

Pandemic H1N1 influenza-associated hospitalizations in children in Madrid, Spain

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Objective To describe the epidemiological and clinical characteristics of children hospitalized with 2009 pandemic influenza (pH1N1) in Madrid, Spain.

Patients/Methods We included patients less than 14 years of age admitted to one of 18 hospitals in Madrid, Spain, between May 1 and November 30, 2009 and diagnosed with pH1N1 by polymerase chain reaction. A retrospective chart review was conducted and data were compared by age, presence of high-risk medical conditions, and pediatric intensive care unit (PICU) admission.

Results A total of 517 pH1N1 cases were included for final analysis. One hundred and forty-two patients (27.5%) had predisposing underlying illnesses, with immunosuppression (36 children, 7%) and moderate persistent asthma (34, 6.6%) being the most common ones. Patients with underlying medical conditions had longer hospital stays [median 5, interquartile range (IQR) 3–8 days, versus median 4, IQR 3–6, $P < 0.001$] and required intensive care (20.4% versus 5.9%, $P < 0.001$) and

mechanical ventilation more frequently than previously healthy children. Globally, intensive care was required for 51 patients (10%) and invasive mechanical ventilation for 12 (2%). Pediatric intensive care unit admission was significantly associated with abnormal initial chest X-ray [Odds Ratio (OR) 3.5, 95% confidence interval (CI) 1.5–8.5], underlying neurological condition (OR 3.1, CI 1.2–7.5) and immunosuppression (OR 2.9, 1.2–6.8). Five patients (0.9%) died; two with severe neurological disease, two with leukemia, and one with a malignant solid tumor.

Conclusions Children with underlying medical conditions experienced more severe pH1N1 disease. Risk factors for admission to the PICU included underlying neurological conditions, immunosuppression and abnormal initial chest X-ray.

Keywords 2009 pandemic influenza A (H1N1), hospitalizations, pediatric influenza, pH1N1.

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Introduction

In April 2009, the first cases of infection by a novel influenza A H1N1 virus (pandemic H1N1 or pH1N1) were registered in Mexico.¹ Since then, the virus spread worldwide causing significant morbidity. The first cases of the new virus in Spain were detected by the end of April 2009.² The highest incidence in Madrid occurred in week 43 (October 25–31, 2009), with 375 cases/100 000 inhabitants.³

Most infected children had a mild clinical picture, but pH1N1 resulted in an unusually high number of serious cases among young people.⁴ Children with underlying health conditions appear to be at higher risk for severe infection.^{5,6} This risk for severe clinical course is highest among children with underlying neurological diseases.^{7,8} Asthma has been described as one of the most common medical conditions among hospitalized children,^{7,9} but to our knowledge, pH1N1 severity has not been analyzed across different asthma severity levels.

The objectives of our study were as follows: (i) to describe the clinical and epidemiological features of hospitalized children with pH1N1; (ii) to compare the characteristics of ward and pediatric intensive care unit (PICU) patients; and (iii) to evaluate the influence of underlying medical conditions on disease course.

Patients and methods

Patients and samples

Children ≤ 14 years with confirmed pH1N1 by reverse-transcriptase polymerase chain reaction (RT-PCR) and admitted to one of 18 public pediatric hospitals in Madrid during a 7-month period (May–November 2009) were included in the study. Older children and those referred from other cities of Spain to PICU in Madrid were excluded from the analysis. All centers routinely tested for pH1N1 every child admitted with fever and respiratory symptoms up to December 2009, as pH1N1 activity markedly declined afterwards in Spain. Up to May 22nd, all positive children were admitted to hospital for isolation purposes. After this date, they were only admitted if the clinical picture recommended to do so.¹⁰

Samples were collected according to the protocol that the Health Department of the Madrid Government set up at the beginning of the pandemic. They were sent to one of the Influenza Laboratories Network of Madrid and processed within 24 hours of collection.¹¹ The diagnosis of pH1N1 was made with the World Health Organisation approved real-time PCR A H1N1 assay in all laboratories.¹²

Clinical assessment

A retrospective chart review was conducted using a standardized questionnaire, collecting data concerning demographics, health status, clinical manifestations, laboratory tests and chest X-ray results, complications, and outcome. There was at least one pediatrician in charge of collecting the data at each participating hospital.

