

Comparative Characteristics of the 2009 Pandemic Influenza A (H1N1) Virus and 2010–2011 Seasonal Influenza in Pediatric Patients

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ABSTRACT: **Background:** In March 2009 the pandemic influenza A (H1N1) strain was identified. The disease initially appeared to be accompanied by complications and high mortality rates. It became an endemic virus during the influenza season in our region, along with the classical seasonal H3N2.
Objectives: To identify the burden of pandemic influenza, its effect in pediatric patients, and complicated hospitalizations, compared to seasonal influenza years after the pandemic.
Methods: A retrospective observational study was conducted at a tertiary hospital. Data were collected from the medical records of all children who were hospitalized from April 2009 to 2011 with laboratory-confirmed influenza.

Results: Of 191 patients with influenza, 100 had the 2009 pandemic influenza, 62 had seasonal influenza, and 29 had H1N1 in 2010–2011. Patients with the 2009 H1N1 were characterized by older age, more co-morbid conditions and more symptoms including fever, cough and rhinitis on admission. No significant differences in outcomes between the groups were recorded. Of patients hospitalized with pandemic influenza in 2009, 28% had complicated hospitalizations, compared with 17.7% of patients hospitalized with seasonal influenza in 2010–11. Children with pandemic influenza received more oseltamivir (Tamiflu®) (94% vs. 19.4%, $P < 0.001$) and more antibiotics than the other groups.

Conclusions: The type of influenza had no effect on outcome. There were no significant differences between groups in the percentages of in-hospital mortality, admission to intensive care units, prolonged hospitalization (> 9 days), or the development of complications during hospitalization.

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KEY WORDS: complications, hospitalization, pandemic influenza A (H1N1), pediatric patients, seasonal influenza

In March 2009 an outbreak of a new strain of influenza A (H1N1) began in Mexico, particularly among young and previously healthy people, with a higher incidence in children [1–3]. In June 2009, following the rapid spread of the disease worldwide, it was declared a pandemic by the World Health Organization (WHO) [3]. By August 2009 the pandemic influenza had caused 477 deaths in the United States, including 36 cases in children under the age of 18 years. Later, in March 2010, almost 60 million cases of H1N1 had occurred worldwide according to the estimation of the U.S. Centers for Disease Control and Prevention (CDC) [3]. According to the reports of the CDC, most cases belonged to at least one of the high risk groups: age < 5 years or having medical conditions that increased the risk for influenza-related complications [4]. In Argentina, the rate of deaths associated with the 2009 pandemic influenza was 10 times the rate of death associated with seasonal influenza in 2007 for the same population, and five times the rate during the influenza season of 2003–2004 for American pediatric patients, according to CDC reports [5]. In Israel, morbidity and mortality were milder [1].

More children with high risk medical conditions (e.g., neurodevelopmental, chronic pulmonary) died due to the pandemic influenza in 2009 than those who died in previous seasons. Children with neurodevelopmental conditions were at high risk for seasonal influenza complications [1,4]. Follow-up and surveillance are needed to determine whether co-morbidities or other variables are significant in pediatric mortality [4].

Pneumonia was the main clinical presentation of patients with pandemic H1N1 infection [1]. The main symptoms were fever, cough and shortness of breath [6]. Diarrhea and vomiting were reported more in pandemic influenza A (H1N1) than in seasonal influenza [7,8].

An empiric treatment with neuraminidase inhibitor was recommended by the WHO and the CDC for all patients at increased risk of influenza complications with suspected or confirmed 2009 H1N1 virus infection [9]. During the 2009 H1N1 pandemic, on the basis of limited pharmacokinetics data, oseltamivir dosing recommendations were developed for

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children aged < 1 year since it was not approved by the Food and Drug Administration (FDA) before for children aged < 1 year [9]. Delayed treatment with antiviral agents (> 48 hours after illness onset) was associated with an increased risk of severe disease [10-12]. However, the FDA approved the use of oseltamivir for treating the pandemic influenza A (H1N1) in 2009, even if treatment was initiated more than 48 hours from the onset of symptoms, as it was found to reduce mortality [8].

In a multicenter study conducted in Israel, due to lack of information concerning the burden of seasonal influenza in pediatric patients, no comparison was made between the burden of the 2009 pandemic influenza A (H1N1) and that caused by seasonal strains [1]. According to various reports and studies, it appears that pandemic influenza A (H1N1) caused severe disease, especially among young people and those with risk factors, but little data are available regarding the severity of A (H1N1) compared with influenza in the subsequent years caused by seasonal strains and A (H1N1). The present study investigated the impact of the type of influenza on complicated hospitalizations.

