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SHORT COMMUNICATION

2009 H1N1: risk factors for hospitalization in a matched case-control study

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Abstract In order to compare sociodemographical data and preexisting risk medical conditions in patients requiring hospital admission for 2009 pandemic influenza A (H1N1) virus infection and those managed on an outpatient basis, a prospective observational, matched case-control study in 36 hospitals of the Spanish National Health Service was conducted from July 2009 to February 2010. Cases were patients aged 6 months to 18 years hospitalized for influenza syndrome, in whom 2009 influenza A (H1N1) virus infection was confirmed using real-time reverse-transcription polymerase chain reaction. Controls were patients aged 6 months to 18 years with confirmed 2009 influenza A (H1N1) infection managed on an outpatient basis. There were 195 cases and 184 controls. In a multivariate model, hospitalization was more frequent in children aged <2 years (odds ratio (OR), 13.8; 95% confidence interval (CI), 1.7–106.4), those with neurological and/or neuromuscular diseases (OR, 3.0; 95% CI, 1.1–8.2), and those whose parents had less than a secondary educational level (OR, 2.7; 95% CI, 1.4–5.2). Children aged <2 years, children with neurological diseases, and children from families with a lower educational status had a higher risk of hospitalization due to influenza A (H1N1) 2009 infection.

Keywords Influenza A virus · Children · Risk factors · Hospitalization · Pediatrics

All authors contributed to the conceptualization of the study. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the development of the final manuscript.

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Introduction

On April 21, 2009, the Centers for Disease Control and Prevention (CDC) reported two confirmed cases of respiratory illness with fever in children in southern California caused by an infection with a previously unidentified influenza virus, which became known as the influenza A (H1N1) 2009 virus. In June 2009, the new influenza infection was declared a global pandemic. In Spain, the incidence of this infection reached its peak between September and November of 2009 (the maximum weekly incidence was 372 infections per 100,000 inhabitants) [5].

Initially, the CDC and the World Health Organization extrapolated the risk factors for developing severe illness from the traditional risk groups for seasonal influenza to establish recommendations for treatment and hospitalization. In Spain, most hospitals developed pandemic plans according to these instructions.

Few studies have compared epidemiological data and comorbidity between children diagnosed with influenza A (H1N1) 2009 infections, who were outpatients, and those who required hospital admission. The attention of an international literature, until now, has focused almost exclusively on describing the most common clinical problems among children requiring hospital admission and the risk factors for fatal outcomes [1, 8, 9, 11].

The purpose of this multicenter study was to compare sociodemographic data and preexisting risk medical conditions in patients with influenza A (H1N1) 2009 infection, who required hospitalization, and those managed on an outpatient basis.

Patients and methods

We carried out a multicenter study in 32 hospitals from seven Spanish regions (Andalusia, the Basque Country, Castile and Leon, Catalonia, Madrid, Navarre, and Valencia Community). Cases were patients aged 6 months to 18 years hospitalized for influenza syndrome, in whom influenza A (H1N1) 2009 infection was confirmed using real-time reverse-transcription polymerase chain reaction (RT-PCR) between July 2009 and February 2010. Patients with influenza A (H1N1) 2009 infection appearing ≥48 h after hospitalization for another cause were excluded. Controls were patients aged 6 months to 18 years with confirmed influenza A (H1N1) 2009 infection using real-time RT-PCR and managed on an outpatient basis. Controls were matched according to the date of hospitalization and province of residence. All cases and controls were recruited in public Spanish National Health Service centers.

Sociodemographic variables and preexisting risk medical conditions were recorded. Seasonal influenza vaccination and seven-valent pneumococcal conjugate vaccination (PCV7) status were also recorded. Patients were considered correctly vaccinated for both vaccines if they had received the last doses of vaccine at least 15 days before the onset of symptoms and if the number doses for age was in agreement with the vaccines' factsheet. Parental sociodemographic and health data were collected.

Descriptive statistics for noncontinuous variables are described using absolute frequencies and rates, and data comparisons were performed using McNemar test. Continuous nonnormally distributed variables are described as medians and interquartile ranges (IQR, 25–75%) and compared using the paired t test. A multivariate analysis was performed using a conditional logistic regression model that included variables with a value of $p \leq 0.1$ in the univariate analysis as independent variables ("enter" method) and "hospital admission" as the output variable. A value of $p < 0.05$ was considered statistically significant. The statistical analysis was made using the SPSS® v19 for Windows® package. The study was approved by each participating hospital's institutional ethics committee, and informed consent was waived.