Underlying health conditions for influenza-related complications were defined according to the recommendations of the Spanish Association of Pediatrics: respiratory diseases (cystic fibrosis, moderate or severe persistent asthma, and bronchopulmonary dysplasia), hemodynamically significant heart diseases, metabolic diseases (diabetes mellitus, morbid obesity), immunosuppression, neurological and neuromuscular diseases, chronic renal failure, and hemoglobinopathies.¹³ Morbid obesity was defined as body mass index at or above the 99th percentile for the child's age. Asthma severity was established according to the classification of the Spanish Society for Pediatric Pulmonology: children with infrequent intermittent and frequent intermittent asthma had less than five and eight exacerbations per year, respectively, remaining completely asymptomatic between them. In contrast, patients with moderate persistent asthma had wheezing episodes at least each 4–5 weeks, with mild symptoms between exacerbations and nocturnal symptoms up to two nights per week. Children with severe persistent asthma had frequent exacerbations with symptoms between them, wheezing with minimal physical efforts and nocturnal symptoms more than two nights per week.¹⁴

Complications among patients hospitalized with confirmed pH1N1 were identified by using data from the discharge summaries and medical records. Respiratory insufficiency was defined as the need for mechanical ventilation (invasive or non-invasive) in patients without asthma. Children who were admitted to PICU because of asthma exacerbation were considered as having severe bronchospasm. We identified patients with suspected or confirmed bacterial pneumonia taking into account the data regarding blood tests, chest X-ray (focal infiltrates or consolidation, pleural effusion), blood cultures, and clinical course. Patients who had altered mental status for ≥ 24 hours were categorized as having encephalopathy.

Statistical analysis

We described the characteristics of children with pH1N1 who were admitted to hospital. Clinical features and outcomes were compared according to age and the presence of underlying health conditions. We also compared PICU and ward patients to identify potential risk factors for a more severe clinical course.

Data analysis was performed at the Biostatistics Unit of Hospital La Paz, using spss statistical software, version 9.0

(SPSS Inc., Chicago, IL, USA). Continuous variables were described with mean and standard deviation or median and interquartile range. Categorical variables were described with absolute and relative frequencies.

The association of possible risk factors and PICU admission was studied using Chi-square test and Fisher's exact test in categorical variables and Student's *t* and Mann-Whitney *U* tests in continuous variables. The area under the ROC curve was estimated to evaluate the discriminating capacity of lymphocyte count, choosing 1840 cells/mm³ as the cut-off that maximized sensitivity (76.2%, 95% CI: 61.5–86.5) and specificity (49.6%, 95% CI: 44.8–54.5).

Finally, all factors that had a significant association ($P < 0.05$) with PICU admission were put into a full model for multiple logistic regression analysis. To estimate the predictive capacity of the model, the area under the ROC curve was calculated.

A two-tailed *P* value < 0.05 was considered statistically significant.

Results

Clinical and demographic characteristics

During the study period, 517 children with confirmed pH1N1 infection were hospitalized. The first pediatric case was confirmed on the 20th of May and hospitalizations for pH1N1 peaked at the end of October. Cases included in this review represent 90% of confirmed hospitalized paediatric cases in Madrid, according to data from the regional epidemiologic bulletin.¹⁰

Main characteristics of the total study group are presented in Table 1. Mean age was 4.7 ± 3.9 years and 59.8% patients were less than 5 years. Median time to consultation from the beginning of symptoms was 3 days (interquartile range, IQR: 1–5). The most frequent reasons for hospital admission were high fever and respiratory distress. Mean maximal temperature before admission was $38.9^\circ\text{C} \pm 0.7^\circ\text{C}$.

One hundred and forty-two patients (27.5%) had high-risk medical conditions, with immunosuppression, moderate persistent asthma, and neurological disease being the most common ones. There were 163 patients (31.5%) with asthma: 87 had infrequent intermittent asthma, 41 frequent intermittent, 34 moderate persistent, and 1 severe persistent asthma. Patients with underlying health conditions were significantly older than those previously healthy (mean age 5.5 ± 3.8 years versus 4.3 ± 3.9 years, $P < 0.01$).