PATIENTS AND METHODS

An observational retrospective study was conducted in the Departments of Pediatrics of the Rappaport Children's Hospital at Rambam Health Care Campus, a tertiary hospital in Haifa. Data were collected from electronic medical records.

The inclusion criteria were: all children hospitalized with influenza from 1 April 2009 until the end of the influenza season on 30 April 2011, with laboratory confirmation of either A (H1N1) 2009 or with seasonal influenza [Influenza A (H3N2), Influenza B] confirmed by reverse transcription polymerase chain reaction (RT-PCR). A test panel of respiratory viruses, including influenza, is mandatory for all children hospitalized with any respiratory symptom.

Variables included demographic data and co-morbidities: asthma and hyper-reactive airway disease, or respiratory, heart and vascular, congenital, neurological, metabolic, immune system and hematological diseases. Chronic medications and current influenza vaccination status were also investigated.

Collected data included presenting signs and symptoms: fever, cough, rhinorrhea, headache, sore throat, gastrointestinal symptoms, muscle pain, tachypnea, and desaturation. Laboratory and X-ray findings, specific treatment (oseltamivir, antibiotics, steroids, inhalations), and duration of treatment during hospital stay were retrieved from the patients' electronic charts.

Severity of illness was defined as: tachypnea > 60 breaths/min, desaturation < 90% saturation, fever > 39°C, duration of symptoms, complication on presentation and during hospitalization (respiratory, neurological, infectious, metabolic, cardiac), hospitalization in the intensive care unit (ICU), need for mechanical ventilation, and 30 day mortality. Underlying

conditions were defined as any chronic condition requiring chronic medications or special treatment (i.e., convulsions, diabetes mellitus, cystic fibrosis). Complicated hospitalization was defined as in-hospital mortality, hospitalization in the ICU, prolonged hospitalization (> 9 days), and development of complications during hospitalization. The study was approved by the local Institutional Review Board.

STATISTICAL ANALYSIS

Demographic data, co-morbidity, presenting signs and symptoms, and differences in treatment between patients with pandemic influenza A (H1N1) in 2009 and patients with seasonal influenza in the years 2010–2011 were compared, as were patients with 2009 pandemic influenza and patients with A (H1N1) in the years 2010–2011, using the chi-square test. Comparison of rates of complicated hospitalization and its components were performed using the same test.

Comparison of duration of antiviral treatment, duration of antibiotic treatment, and length of hospital stay was conducted by using the Mann-Whitney non-parametric test. A *P* value ≤ 0.05 was considered significant. SPSS software version 21.0 (Chicago, IL SPSS statistical software) was used for statistical analysis.

RESULTS

A total of 191 patients were hospitalized with influenza. The first group included 100 children hospitalized with the 2009 pandemic influenza A (H1N1), while 62 children were hospitalized with seasonal influenza in the years 2010–11 and 29 children who were hospitalized due to A (H1N1) in the same season.

The age distribution of hospitalized patients differed between patients with seasonal and pandemic influenza, with a shift toward older age among children with pandemic influenza. In 2009, only 38% of patients hospitalized with pandemic influenza were < 1 year old. The mean age was 7.3 years, compared to children with seasonal influenza where 63% were < 1 year old. Their mean age was 4.3 years (*P* < 0.001) [Table 1]. There were no differences in gender between the groups. Underlying conditions were more common among patients with pandemic influenza than patients with seasonal influenza (69% vs. 50%, *P* = 0.002).

In 2009, no vaccination against the A (H1N1) virus strain was available. Only 2% of all patients were vaccinated against seasonal virus strains, but vaccination status was missing in 77% of the charts. The following year, the influenza vaccination included vaccination against the A (H1N1) strain, but only 10% of all the children who were hospitalized in the years 2010–11 due to both seasonal influenza and to influenza caused by A (H1N1) had been vaccinated. The majority, 56%, had not been vaccinated. There were no relevant data available for the remaining 34% (the third group).

