14 (6)
Respiratory complications			
Wheezing — no. (%)	24 (12)	15 (32)	39 (16)
Bacterial pneumonia — no. (%)	21 (10)	4 (9)	25 (10)
Empyema — no. (%)	4 (2)	0	4 (2)
Pneumothorax — no. (%)	5 (2)	1 (2)	6 (2)
Hypoxemia — no. (%)	163 (80)	43 (91)	206 (82)
Oxygen supplementation			
Patients — no. (%)	163 (80)	43 (91)	206 (82)
Median duration (range) — days	6 (1–43)	7 (1–60)	6 (1–60)
Use of oseltamivir — no. (%)	172 (84)	36 (78)*	208 (83)
Admission to intensive care unit — no. (%)	36 (18)	11 (23)	47 (19)
Use of mechanical ventilation			
Patients — no. (%)	32 (16)	10 (21)	42 (17)
Median duration (range) — days	10 (1–42)	6 (1–24)	10 (1–42)
Death — no. (%)	12 (6)	1 (2)	13 (5)

Table 2. (Continued.)

Variable	H1N1 Influenza Alone (N=204)	H1N1 Influenza plus Viral Coinfection (N=47)	All Patients (N=251)
Laboratory results			
Leukocyte count — per mm³			
Median	10.6	11.0	10.7
Range	0.2–35.0	3.1–41.7	0.2–41.7
Platelet count — per mm³			
Median	347	380	353
Range	6–1540	44–859	6–1540
Hematocrit — %			
Median	31	32	32
Range	18–44	23–41	18–44
Positive blood culture — no./total no. (%)	10/121 (8)	0	10/147 (7)
Coagulase–negative staphylococcus — no.	4		4
Streptococcus pneumoniae — no.	2		2
Methicillin-resistant *Staphylococcus aureus* — no.	1		1
Escherichia coli — no.	1		1
Serratia marcescens and *Burkholderia cepacia* — no.	1		1
S. viridans — no.	1		1

* Data were missing for one patient with viral coinfection.

mia is often observed in this population), although 61 of 214 patients (29%) with available data had thrombocytosis (platelet count, >450,000 per cubic millimeter). Leukopenia (absolute leukocyte count, <1000 per cubic millimeter) was present in only 5 of 221 children (2%).

RADIOGRAPHIC EVALUATION

Ninety-two chest radiographs obtained on admission in 76 patients were available for reevaluation by an independent pediatric radiologist. The most frequent radiographic diagnosis was pneumonia (78%), which was focal in 33% of the patients and multifocal in 45%. Pneumonic processes were more often observed in a single lung (in the right lung in 55% of the patients and in the left lung in 16% of the patients) than in both lungs (in 29% of the patients).

DEATHS

Of 251 patients who were admitted to the hospital, 13 (5%) died, for an overall death rate of 1.1 per 100,000 children (Table 3 and Fig. 1E). Twelve of the children who died had only 2009 H1N1 influenza, and one was coinfected with RSV. The median duration of illness before death was 5 days (range, 1 to 15). Three children (23%) died within 3 days after the onset of symptoms.

The death rate was highest among hospitalized infants, at 7.6 per 100,000 (Fig. 1E). No deaths were identified in infants with seasonal influenza in 2007 and 2008, although in 2007 two older children died from seasonal influenza. The median age of the 13 children who died was 19 months (range, 1 month to 14.5 years). Eleven of the children (85%) were younger than 4 years of age, and 6 (46%) were infants. No association was observed between the parents' educational background or smoking status or the number of persons in the home and the risk of death. No significant differences were observed in the rates of death among the six hospitals (P=0.22).

The majority of patients died from refractory hypoxemia (62%) (Table 3). No patients who died had bacteremia; three had presumptive or confirmed bacterial pneumonia (one with sterile empyema). Nine patients (69%) had a preexisting illness that was associated with increased mortality

Table 3. Characteristics of Hospitalized Children with 2009 H1N1 Influenza Who Died.*

Patient No.	Age	Sex	Preexisting Condition	Illness Duration on Admission	Length of Hospital Stay	Time of Hospitalization	Complications	Cause of Death
				days		*week in 2009*		
1	1 mo	F	None	2	16	25	None	Refractory hypoxemia
2	3 mo	F	Chronic lung disease	1	11	23	Pneumothorax	Refractory hypoxemia
3	6 mo	M	Chronic lung disease	10	9	26	Pneumonia	Refractory hypoxemia
4	8 mo	F	Heart disease	1	17	24	None	Heart failure
5	9 mo	M	Chronic lung disease plus neurologic disease	8	3	25	None	Refractory hypoxemia
6	10 mo	F	None	7	14	26	None	Refractory hypoxemia
7	16 mo	F	Asthma plus neurologic disease	10	13	23	Renal failure	Shock plus refractory hypoxemia
8	2.2 yr	F	None	1	NA	25	Renal failure	Shock
9	2.3 yr	M	Heart disease plus malnutrition	NA	1	25	None	Refractory hypoxemia
10	2.5 yr	F	None	7	0	28	Renal failure	Shock
11	3.8 yr	F	Neurologic disease	NA	9	26	None	Shock plus refractory hypoxemia
12	8.2 yr	F	Asthma plus neurologic disease	4	11	25	Pneumonia plus empyema	Shock
13	14.8 yr	M	Multiple traumatic injuries†	NA	8	25	Pneumonia plus myocarditis	Heart failure

* NA denotes not available.
† This patient had nosocomial acquisition of 2009 H1N1 influenza, with 3 days of symptoms before the diagnosis was suspected.