Radiological, laboratory, and microbiological studies

Chest radiograph was performed on admission in 432 children (84%). Abnormal chest radiographs were significantly more frequent in children that required PICU admission

Table 1. Characteristics of children hospitalized with pandemic H1N1 influenza, Madrid, 2009

	Number of cases	Percentage
Gender		
Female	205	40
Male	312	60
Age group		
<1 year	99	19
1–5 years	210	41
5–11 years	155	30
11–14 years	53	10
Clinical signs and symptoms		
Fever	500	97
Upper respiratory tract manifestations		
Cough	455	88
Rhinorrhea	369	72
Odynophagia	62	12
Breathing difficulty	258	50
General symptoms		
Headache	54	11
Myalgias	43	9
Irritability/malaise	196	38
Gastrointestinal symptoms		
Vomiting	144	28
Diarrhea	69	14
Chest radiograph	432	84
Interstitial pneumonia	187	43
Lobar or segmental consolidation	94	22
Other radiologic findings (atelectasis, pleural effusion)	19	4
Normal	132	31
Treatment		
Oseltamivir	389	76
Antibiotics	264	52
Bronchodilators	244	48
Oxygen supplementation	221	43
Intravenous fluid therapy	204	40
Underlying health conditions*	142	27.5
Moderate or severe persistent asthma	35	6.8
Other chronic lung disorders (e.g., cystic fibrosis, bronchopulmonary dysplasia, obliterant bronchiolitis)	19	3.7
Immunosuppression (because of underlying disease and/or therapy) or immunodeficiency	36	7

Table 1. (Continued)

	Number of cases	Percentage
Neurological or neuromuscular disorders	30	5.8
Heart disease	27	5.2
Diabetes mellitus	5	1
Chronic renal disease	4	0.8
Morbid obesity	3	0.6
Hemoglobinopathy	3	0.6
Complications[†]	132	26
Confirmed or suspected bacterial pneumonia	72	14.5
Severe bronchospasm	16	3.1
Respiratory insufficiency	12	2.3
Seizures	7	1.4
Acute otitis media	7	1.4
Clinical sepsis	4	0.8
Encephalopathy	3	0.6
Other [‡]	19	3.7

*Children may have had more than one of the conditions listed; percentage represents the number with each condition over the total number of children ($n = 517$).

[†]Children may have had more than one of the complications listed; percentage represents the number with each condition over the total number of children ($n = 517$).

[‡]Severe laryngitis (2), decompensation of heart disease (2), bacteremia (2), hepatitis (2), hemolytic crises (1), Stevens–Johnson syndrome (1), urinary tract infection (1), acute tonsillopharyngitis (1), erosive gastritis (1), dehydration (1), hyponatremia (1), incomplete Kawasaki disease (1), myositis (1), pneumothorax (1), and interstitial lung disease (1).

than in ward patients (88% versus 67%, $P < 0.01$). Blood was collected and analyzed for 462 children (89%). Pediatric intensive care unit patients had lower lymphocyte counts (1590 ± 1298 versus 2702 ± 2868 , $P < 0.001$). We observed no differences between PICU and ward patients regarding white blood cell count, neutrophils, and C-reactive protein.

Blood cultures were performed in 341 children (66%), but they were positive only in seven patients (excluding bacterial contaminations). The most frequent isolate was *Streptococcus pneumoniae* (six cases). *Streptococcus pyogenes* was identified in one case. There were no infections by *Staphylococcus aureus*.

Antiviral treatment, clinical course, and complications

Antiviral use was reported in 389 children (76%), oseltamivir being the only drug prescribed. Oseltamivir use was more frequent in PICU than in ward patients (86% versus 74.9%, $P = 0.08$) and significantly lower in infants <1 year

compared with older children (59.6% versus 79.9%, $P < 0.001$). There were no major adverse effects associated with oseltamivir therapy.

The median length of hospital stay was 4 days (IQR: 3–6). Complications were registered in 132 patients (26%), as listed in Table 1. The most frequent one was suspected or confirmed bacterial pneumonia, which occurred in 72 patients (14.5%), followed by severe bronchospasm requiring PICU admission (16 patients, 3.1%).

When comparing infants less than 1 year of age with older children, we found no differences regarding hospital stay [median (IQR) 4 days (3–6) for both groups, $P = 0.59$], PICU admission (11% versus 10%, $P = 0.71$), and invasive mechanical ventilation (3% versus 2%, $P = 0.39$). Underlying medical conditions (14.1% versus 30.6%, $P = 0.001$) and complications (17.2% versus 27.5%, $P = 0.04$) were less frequent in infants.