Table 1. Characteristics and underlying conditions

Group	1	2	3	1 vs. 2	1 vs. 3	2 vs. 3
Variables	Patients with 2009 H1N1 (N=100)	Patients with 2010-11 seasonal influenza (N=62)	Patients with 2010-11 H1N1 (N=29)	2009 H1N1 vs. seasonal influenza	2009 H1N1 vs. 2010-11 H1N1	Seasonal influenza vs. 2010-11 H1N1
	N (%)			P value		
Age (yrs)	< 0.5	22 (22)	25 (40)	10 (34)	0.029	NS
	0.5-1	16 (16)	14 (23)	8 (28)		
	1-6	17 (17)	9 (15)	2 (7)		
	7-10	14 (14)	5 (8)	4 (14)		
	11-15	31 (31)	9 (15)	5 (17)		
Age (yrs)	Mean	7.3 ± 6	4.3 ± 5.3	4.8 ± 5.8	< 0.001	NS
	Median	6	1	1		
Co-morbidity	No	31 (31)	31 (50)	17 (59)	0.02	0.009
	Yes	69 (69)	31 (50)	12 (41)		
Cause of hospitalization	Fever	26 (26)	10 (16)	8 (28)	0.09	NS
	Respiratory	53 (53)	35 (56)	16 (55)		
	Neurological	6 (6)	6 (10)	2 (7)		
Duration of symptoms before hospitalization (days)	Mean (SD)	2.9 (3.2)	5.0 (8.5)	5.0 (4.4)	0.039	0.01
	Median (min-max)	2 (0-14)	3 (0-60)	4 (0-21)		
Symptoms	Temp > 38°C	83 (83)	39 (63)	21 (72)	0.005	NS
	Cough	84 (84)	41 (66)	22 (76)	0.012	NS
	Rhinorrhea	74 (74)	34 (55)	19 (66)	0.016	NS
	Vomiting	35 (35)	18 (29)	7 (24)	NS	NS
	Diarrhea	10 (10)	9 (15)	3 (10)	NS	NS
	Tachypnea	34 (34)	24 (39)	12 (41)	NS	NS

*Data are in numbers of patients or percentage

N = number of patients, % = percent of group, Min = minimum, Max = maximum, SD = standard deviation, NS = not significant

No differences were observed in terms of indications for hospitalization, clinical syndrome, complications on admission, and duration of symptoms before hospitalization between children with pandemic influenza and children with seasonal influenza. However, a statistically significant difference in the duration of symptoms before hospitalization was found between patients with pandemic influenza and patients who were infected with A (H1N1) influenza in the years 2010–11 ($P = 0.038$); 19% of the children in the first group were hospitalized on the day that symptoms started, compared with only 3% of the patients in the third group. The mean duration of symptoms before hospitalization was shorter among patients with pandemic influenza: 2.9 days vs. 5 days in patients with seasonal influenza and patients infected with influenza caused by A (H1N1) in the years 2010–11.

The proportion of children hospitalized with pandemic influenza who presented with fever $> 38^\circ\text{C}$ (83% vs. 63%, $P = 0.05$), cough (84% vs. 66%, $P = 0.012$), and/or rhinorrhea (74% vs. 55%, $P = 0.016$) was significantly higher than

those with seasonal influenza. Other symptoms showed no difference [Table 2]. No significant difference between the components of severity of illness on admission was noticed between the groups.

A higher percentage of pathological chest X-rays was found in both children with pandemic influenza and in children infected with the A (H1N1) virus in the years 2010–2011 (23% of patients in the first group, 28% of patients in the third group). Chest X-ray was suspicious of alveolar pneumonia, compared with 10% of patients with seasonal influenza.

More co-infections were found in patients hospitalized during 2010–2011 due to both seasonal strains and A (H1N1) virus strain. Only 1% of patients with 2009 H1N1 had co-infection with respiratory syncytial virus (RSV), compared with 18% of the patients with seasonal influenza during 2010–11 who had co-infection with RSV ($P < 0.001$), while 8% had co-infection with adenovirus ($P = 0.007$). In patients with H1N1 during 2010–11, 10% had co-infection with adenovirus ($P = 0.01$) and 17% with RSV ($P = 0.002$).