Results

A total of 379 patients were included during the study period, of which 212 (56%) were males. The median age was 5.8 years (IQR, 2.2–11.4); 232 (61%) were previously healthy. Preexisting conditions included respiratory illness (92, 24%), neurological and neuromuscular illness (41, 11%), primary or secondary immunodeficiency (27, 7%), and chronic heart disease (15, 4%). Twenty-one patients (5%) had ≥1 preexisting conditions. Fifty-six patients (15%) had received the seasonal influenza vaccination, and 88 (23%), the PCV7. No patient received the pandemic vaccine containing A/California/04/2009 (H1N1), which was first used in Spain on November 16, 2009. Tobacco exposure was recorded in 134 (35%) patients, and in 166 (46%) cases, parents had a secondary or higher educational level. A total of 325 (86%) patients were Caucasian; 23 (6%), Amerindian; 11 (3%), Arabic; and 7 (2%), Gipsy. For reference, among the 125 children with a chronic condition, seasonal influenza vaccination had been administered to 42 (34%). Only 4 of 78 (5%) children aged <2 years had been vaccinated for seasonal influenza. Of those, only one was a previously healthy child.

Of the 195 children requiring hospitalization, 105 (54%) were male. The median was of 5.6 years (IQR, 1.4–10.5), with 74 (38%) aged 5–12 years, and 102 (52%) were previously healthy. Preexisting risk conditions included respiratory illness (55, 28%), neurological and neuromuscular disease (31, 16%), primary or

secondary immunodeficiency (18, 9%), and chronic heart disease (11, 6%). Twenty-nine patients (15%) had received the seasonal influenza vaccination, and 44 (22%), the PCV7. A total of 67 (34%) were exposed to tobacco, and the parental educational level was primary or lower in 105 (63%). A total of 159 (82%) patients were Caucasian; 18 (10%), Amerindian; 9 (5%), Arabic; and 5 (3%), Gipsy.

When hospitalized patients were compared with those treated on an outpatient basis, hospitalized children were younger, aged 5.6 years (IQR, 1.4–10.5) vs 6.2 years (IQR, 3.3–12.0) (p=0.01). Children aged <2 years were more frequently hospitalized than the older children (Table 1). Patients with neurological or neuromuscular diseases (odds ratio (OR), 3.0; 95% confidence interval (CI), 1.4–6.3), diabetes mellitus (OR, 7.0; 95% CI, 0.9–56.9), non-Caucasian ethnicity (OR, 1.5; 95% CI, 0.9–2.9), and parents without secondary or higher educational level (OR, 2.8; 95% CI, 1.5–5.0) were more frequently hospitalized. No differences in seasonal influenza vaccination, and PCV7 vaccination rates were observed.

In the multivariate analysis, age of <2 years, chronic pulmonary, neurological, metabolic, and cardiovascular diseases; non-Caucasian ethnicity; and educational level were entered as independent variables, and hospital admission was the output variable. Age of <2 years, preexisting neurological or neuromuscular condition and the low parental educational level remained associated with a higher risk of hospitalization (Table 1). Ethnicity did not remain significant due to an association between non-Caucasian ethnicity and lower age, median 3.16 (IQR, 1.2–8.1) vs 6.2 (IQR, 2.5–11.5) (p=0.01).

Discussion

Predisposing health conditions for severe influenza disease (fatal cases or Intensive care admission) in admitted children, including chronic lung disease, heart disease, neurological disease, and oncologic-hematologic malignancies have reported in many studies [6, 8, 9, 11]. Case-fatality rate in patients aged <1 year was also higher than that in the older children [13]. However, few reports have analyzed risk factors for pediatric hospital admission, and most are observational descriptions of prospective or retrospective cohorts in emergency departments [7]. This case-control study design is novel in comparing children who are hospitalized and those managed as outpatients. As this is a multicentre study, we consider that we have a truly representative sample in order to evaluate the main risk factors for hospital admission of Spanish children during the 2009 pandemic.

