

REVIEW

Pediatric hospital admissions from influenza A (H1N1) in Brazil: effects of the 2010 vaccination campaign

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In 2009, the influenza A (H1N1) virus spread rapidly around the world, causing the first pandemic of the 21st Century. In 2010, there was a vaccination campaign against this new virus subtype to reduce the morbidity and mortality of the disease in some countries, including Brazil. Herein, we describe the clinical and epidemiological characteristics of patients under 19 years of age who were hospitalized with confirmed influenza A (H1N1) infection in 2009 and 2010. We retrospectively reviewed files from the pediatric patients who were admitted to a university hospital with real-time polymerase chain reaction (RT-PCR) confirmed influenza A (H1N1) infection in 2009 and 2010. There were 37 hospitalized patients with influenza A (H1N1) in 2009 and 2 in 2010. In 2009, many of the hospitalized children had an underlying chronic disease and a lower median age than those not hospitalized. Of the hospitalized patients, 78% had a chronic disease, primarily pneumopathy (48%). The main signs and symptoms of influenza were fever (97%), cough (76%), and dyspnea (59%). Complications occurred in 81% of the patients. The median length of hospitalization was five days; 27% of the patients required intensive care, and two died. In 2010, two patients were hospitalized with influenza A (H1N1): one infant with adenovirus co-infection who had received one previous H1N1 vaccine dose and presented with respiratory sequelae and a 2-month-old infant who had a hospital-acquired infection. An impressive reduction in hospital admissions was observed in 2010 when the vaccination campaign took place in Brazil.

KEYWORDS: Influenza A Virus; H1N1 Subtype; Chronic Disease; Vaccination.

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INTRODUCTION

In 2009, the world faced the emergence of a new strain of influenza virus (1). The influenza A (H1N1) virus spread rapidly, causing the first pandemic of the 21st Century (2). In Brazil, the first confirmed case of infection with the new virus was reported on May 7th, 2009 by the Brazilian health minister (3). On July 16th, 2009, the sustained human transmission of the virus in Brazil was declared, and the mandatory reporting of each patient diagnosed with acute respiratory distress syndrome caused by the influenza A (H1N1) virus was established (4).

Several actions were taken to control the epidemic in Brazil, including the establishment of hospital admission criteria for suspected cases. São Paulo Hospital was one of the reference hospitals for such patients.

Beginning in March 2010, the pandemic influenza vaccine was available in Brazil for the population groups who presented with higher morbidity and mortality after H1N1 infection in 2009 and for healthcare professionals and native Indians (5-7). In the pediatric age group, first children aged six months to two years were vaccinated; vaccinations were subsequently extended to all children under age five.

In the literature, studies have discussed the characteristics of the pediatric patients who were admitted to the hospital with influenza A (H1N1) infection. However, to our knowledge, no published study has compared the 2009 and 2010 hospitalizations. In this study, we describe the clinical and epidemiological characteristics of patients under age 19 who were hospitalized with confirmed influenza A (H1N1) infection in 2009 and 2010, the year that the vaccination campaign against pandemic influenza began in Brazil.

METHODS

This study was conducted at São Paulo Hospital, a tertiary university hospital in São Paulo, Brazil, with pediatric wards, semi-intensive, and intensive care units (ICU).

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No potential conflict of interest was reported.

This is a retrospective study of suspected cases of influenza A (H1N1) infection reported to the disease control surveillance system of our hospital. We selected patients under 19 years and separated them into confirmed cases admitted and confirmed cases not admitted to hospital. We considered confirmed cases of influenza A (H1N1) those with virus detection in nasopharyngeal and pharyngeal swabs. Briefly, viral RNA was extracted using QIAamp Viral RNA extraction kit (Qiagen, Germany) according to manufacturer's instructions. Influenza A (H1N1) detection was performed at Adolfo Lutz Institute, a Brazilian government laboratory, or at the Clinical Virology Laboratory at the Federal University of São Paulo using the Real Time protocol published by the CDC on April 28, 2009 (8).

Data on gender, age, and comorbidities were collected from all of the patients who were not admitted to the hospital. Patients who were hospitalized for longer than 24 hours were assessed for demographic data, including a review of clinical data described in the medical chart, such as the unit to which the patient was admitted, early symptoms, complications, major medical procedures, and treatment. Vaccination records on influenza A (H1N1) were also collected from the patients who were admitted in 2010.

We defined respiratory failure as dyspnea with hypoxemia (oximetry less than 95% in ambient air) (9). Acute respiratory distress syndrome was defined as fever, cough, and dyspnea (4,7).

A suspected case of influenza A (H1N1) was defined as febrile acute disease with cough or sore throat in the absence of other diagnoses (5).

In the beginning of the pandemic, all influenza A (H1N1) cases had to be reported. This rule was modified on July 16, 2009 (28th epidemiological week), when priority reporting for laboratorial diagnosis and treatment was established for patients presenting with severe acute respiratory distress syndrome and those with associated risk factors (4).