Table 2. Severity of illness and complications on admission

Group	1	2	3	1 vs. 2	1 vs. 3	2 vs. 3
Variables	Patients with 2009 H1N1 (N=100)	Patients with 2010-11 seasonal influenza (N=62)	Patients with 2010-11 H1N1 (N=29)	2009 H1N1 vs. seasonal influenza	2009 H1N1 vs. 2010-11 H1N1	Seasonal influenza vs. 2010-11 H1N1
Antiviral treatment (oseltamivir)	94 (94)	12 (19.4)	16 (55.2)	< 0.001	< 0.001	0.00
Antibiotic treatment	57 (57)	34 (54.8)	20 (69)	NS	NS	
Severity of illness	0	9 (9)	13 (21)	2 (7)	NS	NS
	1	55 (55)	26 (42)	16 (55)		
	2	20 (20)	13 (21)	7 (24)		
	3	16 (16)	10 (16)	4 (14)		
Complications on admission	No complication	93 (93)	51 (82)	27 (93)	0.09	NS
	Respiratory	3 (3)	2 (3)	2 (7)		
	Neurological	3 (3)	7 (11)	0		

*Data are in numbers of patients or percentage

N = number of patients, % = percent of group, SD = standard deviation, NS = not significant

Laboratory findings, including blood and sputum cultures, and average duration of hospitalization did not differ significantly between the groups. The outcomes of complicated hospitalizations were not significantly different between the groups (21% vs. 17.7% vs. 20.7%). In the components of complicated hospitalizations there were also no differences.

Antiviral medications were prescribed more often during 2009; 94% of the patients infected with the pandemic influenza received antiviral treatment with oseltamivir, compared with 19.4% hospitalized in 2010–2011 with influenza caused by seasonal strains, and 55.2% of patients with influenza caused by the A (H1N1) virus strain ($P < 0.001$). Antiviral treatment was mandated by the health authorities when the pandemic began. Other supportive treatments provided to patients during hospitalization, including antibiotics, steroids and inhalation, did not differ between the groups. However, antibiotics were prescribed more commonly in patients infected with the pandemic influenza than in patients with seasonal influenza ($P < 0.001$).

Two children died, one with a metabolic disorder who had pandemic H1N1 during 2009, and one with seizure and underlying neurologic disorder who had seasonal influenza (H3N2 or B) in 2010–11.

DISCUSSION

The main aim of this study was to identify the impact of different influenza strains on complicated hospitalizations, and to compare the characteristics of children infected with pandemic influenza A (H1N1) in the year 2009 with those hospitalized in 2010–2011 with seasonal influenza. There was no significant effect of the influenza strains on complicated hospitalizations.

In 2009, the pandemic influenza A (H1N1) had a severe course, as a number of reports have stated, in terms of

complications and mortality among children [1,4,5,8,13–15]. Accordingly, we assumed that the type of influenza would have an impact on the course of the disease, eventually leading to complicated hospitalizations. One patient with H1N1 died in 2009, due to complications of a severe metabolic disorder, and another child who had a severe convulsive disorder died from respiratory failure during 2010–11 with seasonal influenza. No patient with H1N1 died during 2010–11.

The mortality rate during hospitalization did not differ between the groups. However, the study from Argentina reported that the mortality rate among children infected with pandemic influenza was 10 times higher than in children with seasonal influenza in previous years [5]. This may have resulted from the fact that there were few deaths among children who were infected with influenza, as shown in another study from Israel [1].

A study from Canada conducted in 12 pediatric hospitals compared the outcomes of children infected with pandemic influenza with children infected with seasonal influenza A in the previous 5 years. This study found longer hospitalizations for patients with pandemic influenza, but no difference in hospitalization rates in the pediatric ICU and in mortality [16].

Another study from Israel showed that pandemic influenza A (H1N1) in 2009 was a mild disease in southern Israel with a low percentage of hospitalizations in the pediatric ICU, shorter duration of hospitalization, and no mortality [17]. This study showed that the rate of hospitalization, severity of illness, and mortality were similar to the data on seasonal influenza in the USA. In the current study, there was no significant difference in the components of complicated hospitalization between the children infected with pandemic influenza and children infected with seasonal influenza in the years 2010–11.

In a German nationwide hospital-based prospective study, which compared influenza caused by A (H1N1) virus strain

in critically ill children between the pandemic season in 2009 and the season that followed 2010–11, there was no difference in mortality and severity between the groups [18]. These results support our outcomes, as we did not find a significant difference in complicated hospitalizations that reflect disease severity between patients infected with pandemic influenza A (H1N1) in 2009 compared with patients with influenza caused by the same virus strain in the season that followed. Another study that was published recently showed higher mortality during the pandemic compared with the years after [19].