Table 1 Demographic factors and comorbidities in hospitalized and outpatient patients

	Hospitalized (n=195)	Outpatients (n=184)	p value	Multivariate model*	
				p value	Odds ratio
Age (median (IQR))	5.6 (1.4–10.5)	6.2 (3.3–12.0)	0.01		
• <2 years	56 (29%)	23 (12%)	<0.01	0.01[a]	13.8 (1.7–106.4)[a]
• 2–5 years	37 (19%)	51 (28%)	0.04		
• 5–12 years	74 (38%)	72 (39%)	0.81		
• >12 years	28 (14%)	38 (21%)	0.11		
Sex (male)	105 (54%)	107 (58%)	0.40		
Patients with ≥1 preexisting condition/s[b]	93 (48%)	54 (29%)	<0.01		
Pulmonary disease	55 (28%)	37 (20%)	0.06	0.84	1.1 (0.5–2.1)
Neurologic disease	31 (16%)	10 (5%)	<0.01	0.03	3.0 (1.1–8.2)
Cardiovascular disease	11 (6%)	4 (2%)	0.07	0.35	2.0 (0.5–8.7)
Renal chronic disease	4 (2%)	6 (1%)	0.40		
Diabetes mellitus	9 (5%)	1 (0.5%)	0.01	0.18	4.5 (0.5–39.1)
Primary or secondary immunodeficiency	18 (9%)	9 (5%)	0.11		
Seasonal influenza vaccination	29 (15%)	27 (14%)	0.90		
PCV7 vaccination	44 (22%)	44 (24%)	0.70		
Non-Caucasian ethnicity	36 (18%)	18 (10%)	0.01	0.39	1.0 (0.4–2.1)
Primary or lower education	105 (63%)	57 (35%)	<0.01	<0.01	2.7 (1.4–5.2)
Tobacco exposure	67 (34%)	67 (36%)	0.80		

*p=0.38, Hosmer–Lemeshow

[a]<2-year-old (yes)

[b]Twenty-one (5%) patients had ≥1 preexisting conditions

Patients aged <2 years had the highest rate of hospitalization, as observed by Lera et al. [7]. A higher rate of hospitalization was also observed in children with neurological disease and diabetes patients. In our series, children of parents without secondary or higher education were also more likely to be hospitalized than children of parents with higher education. Strong associations between parental education and health indicators of children have been reported elsewhere. Higher educated parents report more diagnoses and symptoms of children than the less educated [4], and this could also imply an earlier access to health care centers. Moreover, certain conditions that may favor a worse prognosis in acute respiratory diseases, such as higher airway resistance and overweight, were more frequent in children of parents with a low educational level [4].

Other reports have suggested ethnicity as a factor for increased hospitalization in adults. Non-Caucasian patients (mostly Amerindians) were also more likely to be hospitalized in our series, although this was not significant in the multivariate analysis. Non-Caucasian patients were younger, and this could explain a higher rate of admission among them. Mortality due to influenza A (H1N1) 2009 infection was higher in immigrant children in some studies, independently of the origin [3, 13]. Possible explanations for a more severe disease in immigrant children include the prevalence of chronic health conditions, poor living conditions, and delayed access to health care. In our opinion, socioeconomic and cultural factors are also being considered when physicians decide to admit or not those children, even more in younger ones.

Some studies observed that *Streptococcus pneumoniae* was important in the pathogenesis and prognosis of influenza disease [12], although the association of specific serotypes with a more severe clinical course remains to be determined. In our series, PCV7 vaccination coverage did not differ between admitted and nonadmitted patients. Nonetheless, the pneumococcal vaccination coverage among both groups was too low to draw any conclusion.

Another important point is that the prevalence of seasonal influenza coverage was very low both in hospitalized and outpatient children. In Spain, influenza vaccination of children with medical risk conditions is recommended and administered free of charge [10], and so the low level of coverage is something concerning.

The main limitations of the study were the low number of patients included with certain comorbidities and the lack of more clinical data to distinguish the reasons for admission.

To conclude, age of <2 years and parental educational level were important factors in the hospitalization of Spanish children for influenza A (H1N1) 2009 infection. As recommended by the American Academy of Pediatrics [2], our results support the need for preventive strategies in children aged 6 months to 2 years and those with high-risk conditions such as chronic neurological disease and diabetes mellitus. Early initiation of antiviral treatment could also prevent a more severe influenza disease in them [6]. The results also suggest the need to increase awareness of influenza in families with lower educational status.

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Conflict of interest None.

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