As for patients with high-risk medical conditions, they had longer hospital stay [5 days (3–8) versus 4 (3–6), $P < 0.001$] and required PICU admission (20.4% versus 5.9%, $P < 0.001$) and invasive mechanical ventilation (6.3% versus 0.8%, $P < 0.01$) more frequently than previously healthy children.

However, the presence or severity of asthma was not significantly associated with PICU admission or mechanical ventilation. Pediatric intensive care unit admission and invasive mechanical ventilation proportions were respectively 6.9% and 1.1% in patients with infrequent intermittent asthma ($n = 87$), 12.2% and 2.4% in patients with frequent intermittent asthma ($n = 41$), and 11.8% and 2.9% in patients with moderate persistent asthma ($n = 34$). There was only one patient with severe persistent asthma, who required PICU admission but not invasive mechanical ventilation. Among non-asthmatic children ($n = 354$), 9.9% required PICU admission and 2.5% invasive mechanical ventilation ($P = 0.51$ for PICU admission and 0.82 for mechanical ventilation, when comparing non-asthmatic and asthmatic children across the different asthma severity levels).

Risk factors for PICU admission

Intensive care was required for 51 patients (10%), breathing difficulty being the most frequent reason for admission at the PICU. Comparison of ward versus PICU patients is showed in Table 2.

Thirty-one patients (6%) received non-invasive ventilation and 12 (2%) invasive mechanical ventilation. Of the 12 patients who required invasive mechanical ventilation, nine (75%) had underlying medical conditions and four died. The most frequent underlying medical conditions in these patients were neurological or neuromuscular disorders and immunosuppression (four patients, 33% each).

Table 2. Comparison of characteristics of ward versus pediatric intensive care unit (PICU) patients

	Ward patients <i>n</i> = 466 Number (%)	PICU patients <i>n</i> = 51 Number (%)	<i>P</i> *
Male sex	283 (60.7)	29 (56.9)	0.59
Mean age (years)	4.7 ± 3.9	4.4 ± 3.7	0.6
Clinical signs and symptoms			
Fever	452 (97.2)	48 (94.1)	0.23
Upper respiratory tract manifestations			
Cough	413 (88.8)	42 (82.4%)	0.17
Rhinorrhea	335 (72)	34 (69.4)	0.69
Odynophagia	57 (12.4)	5 (10.9)	0.76
Breathing difficulty	219 (47.2)	39 (78)	<0.001
General symptoms			
Headache	53 (11.6)	1 (2.2)	0.07
Myalgias	42 (9.2)	1 (2.2)	0.16
Irritability/malaise	178 (38.4)	18 (38.3)	0.98
Gastrointestinal symptoms			
Vomiting	136 (29.4)	8 (16.3)	0.05
Diarrhea	67 (14.4)	2 (4.1)	0.04
Mean time from symptom onset to hospital admission (days)	4.1 ± 10.7	2.5 ± 1.7	0.3
Abnormal chest radiograph	67%	88%	<0.01
Blood test results			
White blood cell count (cells/mm ³)	9994 ± 5988	9430 ± 6537	0.57
Lymphocytes (cells/mm ³)	2702 ± 2868	1590 ± 1298	<0.001
Neutrophils (cells/mm ³)	6026 ± 4970	6804 ± 5981	0.41
C-reactive protein (mg/l)	34.3 ± 52.7	45 ± 68.6	0.31
Treatment			
Oseltamivir	346 (74.9)	43 (86)	0.08
Antibiotics	223 (49.2)	41 (80.4)	<0.0001
Bronchodilators	215 (46.6)	29 (58)	0.12
Oxygen supplementation	173 (37.7)	48 (94.1)	<0.0001
Intravenous fluid therapy	161 (35.2)	43 (87.8)	<0.0001
Underlying health conditions			
Any	113 (24.2)	29 (56.9)	<0.001
Moderate or severe persistent asthma	30 (6.4)	5 (9.8)	0.36
Other chronic lung disorders (e.g. cystic fibrosis, bronchopulmonary dysplasia, obliterant bronchiolitis)	15 (3.2)	4 (7.8)	0.11
Immunosuppression (because of underlying disease and/or therapy) or immunodeficiency	28 (6)	8 (15.7)	<0.01
Neurological or neuromuscular disorders	22 (4.7)	8 (15.7)	<0.01
Heart disease	23 (4.9)	4 (7.8)	0.33
Complications			
Any	85 (18.2)	47 (92.2)	<0.0001
Confirmed or suspected bacterial pneumonia	52 (11.1)	20 (39.2)	<0.0001

Statistically significant differences are shown in bold.

