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Clinical features of influenza disease in admitted children during the first postpandemic season and risk factors for hospitalization: a multicentre Spanish experience

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Abstract

The main objectives of this study were to describe the characteristics of children with influenza infection during the postpandemic outbreak, and to compare sociodemographic and clinical data between patients who required hospitalization and those managed on an outpatient basis with a matched case–control study design. This is a multicentre paediatric study in Spain that included patients aged 6 month to 18 years in whom influenza infection was confirmed by real-time reverse transcription–polymerase chain reaction between December 2010 and March 2011. Among the 143 admitted patients, the main reason for admission was respiratory failure (123/143). In 55 there was some previously known disease. The median age was lower in patients without comorbidity (1.8 years: interquartile range 1.0–3.0 versus 5.3 years: interquartile range 1.3–10.7); p <0.01). The lag time from onset of symptoms to starting antiviral treatment was correlated with the length of hospital stay (Rho Spearman = + 0.32; p 0.01). Twenty patients required admission to the paediatric intensive care units, all due to respiratory failure. Children with chest X-ray opacities in more than one quadrant more frequently required admission to intensive care. Having a neurological disease conferred the highest risk of requiring hospitalization (OR 17.18) in a multivariate analysis. This study concludes that influenza in the paediatric population requiring hospitalization during the postpandemic season affected mainly children with neurological or pulmonary comorbidities and children of parents with a lower educational level. Most of the influenza infections caused respiratory symptoms, although neurological manifestations were also observed. Early initiation of oseltamivir was associated with a shorter length of hospital stay.

Keywords: Postpandemic, influenza, paediatrics, case–control, risk factors
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Introduction

During 2009 and 2010 the new influenza virus, A(H1N1) pdm09, spread worldwide. Most of the influenza infections during the pandemic season were caused by this novel virus and, typically, the infection caused a mild respiratory disease in children, but severe manifestations and mortality also occurred [1,2]. Although the most common clinical manifestations were similar to those caused by previous circulating influenza viruses [3], severe manifestations were slightly more frequent with the influenza A(H1N1)pdm09 virus [4,5], especially in children with respiratory or neurological comorbidities [2,6].

It is well-known that novel influenza viruses caused morbidity and mortality during previous postpandemic outbreaks [7]. Influenza caused by the novel virus was expected to occur again during the first postpandemic season and to

co-circulate with previous influenza viruses. In autumn 2010, the World Health Organization gave advice on maintaining awareness of changes in the epidemiology and clinical expression of the disease [8].

Recently, Rahamat-Langendoen *et al.* [4] published a study comparing prepandemic, pandemic and postpandemic influenza cases in a single institution including patients of all ages. Poulakou *et al.* [9] have also described the disease in adults and children who required intensive care unit admission during the postpandemic period. As far as we know, there is still not a specific paediatric report that assesses the clinical and epidemiological characteristics of patients with influenza infection after the 2009 pandemics. The main objectives of this study are to describe the epidemiology and clinical characteristics of those patients with influenza infections during the 2010–2011 influenza outbreak, and to compare sociodemographic and clinical data between patients who required hospitalization and those managed on an outpatient basis.

Patients and Methods

This is a multicentre paediatric study in Spain. Hospitalized patients and outpatients were recruited in public Spanish National Health Service centres. We carried out a multicentre study in 17 hospitals from seven Spanish regions (Andalusia, the Basque Country, Castile and Leon, Catalonia, Madrid, Navarre and Valencia Community). Two of these hospitals (Hospital Sant Joan de Déu and Hospital Vall d'Hebrón, both of the province of Barcelona) were paediatric hospitals and the others were general hospitals with paediatric departments. We included patients aged 6 month to 18 years with influenza syndrome in whom influenza infection was confirmed by real-time RT-PCR between December 2010 and March 2011. A prospective matched case–control design was used to compare epidemiological and clinical characteristics between children who required hospital admission (cases) and children who were treated on an outpatient basis (controls). Controls were matched with each case according to age (±3 years), date of hospitalization (±10 days) and province of residence. Patients who could not be matched according to date of hospitalization and province of residence were excluded from the case–control analysis. Sociodemographic and clinical data were gathered using a standard form that was completed by a trained medical interviewer during the hospitalization or at the outpatient clinics. Seasonal and pandemic influenza vaccination and pneumococcal conjugate vaccination status for any of the commercialized vaccines were also recorded. Information on the vaccination status was obtained from hospital medical records or vaccination card; if neither was available, primary healthcare centre registers were consulted. Patients were considered correctly vaccinated if they had received at least two doses of influenza vaccine (including the 2010–2011 influenza virus vaccine strains), the last one >14 days before the onset of influenza symptoms, or only one dose if they were older than 9 years old, according to the recommendations of the American Academy of Pediatrics and the American Advisory Committee on Immunization Practices. Patients were considered correctly vaccinated for pneumococcal conjugated vaccine if they had received the last dose of vaccine at least 14 days before the onset of symptoms and if the number of doses for age was in agreement with the vaccines' factsheets. Parental sociodemographic and health data were also collected.