(odds ratio, 4.87; 95% CI, 1.30 to 22.23; P=0.005), including a neurologic disorder (odds ratio, 5.62; 95% CI, 1.13 to 22.63; P=0.003) and chronic lung disease (including asthma) (odds ratio, 3.69; 95% CI, 1.03 to 13.64; P=0.02). Of the 13 patients who died, 5 were hospitalized within 48 hours after the onset of symptoms; none received timely oseltamivir. No autopsies were performed.

DISCUSSION

In our study, we found that the hospitalization rate for 2009 H1N1 influenza among children was twice that for 2008 seasonal influenza in the same population. The rate of death was 10 times the rate associated with seasonal influenza for the same population in 2007 and 5 times the rate reported by the CDC for the U.S. pediatric population during the relatively severe 2003–2004 influenza season (0.2 deaths per 100,000 children).[16] Mortality was particularly high among infants (7.6 deaths per 100,000 children), which was 10 times the U.S. infant death rate from seasonal influenza in 2003–2004.[16] Notably, no deaths of infants with seasonal influenza were identified in Buenos Aires hospitals in either 2007 or 2008. Bacterial coinfection was uncommon in 2009. Most deaths were attributable to refractory hypoxemia.

Pediatric 2009 H1N1 influenza is distinguished by its severity. As is consistent with our current findings, a population-based study that was conducted in the United States showed a high rate of hospitalization for seasonal influenza among children who were under the age of 2 years, and 11% of the hospitalized children had coinfection with RSV; 72% of the cases of influenza were initially unrecognized, precluding timely antiviral treatment.[17] However, only 5% of those hospitalized children were admitted to the ICU, only 22% required oxygen supplementation, and none required mechanical ventilation or died.[17,18] This is in marked contrast to our findings for the current pandemic, in which 19% of the children were admitted to the ICU, 82% required oxygen, 17% required mechanical ventilation, and 5% died. In the United States, the estimated yearly number of

deaths related to seasonal influenza in children under the age of 5 years is 92,[19] with 153 reported deaths in 2003–2004 for children under the age of 18.[16]

During the pandemic season, pediatric units in Buenos Aires that provide medical care to 1.2 million children collectively reported 13 influenza-related deaths. This season was unprecedented in the number of cases, disease burden, and severity. Elective surgeries were canceled for infection-control purposes, emergency rooms and hospital wards were overwhelmed with sick children, and ICUs were forced to expand their regular facilities. Recent reports point to the severity of the upcoming pediatric influenza season in the United States.[20] Hospitalized children with 2009 H1N1 influenza in the Northern Hemisphere also had high rates of preexisting illness, especially asthma and neurologic disorders.[20-22]

Deaths that were associated with 2009 H1N1 influenza in Buenos Aires occurred predominantly in young children. Two thirds of fatal cases were attributed to refractory hypoxemia. Bacterial coinfection was identified in few patients from cultures of blood or pleural fluid, a finding that is in agreement with recent reports.[20,21] In a retrospective case series of influenza-associated deaths in the United States during the 2003–2004 influenza season, 24% of children had coinfection on the basis of cultures from multiple sites.[16] In that retrospective series, mortality was highest among children under the age of 6 months, the median age among fatal cases was 3 years, and 53% of the patients who died had chronic medical conditions.[16] The median duration of illness was 5 days, and 29% of patients died within 3 days after the onset of symptoms.

Some similarities exist between the above-mentioned patients in the United States and the children who were hospitalized with 2009 H1N1 influenza in Buenos Aires. In Argentina, the death rate was also highest among infants but was 10 times the rate during the 2003–2004 influenza season in the United States, and 69% of the patients who died had chronic medical conditions. Preexisting neurologic and chronic lung disorders specifically increased the odds of death. The median duration of illness in patients who died was 5 days, and 23% died within 3 days after the onset of symptoms, findings that are consistent with the CDC report.[16] Factors that may have contributed to the high proportion of deaths in Buenos Aires include the rate of chronic medical conditions (69%), delayed consultation or hospital admission, and the unrecognized presentation of 2009 H1N1 influenza.[17]

In the United States, current recommendations for vaccination give priority to children between the ages of 6 months and 18 years.[23] The results of our study support the finding that children under the age of 4 years are at markedly increased risk for severe disease. In addition, children with asthma or neurologic disorders have an increased risk of death.[20-22,24]

Severe illness from pandemic influenza viruses preferentially occurs in young patients who may have a preexisting, although nonprotective, immunity against the new strain or serotype.[2,3,25-29] Therefore, if the severity of infection is indeed decreased by immunosuppression, cross-reactive nonprotective immunity might contribute to pathogenesis.

At the peak of the epidemic, the Argentine government closed schools, suspended community gatherings, encouraged social distancing, and conducted an intense awareness campaign. Empirical therapy with oseltamivir for patients with influenza-like symptoms was also recommended for high-risk and hospitalized children.[30] The number of cases subsided soon thereafter. Yet seasonal influenza in 2007 followed a very similar pattern, complicating the interpretation of the specific effect of these interventions. A similar campaign nevertheless seemed to be successful in Mexico.[31]

There are several limitations of our study. First, experiences may vary in scope and magnitude in other countries. Second, the detection of influenza in 2007–2008 was performed by means of a direct immunofluorescence assay, which underestimated the number of infections, as compared with the RT-PCR assay, for 2009 H1N1 influenza. Third, clinical evaluation and data recording were not standardized, and observations may have differed among hospitals or health care providers.

Pediatric infection with the pandemic influenza virus is associated with substantial mortality. Important tools for minimizing the severity of infection include educating the general population and health care providers in order to promote early case recognition, considering early empirical antiviral therapy for children with 2009 H1N1 influenza–like illness who have preexisting neurologic disorders or chronic lung diseases, and promoting the availability of the H1N1 vaccine.

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APPENDIX

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