In a multivariable model that included underlying medical conditions, lymphocyte count and chest radiograph result, we identified four statistically significant risk factors associated with PICU admission: underlying neurological or neuromuscular disease [$P = 0.006$, Odds Ratio (OR) 4.2, 95% CI 1.5–11.3], immunosuppression ($P = 0.008$, OR 4.4, 95% CI 1.5–13.2), abnormal initial chest X-ray ($P = 0.005$, OR 5.2, 95% CI 1.7–16.5), and lymphocytes under 1840 cells/mm^3 ($P = 0.006$, OR 2.9, 1.3–6.2). The estimated effects in this model were similar to those estimated in the previous univariate analysis. The area under the ROC curve was 0.720 (95% CI 0.66–0.80).

Mortality

Five patients (0.9%) died, all of them suffering of underlying health conditions. Two children (both 4 years old) had leukemia with severe pancytopenia and developed acute respiratory distress with refractory hypoxemia. A 10-year-old patient had a malignant peripheral nerve sheath tumor with cerebral metastasis. He developed bronchopneumonia and acute respiratory distress syndrome with progressive worsening, and limitation of therapeutic effort was decided. A 3-month-old infant with Edwards' syndrome developed respiratory insufficiency with severe hypoxemia, and limitation of therapeutic effort was decided. The last patient was 4 years old and had a severe encephalopathy with cerebral palsy and a seizure disorder. Her chest radiograph showed a large pleural effusion and developed severe breathing difficulty and refractory hypoxemia. Four out of five of these patients, the exception being the one affected by Edwards' syndrome, received oseltamivir, were admitted to PICU and put on mechanical ventilation.

Discussion

Children hospitalized for pH1N1 infections in Madrid had a wide spectrum of clinical pictures, ranging from mild respiratory symptoms and fever to severe illness and death. The majority of children in our study were less than 5 years of age. Presenting features and median length of hospital stay were similar to those described in other series.^{5,15,16} Underlying medical conditions were frequent, mainly asthma, immunosuppression, and neurological disease. Patients with underlying health conditions were older than previously healthy children. Abnormal chest radiograph, low lymphocytes, and underlying health conditions were associated with PICU admission, while asthma was not.

Infants less than 1 year have been considered at increased risk for influenza-related complications only on the basis of age and had the highest hospitalization rates at the beginning of the pandemic.¹⁷ In our study, the clinical course was similar in this age group than in older children,

which could be related to a higher hospitalization rate among infants (even when presenting with mild symptoms) and to the fact that the majority of infants were previously healthy. Perhaps, children less than 1 year did not yet have the opportunity to be diagnosed with some of the high-risk medical conditions that increase the risk for severe disease. A recent pediatric study showed that older hospitalized children with pH1N1 were significantly more likely to require PICU admission than hospitalized children <2 years of age.⁷ Besides, previous studies of seasonal influenza in Spain did not find more complications among hospitalized infants younger than 6 months.^{18,19} Notably, there was only one death in the infant group, and the patient suffered from Edwards' syndrome. Oseltamivir treatment was significantly less likely in infants less than 1 year of age, although an Emergency Use Authorization was issued temporarily allowing its use in infants during the H1N1 pandemic. However, some pediatricians may have been reluctant to use oseltamivir because of the limited data in patients younger than 1 year of age.

Overall, asthma was the most frequent underlying health condition (31.5% of cases, including intermittent asthma), as other authors have reported.^{5,14,20} It seems that children admitted to hospital with pH1N1 are more likely to have asthma than those with seasonal influenza.^{7,21} To our knowledge, there are no published data assessing the severity of pH1N1 infection across different asthma severity levels. In our case series, most hospitalized children with asthma and no other health conditions had intermittent asthma (79%), suggesting that children with intermittent asthma are at risk of pH1N1 infection requiring hospital admission, which is in accordance with other pediatric series.^{20,21} However, when analyzing severity of pH1N1 in patients with asthma in our series (PICU admission, death), it was similar to that of children without underlying medical conditions, and also similar in each asthma severity level. Nevertheless, only one child suffered from severe persistent asthma, and this may limit the validity of our results in this group of patients.