Descriptive statistics for non-continuous variables are described using absolute frequencies and rates, and data comparisons between cases and controls were performed using McNemar test. Continuous non-normally distributed variables are described as medians and interquartile ranges (IQR, 25–75%) and compared using the paired *t*-test. A multivariate analysis was performed to estimate the adjusted odds ratio of several variables as potential risk factors for hospitalization. The multivariate analysis used a conditional logistic regression model with backward selection of variables with a cut-off point of $p < 0.1$ and 'hospital admission' as the output variable. As a measure of goodness of fit we calculated the Hosmer–Lemeshow test and the predictive accuracy of the model was determined by calculating the area under the curve.

For statistical analysis of the admitted patients, data comparisons were performed using Pearson's chi-square test or Fisher's exact test when the expected count in any category was <5. Continuous non-normally distributed variables were compared using the Mann–Whitney *U* test.

Values of $p < 0.05$ were considered statistically significant. The statistical analysis was made using the SPSS® v19 FOR WINDOWS® package (SPSS Inc., Chicago, IL, USA).

The study was approved by each participating hospital's institutional ethics committee and written informed consent was waived.

Results

During the study, 323 children were recruited (143 hospitalized and 180 outpatients). Of the 143 hospitalized children, 43 (30%) were in paediatric hospitals and the others (100; 70%) were in paediatric departments of general hospitals. Overall, the median age was 2.9 years (IQR: 1.2–6.7). Of the 323 children, 163 (50%) were male and 247 (76%) had no

pre-existing condition. The main previously known comorbidities were pulmonary diseases (mainly asthma) in 41 (13%) patients, neurological and neuromuscular diseases in 27 (8%), and primary or secondary immunodeficiencies in eight (2%). Eleven (3%) patients had two or more pre-existing conditions. A total of 266 (82%) patients were Caucasian.

Only eight (2%) of the 323 patients were correctly immunized with seasonal and pandemic influenza vaccines. Of those, six had some comorbidity. Only one of the 126 (<1%) children who were <2 years old was correctly vaccinated.

On the other hand, 102 (32%) of the 323 patients were fully immunized with some of the commercialized conjugated pneumococcal vaccines (PCV7, PCV10 or PCV13). Most of them (80 of the 102; 78%) were previously healthy children.

Hospitalized patients

The main clinical and epidemiological variables of the 143 admitted patients are shown in Table 1. Antiviral treatment was given to 69 of 111 (48%). In 32 patients data on antiviral treatment were not recorded. Median time to initiation of antiviral treatment after onset of clinical symptoms was 4 days (IQR: 2–7). Length of hospital stay was higher in patients that either did not receive antiviral treatment or received it later than 3 days after the onset of symptoms in comparison to the patients who received it within the first 3 days of symptoms (median 7 days, IQR: 4–11 versus 5, IQR: 3–7.5; p 0.04). The lag time from onset of symptoms to starting antiviral treatment was positively correlated with the length of hospital stay (Spearman $\rho = +0.32$; p 0.01). Twenty-seven of 55 patients (49%) with at least one comorbidity did not receive antiviral treatment. Length of stay was not different between patients with and without comorbidity (median 6.5, IQR: 4–10 versus 6, IQR: 4–11, respectively; p 0.6).

Forty-one of 129 (32%) patients with respiratory symptoms had chest X-ray opacities. To have chest X-ray opacities in at least two quadrants was associated with a longer hospital stay in comparison to those without infiltrate or with opacities in only one quadrant (median 10 days, IQR: 6–13 versus 5, IQR 4–10, respectively; p 0.01).