The statistical analysis was performed with BioEstat 5.0 (published by the Institute for Sustainable Development of Mamirauá, Brazil). The Mann-Whitney U-test was used for continuous variables, and the Chi-squared test was used for categorical variables. Statistical significance was set at $p < 0.05$.

This study was approved by the Ethics Committee at the Federal University of São Paulo, Brazil.

RESULTS

Year: 2009

There were 282 suspected cases of pandemic influenza A (H1N1) in children and adolescents under age 19 in our hospital, and 37 patients were hospitalized with confirmed infection. Three patients had already been hospitalized for other reasons when they became infected. The majority of admissions occurred in the 30th epidemiological week (Figure 1).

Among those patients with confirmed pandemic influenza A (H1N1), 41 were not hospitalized. The hospital-admitted group had more chronic diseases (29/37 *versus* 13/41; Chi-squared test, $p < 0.001$) and a lower median age (4.9 y *versus* 10.4 y; Mann-Whitney U-test, $p < 0.001$) than the non-admitted group. Also, 65% of the admitted children *versus* 95% of the non-admitted were over age 2 (Chi-squared test, $p < 0.001$). Table 1 shows the results.

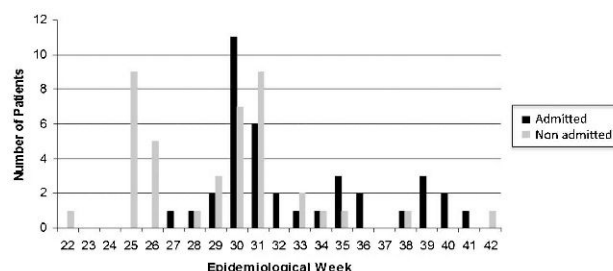


Figure 1 - The number of patients with confirmed influenza A (H1N1) per epidemiological week at São Paulo Hospital in 2009, separated by hospital-admitted group and non-hospital-admitted group.

Of the patients with confirmed influenza A (H1N1), 36 were admitted to the hospital on the same day they arrived in the emergency room. The median time between the first symptoms and the hospital admission was four days (range, 1 to 10). Four days was also the median time between the first symptoms and the collection of a nasopharynx swab (range, 1 to 10). The median hospital stay was five days. For treatment, 34/37 (91.9%) patients received oseltamivir, and 24/34 (70.6%) started oseltamivir within 48 hours of the first symptoms.

The major signs and symptoms presented at admission were fever (97%), cough (76%), dyspnea (59%), decreased food intake (35%), rhinorrhea (32%), and hypoactivity (32%).

A total of 29 of the 37 hospitalized patients (78%) had at least one underlying medical condition. Pneumopathy was the most commonly observed condition (14/29; 48%), followed by neuropathy (8/29; 28%), hemoglobinopathy (5/29; 17%), immunosuppression (4/29; 14%), and heart disease (3/29; 10%). Nine patients had more than one disease.

Complications occurred in 81% (30/37) of the patients, respiratory failure in 51%, pneumonia in 49%, and sepsis in 16%. Two (5.4%) patients had reversed cardiopulmonary arrest; one (2.7%) had rejection of a transplanted kidney; one (2.7%) had acute metabolic acidosis at the onset of diabetes mellitus type 1, and two (5.4%) died. Furthermore, 73% of patients required oxygen supplementation, 19% required mechanical ventilation, and 62% received antibiotics.

Of the 37 patients hospitalized with confirmed infection, ten were admitted to the ICU. The median age in this group was 5.1 years; 50% were male, and 90% had some underlying condition. All of the patients presented with complications (nine had acute respiratory failure, nine had pneumonia, one had hypoxia), and 70% required mechanical ventilation. All of the patients admitted to the ICU received oseltamivir. The median ICU stay was 3.5 days (range 2–81 days).

Two children died in 2009 from influenza A (H1N1) infection in our hospital; one child was a 4-year-old female who had intermittent asthma. The symptoms had started three days prior to her hospital admission with cough, fever, diarrhea, and sore throat. The child was admitted to the ICU with acute respiratory failure on the day she arrived at the hospital, and mechanical ventilation was required. She developed pneumonia, septic shock, and pulmonary hemorrhage and died on the second day of hospitalization.

Table 1 - Characteristics of patients infected with influenza A (H1N1) in 2009.

2009	Admitted Patients	Non-Admitted Patients	p-value
Male gender	19/37 (51%)	23/41 (56%)	0.6
Median age in years (range)	4.9 (0.2 - 16.9)	10.4 (0.4 - 18.9)	<0.001
Age >2 years	24/37 (65%)	39/41 (95%)	<0.001
Underlying conditions	29/37 (78%)	13/41 (32%)	<0.001

The other deceased patient was a 16-year-old girl with Down's syndrome, heart disease, diabetes mellitus, hypothyroidism, and hypertension. The symptoms had started four days prior to admission with fever, dyspnea, diarrhea, vomiting, and abdominal pain. The patient was admitted to the ICU on the second day of hospitalization and developed acute respiratory failure, pneumonia, hepatitis, heart failure, acute renal failure and shock; she died 14 days after hospital admission.