In addition, there was no significant difference between the impact of seasonal influenza and influenza caused by A (H1N1) virus strain in the same season on complicated hospitalizations. Our results differ from findings in a study conducted in the USA that collected data from several hospitals, exploring the relationship of strains and sub-strains of influenza virus to outcomes in children and adults. They found that in the first season (2010–11) after the pandemic season 2009, patients who were hospitalized with infection with A (H1N1) virus strain were at a twofold risk for severe influenza compared to patients who were hospitalized due to influenza caused by the H3N2 virus strain or influenza due to the B virus strain [20]. The difference in severity might be explained by the fact that the evaluation was performed in different populations. Therefore, more prospective studies are needed to prove the relationship between the type of influenza and the severity of disease.

In the current study, children infected with pandemic influenza were older than children hospitalized with seasonal influenza in the years after. These findings are similar to those described in previous series from Canada and Israel [16,17].

A higher percentage of co-morbidities was found in children with pandemic influenza, similar to another report from the USA [8]. More asthma was found in children with pandemic influenza compared to children with seasonal influenza in the previous five seasons [16].

About 19% of the children in 2009 were admitted to the Pediatric Emergency Room on the day of symptoms onset, compared with only 3% of children with influenza caused by the A (H1N1) virus strain in the years 2010–11. This was attributed to anxiety among people and the influence of the media regarding the outcomes of the pandemic influenza, leading them to seek medical treatment in an earlier phase of the disease. Furthermore, the average duration of symptoms before hospitalization was shorter in those patients, 2.9 days compared with 5 days in the second group ($P = 0.039$) and the third group ($P = 0.01$) in the years 2010–11.

When comparing chest X-rays between patients with pandemic influenza and patients with seasonal influenza, we found that the same virus A (H1N1) was associated with pathological chest X-rays in both seasons, during the pandemic season and in the following years 2010–11. During 2010–11, the percentage of children infected with A (H1N1) virus strain

hospitalized in the pediatric ICU or needing mechanical ventilation was similar to the percentage of patients during the pandemic year 2009, indicating the same severity among patients in both seasons [20].

During the pandemic influenza, the prevalence of other pathogens presenting with the pandemic virus was low; this might be associated with the low prevalence of other pathogens in the winter season. Co-infection with two viruses during a normal winter season in a child is quite common [21]. The differences in co-infections with other viruses may have been due to the misplacement of the pandemic 2009 season.

Treatment during hospitalization included oseltamivir, antibiotics, systemic steroids and inhalations. Children with pandemic influenza received more oseltamivir (94%) than children with seasonal influenza in the years 2010–11 (19.4%), and in children who were hospitalized in the same season infected with A (H1N1) (55.2%). During 2009, the guidelines of the Israel Ministry of Health advised providing treatment with oseltamivir to patients with pandemic influenza. To prevent mortality and complications in the subsequent years, the guidelines were different, limited and less committed.

Due to the lack of a statistically significant difference between the types of influenza with regard to complicated hospitalization, we settled for univariate analysis and no multivariate analysis or models were done to verify the influence of the type of influenza on the results.

Our hypothesis was that there would be more complications, a higher mortality rate, more hospitalizations in the intensive care unit and prolonged hospitalization among patients with pandemic influenza, compared with patients with seasonal influenza in the subsequent 2 years (similar to some studies [5,8], when compared with seasonal influenza in previous years). The contrary results we achieved at the end of the study might be explained by the fact that our study was conducted in a relatively small population and in one medical center, unlike other studies, some of which were multicenter studies in various hospitals in the world with a larger sample of patients and more cases of mortality and morbidity. In addition, access to medical centers in other countries in the world is different and with different indications for hospitalization. It is possible that patients were hospitalized earlier in 2009, close to the beginning of the disease, and received antiviral therapy, antibiotics and supportive care sooner than in the subsequent years.

The media and public interest in the pandemic influenza, along with the uncertainty that accompanied the start of the disease, influenced the approach to influenza in 2009. From a physician's point of view, public interest and the media had shaped, in a sense, the indications for hospitalization and transfer to intensive care during hospitalization, with the unknown course of a new pandemic. From the patient's point of view, there was more public awareness regarding the pandemic influenza, which might have contributed to the immediate

admission of patients to hospital, more hospitalizations and more reporting, and performance of laboratory respiratory virus tests, which may have given the impression that this was a serious illness.

In conclusion, the strain and burden of the pandemic influenza virus A (H1N1) on complicated hospitalizations did not differ from the burden of seasonal influenza in the following 2 years. Furthermore, the type of the influenza did not have an effect on complicated hospitalization, although there are slight differences between the various types expressed, relating especially to the patient's age and duration of symptoms until admission.

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