In 38 of 129 (29%) patients with respiratory symptoms oral or intravenous corticosteroids were initiated. There were no differences in length of stay between patients who received this therapy and patients who did not receive it (median 6, IQR: 4–11 versus 6, IQR: 4–10; p 0.48).

TABLE 1. Main clinical and epidemiological variables among the 143 children who required hospitalization.

Reasons for admission, *n* (%)	
Respiratory failure or respiratory distress	123 (86)
Fever with a high-risk condition	6 (4)
Vomiting requiring intravenous hydration	6 (4)
Seizures and other neurological symptoms	4 (3)
Others	4 (3)
Age (median, IQR)[a]	2.0 years (1.0–6.0)
Patients without comorbidity	1.8 years (1.0–3.0)
Patients with comorbidity/ies	5.3 years (1.3–10.7)
Comorbidity, *n* (%)	
None	88 (62)
Pulmonary conditions	26 (47)
Neurological disease	23 (42)
Cardiovascular disease	5 (4)
Renal chronic disease	4 (3)
Diabetes mellitus	1 (1)
Primary or secondary immunodeficiency	7 (5)
Patients with two or more pre-existing conditions	10 (7)
Main clinical symptoms, *n* (%)	
Fever	133 (93)
Respiratory symptoms	129 (90)
Gastrointestinal symptoms	57 (40)
Myalgia	38 (27)
Headache	25 (17)
Other neurological symptoms	25 (17)
Length of hospital stay (median, IQR)[b]	6 days (4–10)
Patients without comorbidity	6 days (IQR: 4–11)
Patients with comorbidity/ies	6.5 days (IQR: 4–10)
Use of antiviral agents during hospitalization, *n* (%)[c]	
Within the first 72 h of clinical symptoms	25 (23)
More than 72 h after the onset of symptoms	44 (40)
Chest X-ray, *n* (%):	
Absent or without opacities	102 (71)
Opacities in one quadrant	19 (13)
Opacities in more than one quadrant	22 (15)
Patients who required PICU admission, *n* (%)	20 (14)

[a]The median age was lower in patients without comorbidity (p <0.01).
[b]Length of stay was not different between patients with and without comorbidity (p 0.6).
[c]Over 111 patients. These data were not recorded in 32 patients.

Severe cases

None of the patients died in this series. Twenty patients required admission to the paediatric intensive care units (PICUs), all due to respiratory failure. Eleven of the 20 patients (55%) were <2 years old; ten (91%) were previously healthy infants and one had a congenital heart disease. Four of the nine (44%) patients who were >2 years old had some comorbidity (two had a neurological impairment, one had asthma, one was an immunocompromised child). However, to be <2 year old and/or to have at least one pre-existing condition was not associated with a higher frequency of requiring admission to PICU in comparison to healthy children >2 years old: five of 41 (12%) previously healthy children aged >2 years required PICU admission and a similar rate, 15 of 102 (15%), of those aged <2 years and/or who had at least one pre-existing condition required PICU admission (p 0.7).

Seven of the 22 (32%) children with chest X-ray opacities in more than one quadrant required admission to PICU, whereas 13 of 121 (11%) patients without chest X-ray opacities or with opacities in only one quadrant were admitted to the PICUs (p <0.01).

Eighteen of the 86 (21%) patients who did not receive antiviral therapy or who received it more than 3 days after the onset of symptoms were admitted to the PICU whereas only two of the 25 (8%) patients who received antiviral agents within the first 3 days of symptoms were admitted to the PICU (both of them were previously healthy patients aged <2 years). This difference was not statistically significant (p 0.23).

Risk factors for hospitalization

For the case–control analysis we included 135 admitted patients and 137 outpatients (Table 2). Having a neurological disease conferred the highest risk of requiring admission (adjusted OR 17.18; 95% CI 3.44–85.90) in the multivariate analysis. Other variables that were related to admission were having a chronic pulmonary disease, having neurological symptoms due to the influenza infection, having a longer duration of symptoms, receiving antibiotics before consulting, and being a child of parents with a lower educational level. Only two of the patients who required hospitalization had been receiving antiviral agents before admission (both with an underlying condition). None of the outpatients received antiviral agents.