PICU admission rates range from 5.4 to 27% in the literature.^{5,7,15,16,21–23} Our rate of 10% is similar to that of seasonal influenza.^{21,24–26} As it has been previously reported, PICU admission and mechanical ventilation have occurred mainly in children with known comorbidities.^{27,28} The proportion of high-risk medical conditions among patients admitted to intensive care units is similar to that reported for adults in our country. However, for adults, the most common underlying medical condition was obesity.²⁹ In our series, immunosuppression and neurological disorders were the most common underlying medical conditions among PICU patients, and they were significantly associated with PICU admission. Several reports on seasonal influenza had previously shown the importance of neuro-

logical and neuromuscular conditions as a predisposing risk factor for severe disease.^{30–32} As for pH1N1 influenza, it seems that these patients are also at higher risk for complications and PICU admission, mainly those children with multiple developmental diagnoses and/or comorbid pulmonary conditions.^{7,8,22,33,34} The underlying mechanisms of vulnerability in these children may include problems with muscle tone, weakness, inadequate clearance of respiratory tract secretions, and susceptibility to recurrent respiratory infections.^{32,33} Complicated cases among children are mostly attributable to secondary bacterial infection, which is more common in children than in adults.³⁵ The incidence of suspected bacterial pneumonia was similar to the one reported for seasonal influenza.^{31,36} The low rate of confirmed bacterial coinfections in our study is similar to that observed in other pH1N1 case series,^{9,33} in which *S. pneumoniae* has also been the most frequent isolated pathogen.^{5,15} However, bacterial diagnostic tests were not performed in all cases, and many patients received antibiotics around the time of culture collection, which could have reduced the diagnostic sensitivity.³³ In hospitalized patients with seasonal influenza, culture-proven bacterial infection is also rare, and *S. aureus* and *S. pneumoniae* are the predominant pathogens isolated.²⁴ Notably, there were no *S. aureus* infections in our series. In Spain, community-acquired staphylococcal pneumonia is rare, but infections caused by methicillin-resistant *S. aureus* are emerging.³⁷ A coinfection by methicillin-resistant *S. aureus* and pandemic influenza H1N1 was recently documented in a child in our country.³⁸

During the 2009 influenza H1N1 pandemic, global hospitalization rates have been higher for children less than the age of 5 years, but the need for mechanical ventilation and the overall case fatality rate among hospitalized patients appears to be lowest among children.^{20,22,29,33,35,39,40} Mortality proportions among hospitalized children with pH1N1 show marked differences; from 0^{21,28} to 5%.¹⁵ Most pediatric deaths have affected patients with underlying medical conditions.^{5,15,27,34} Our mortality data are comparable to seasonal influenza, with the likely exception of the 2003–2004 H3N2 season, which was associated with increased mortality and morbidity.^{30,31,36}

There are several limitations in our study. First, although data recording was standardized, observations may have differed among hospitals or healthcare providers, and not all information was collected for all patients. Second, routine diagnostic testing recommended by public health authorities for hospitalized children with fever and respiratory symptoms may have led to a greater number of confirmed cases than in previous influenza seasons. Third, admission criteria may have not been the same in all the hospitals that participated in the study.

However, we provide global information from a large sample, not only from tertiary care pediatric hospitals but also from local hospitals. Diagnostic methods were the same among all centers and during the whole study period.

In conclusion, pH1N1 in hospitalized children in Madrid (Spain) has affected mainly children less than 5 years of age, and asthma was the most common underlying medical condition. Children less than 1 year were less likely to have high-risk health conditions and develop complications. Patients with predisposing health conditions, especially those with neurological disease, were more likely to experience severe pH1N1 infection. Therefore, this group of children should be carefully assessed for early recognition and adequate follow-up and treatment of pH1N1 infection. As for asthmatic patients, although they did not experience more severe disease, it seems that even children with intermittent asthma are at risk of pH1N1 infection requiring hospital admission and should therefore receive vaccination and be considered for early antiviral therapy.

Addendum

This is a multicentric study conducted in 18 different hospitals by a Study Group. In each hospital, there was at least one investigator (depending on the number of cases), who collected data and contributed to their interpretation. All authors have revised the intellectual content of the manuscript.

Conflicts of interest

The authors declare to have no conflicts of interest.

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