Year: 2010

In 2010, there were 69 reported cases and only two confirmed cases of influenza A (H1N1) infections at São Paulo Hospital. Both of the confirmed infections required hospitalization. The first case was a 9-month-old, previously healthy boy with coughing and rhinorrhea two weeks prior to his hospitalization; the symptoms had worsened five days prior to admission; he developed fever, hypoactivity, and dyspnea. The boy had received one previous H1N1 vaccine dose 13 days before the first symptoms appeared. Oral antibiotics, oral corticosteroids and inhalation with saline solution had already been administered for four days before the hospital admission. Acute respiratory failure and bilateral pneumonia were diagnosed in the emergency room, and the child was placed on mechanical ventilation for 13 days and treated with broad-spectrum antibiotics and two cycles of oseltamivir. He developed subglottic stenosis and was discharged with a tracheostomy after 47 days of hospitalization. A nasopharynx swab was collected on the 13th day of hospitalization. Both influenza A (H1N1) and adenovirus were detected.

The other patient was a 2-month-old boy with encephalocoele and sepsis; he was admitted to the same ICU as the other child diagnosed with influenza A (H1N1) and was treated with oseltamivir and noninvasive oxygen therapy. He was discharged without any respiratory sequelae.

DISCUSSION

In 2009, we witnessed a pandemic of the previously unknown subtype influenza A (H1N1) virus (10). The first confirmed cases in our hospital were in the 22nd epidemiological week, and the majority of the admissions and confirmed cases occurred during the 30th epidemiological week. In Brazil, the peak confirmation rate of cases was seen in the 31st epidemiological week (7).

During the pandemic, changes were made to the reporting and selection criteria for laboratorial diagnosis. In the 28th epidemiological week, reporting was required only for the cases with severe acute respiratory distress syndrome or those with risk factors for worse outcomes (4). At our hospital, the majority of hospitalizations occurred after this date.

In our study, the admitted children were younger than the non-admitted children. In Brazil, the age groups that had more frequent acute respiratory distress syndrome

were children under age 2 and adults between the ages of 20 and 29 years (7,11).

In concordance with other studies, the children who were admitted to our hospital with influenza A (H1N1) infection had a high prevalence of chronic disease, with a predominance of pneumopathy (5,12-17). However, we must consider that the high percentage found here might represent a bias because São Paulo Hospital is a tertiary hospital.

In this study, there were two deaths, two reversed cardiopulmonary arrests, one rejection of a transplanted kidney and an acute metabolic acidosis at the onset of diabetes mellitus type 1, all of which were critical cases. A recent Brazilian study demonstrated a more severe course of the disease in children infected with the H1N1 virus than in children with flu-like symptoms who received negative rapid tests for H1N1 (18).

As observed in the United States (12), Argentina (15), Canada (17), and in another Brazilian study (18), most patients who were hospitalized with influenza A (H1N1) had complications, and many needed intensive care, despite immediate hospitalization from the emergency room and prompt oseltamivir initiation. Seventy-one percent of the hospitalized patients in our study started this medication more than 48 hours after the symptoms began. This delay could have contributed to a worsening of their clinical condition.

In this study, 27% of the 37 children who were hospitalized were admitted to the ICU, and 78% had some underlying disease. Likewise, among the first 272 patients hospitalized with influenza A (H1N1) reported in the United States, 25% were admitted to an ICU, and 73% had at least one underlying medical condition (12).

During annual outbreaks of seasonal influenza, most patients who require hospitalization are at the extremes of age distribution. There are also a greater number of hospitalizations in patients with chronic diseases, such as diabetes, cardiovascular disease, neurological disease, and pulmonary disease (including asthma) (12,19,20). A significant number of hospitalizations are caused by influenza every year (19-21).

Despite a stable total number of hospital admissions in all pediatric units at our hospital in 2009 and 2010, there was a reduction in the hospital admissions of confirmed pediatric influenza A (H1N1) patients after the vaccination campaign in 2010. This result is in accordance with other data from our country (22).

The total number of influenza A (H1N1) vaccine doses administered in Brazil was 89,580,203. The vaccination coverage for children under age 2 was 100% (5,580,671 vaccine doses) and 60% for the 2 to 4 year-old age group, with 5,202,438 vaccine doses given (23).

Here, we have described influenza A (H1N1) pediatric cases admitted to a tertiary hospital in São Paulo, Brazil over two consecutive years. The striking decrease in the number of cases from 2009 to 2010 is likely an effect of the massive

influenza A (H1N1) vaccination campaign in Brazil in 2010, along with the immunity acquired by the population because of the intense viral circulation.

AUTHOR CONTRIBUTIONS

Marcos AC and Pelissoni FA participated in data collection, data analysis and manuscript writing. Cunegundes KS participated in data analysis. Abramczyk ML and Sanches NA participated in data collection. Bellei NC participated in PCR laboratory analysis and data collection. Moraes-Pinto MI participated in data analysis, writing and review of the manuscript.

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