Discussion

This is one of the first paediatric postpandemic series in international literature that allows us to describe influenza during the 2010–2011 season in a representative sample of children admitted to 17 Spanish hospitals and to study specific risk factors for a more severe disease requiring hospitalization using a design of a matched case–control study.

Most of the admitted children with influenza infection did not have any comorbidity. This is similar to other prepandemic paediatric reports [10,11]. The age distribution of hospitalizations was in accord with the pattern of children aged <2 years without comorbidities and older children with some previously known disease, as observed by others during the pandemics [12,13]. In another series that included patients of all ages [4], the hospitalized patients in the immediate postpandemic period were significantly older than those admitted during the 2009 pandemic season. However, focusing on paediatrics, we observed that the median age of the infected children was lower in comparison with the median age of those who were infected during the pandemic season [14]. This observation was also made by Poulakou *et al.* [9]. Older children might have been less susceptible because of a relatively high attack rate during the previous pandemic influenza season [15]. Of note, although influenza vaccine coverage was very low, it was almost non-existent among patients <2 years old in our series and most of the patients with comorbidities were not well immunized. In Spain, the influenza vaccine is administered free of charge to patients with some high-risk conditions. Some studies have reported that lower patient volume and strategies to extend the opening hours of vaccine offices/clinics to evenings and weekends have

TABLE 2. Epidemiological and clinical variables as risk factors for hospitalization.

			Univariate analysis		Multivariate analysis[a]	
	Hospitalized (*n* = 135)	Outpatients (*n* = 137)	Crude OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Age (median), *n* (%)	2.0 years (IQR: 1.0–6.0)	2.6 years (IQR: 1.2–6.3)	1.02 (0.91–1.14)	0.69		
<2 years	59 (44)	57 (42)	1			
2–5 years	36 (27)	39 (28)	0.81 (0.36–1.81)	0.61		
5–12 years	30 (22)	34 (25)	0.91 (0.34–2.43)	0.86		
≥13 years	10 (7)	7 (5)	2.00 (0.38–10.36)	0.41		
Sex (male), *n* (%)	68 (50)	65 (47)	0.88 (0.54–1.44)	0.62		
Comorbidities, *n* (%)						
Patients with one or more pre-existing conditions	52 (38)	14 (10)	7.55 (3.22–17.72)	<0.001		
Pulmonary disease	24 (18)	12 (9)	2.57 (1.13–5.84)	0.02	3.31 (1.01–10.88)	0.04
Neurological disease	22 (16)	2 (1)	11.86 (2.78–50.58)	0.001	17.18 (3.44–85.90)	0.001
Cardiovascular disease	5 (4)	0 (0)	65.29 (0.05–86658.5)	0.25		
Renal chronic disease	4 (3)	0 (0)	65.29 (0.02–202501.6)	0.31		
Diabetes mellitus	1 (1)	0 (0)	65.29 (0–6.3e8)	0.61		
Primary or secondary immunodeficiency	7 (5)	0 (0)	65.29 (0.15–28459.84)	0.18		
Patients with two or more pre-existing conditions	10 (7)	0 (0)	65.29 (0.40–10546.6)	0.11		
Full influenza vaccination coverage	5 (4)	2 (1)	4.00 (0.45–35.79)	0.21		
Full pneumococcal vaccine, PCV7, immunization	41 (31)	51 (39)	0.68 (0.36–1.28)	0.23		
Non-Caucasian ethnicity	37 (27)	16 (12)	2.66 (1.40–5.04)	0.003		
Parents with primary or lower education	44/127	17/136	4.19 (2.02–8.68)	<0.001	6.21 (2.47–15.65)	<0.001
Clinical symptoms, *n* (%)						
Fever	125 (93)	119 (87)	1.89 (0.84–4.24)	0.12		
Respiratory symptoms	121 (89)	111 (81)	2.15 (1.01–4.58)	0.04		
Digestive symptoms	56 (41)	32 (23)	2.57 (1.44–4.59)	0.001		
Neurological symptoms	25 (18)	3 (2)	8.33 (2.52–27.60)	0.001	4.75 (1.03–21.83)	0.04
Days of clinical symptoms, median (IQR)	3 (IQR: 1–5)	2 (IQR: 1–3)	1.23 (1.10–1.38)	<0.001	1.20 (1.01–1.43)	0.04
Antibiotics before consulting, *n* (%)	48 (36)	24 (18)	3.29 (1.67–6.50)	0.001	2.70 (1.14–6.38)	0.02

[a]Area under the curve = 0.73; Hosmer–Lemeshow: p 0.48.

been associated with higher rates of vaccine coverage [16]. However, to promote information about the safety and immunogenicity of influenza vaccination among paediatricians and the target population is also important [17]. With regard to universal child vaccination, it may be an appropriate public health priority because vaccination is both cost saving and cost effective; children have high rates of healthcare utilization due to influenza and are the main transmitters of the virus [18].

Almost all the patients had respiratory symptoms and respiratory distress and hypoxaemia were the main reasons for hospitalization in our series. Severity of illness was comparable among prepandemic, pandemic and postpandemic seasons as stated by Rahamat-Langendoen *et al.*, but more radiographic pneumonia was diagnosed in patients with influenza A(H1N1)pdm09 [4,6]. It is well know that having viral pneumonia was a risk factor for admission due to influenza disease in children [5,19]. We observed that having chest X-ray opacities in two or more quadrants was associated with a longer hospital stay and a higher risk of PICU admission.

Less than a half of the hospitalized children received antiviral agents and there were also children with high-risk conditions who did not received oseltamivir. During the first postpandemic season the use of antiviral agents has probably been too low compared with their use during the pandemic outbreak [20]. In our opinion, this could increase the risk of severe disease, as stated in other studies [2,21], and it caused a longer hospital stay in our series, as observed during the pandemic season [22]. There are still controversies in the use of antivirals in children; first, because of the ill-defined conclusions of several trials and meta-analyses published before the pandemics; although the evidence supports a direct mechanism of action for oseltamivir on symptoms [23]. On the other hand, there may be a fear that widespread use of antiviral agents facilitates the expansion of resistant viruses [24]. We are still unable to draw conclusions about the effect of antiviral treatment on complications or transmission as stated by the last Cochrane review about neuraminidase inhibitors for preventing and treating influenza in children [23], but the results of several observational studies published elsewhere support the use of antiviral agents in children with risk of severe disease [25]. Children who require hospitalization and those outpatients with a high-risk condition should be considered for antiviral treatment.

Regarding other treatments, no differences in length of hospital stay were observed between children who received systemic corticosteroids and patients without corticosteroids in this study. There are no specific guidelines for using this treatment in children with influenza infection, even in those with severe influenza disease. Studies in adult settings have shown no benefit of using corticosteroids or other immunomodulatory treatments [26,27], despite observing an exaggerated inflammatory response in several cases of severe influenza disease [28]. There is not much information regarding the role of immunopathology in severe influenza disease in children [29]. The adult immune response cannot be extrapolated to children, and direct viral damage could be important enough to cause severe manifestations in children [30]. In our opinion, there could be high diversity in corticosteroid use in our series, so this is a variable that is difficult to analyse. Similarly, we did not find much specific information on antibiotic therapies, but it is remarkable that patients with antibiotic treatment were more likely to be admitted than patients without antibiotics. It is probable that some patients had been receiving antibiotics empirically because they had symptoms of a more severe respiratory disease before being admitted.

Finally, according to the results we obtained for the pandemic season [14], children with a previously known disease (especially neurological and pulmonary), and children of parents with lower educational levels were more frequently admitted to the case–control study analysis. Specific strategies to promote the prevention of severe influenza disease in these children should be considered.

The main limitations of this study are that it is an observational report and treatments (antiviral agents, antibiotics, corticosteroids) were given according to each participating hospital's guidelines. Different criteria for hospital and PICU admission may also be one of the biases of the study.

To summarize, influenza disease in the paediatric population requiring hospitalization during the first postpandemic season in Spain affected mainly children with neurological or pulmonary comorbidities and children of parents with a low educational level, as reported elsewhere during the pandemics and other pre-2009 pandemic outbreaks. Most of the influenza infections caused respiratory symptoms, although neurological manifestations were also observed and those patients were more frequently admitted. Early initiation of oseltamivir was associated with a shorter length of hospital stay.

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Transparency Declaration

No conflicts of interest to declare.

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